Outcome in Juvenile Rheumatoid Arthritis in India

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Manuscript received: August 28, 2002, Initial review completed: May 9, 2003; Revision accepted: June 26, 2003.

Juvenile rheumatoid arthritis (JRA) leads to significant morbidity due to continued disease activity and drug toxicity. Retrospective analysis of patients with JRA seen at a tertiary care hospital between 1990-2000 was done. Data regarding the type of onset, course of disease, joints involved, treatment received, drug toxicity and outcome at last visit were retrived from case records. There were 214 children (76 oligoarticular, 93 polyarticular and 45 systemic onset) with 135 of them being boys. At last followup, with median disease duration of 6 years; 128 had active disease, 58 had stable disease and 28 had inactive disease. Polyarticular group had the worst outcome with only 3 of the 93 having inactive disease (13/76 in oligo articular group and 12/45 in systemic onset disease). Intramuscular gold and D-Penicillamine were associated with significant drug toxicity. Outcome of children with JRA in our country is poorer as compared to developed countries.

Key words: *Juvenile rheumatoid arthritis, DMARD.*

Juvenile rheumatoid arthritis is the most common cause of chronic arthritis in childhood. It is a heterogeneous disease with three onset types *i.e.*, polyarticular, pauciarticular and systemic onset disease(1). The major morbidity is related to chronic synovitis and joint destruction. Amyloidosis and drug toxicity also contribute to morbidity.

Studies in eighties suggested that most patients with JRA are free of symptoms when they reach adulthood(2), but recent studies reflect a less favorable outcome with almost 40% of them continuing to have active disease at the end of 10 years(3-9). The data available are difficult to compare, due to use of different diagnostic criteria for defining patients, proportion of patients of each subset of JRA in the study cohort and study setting (hospital or primary care). Population based cohort studies with stringent criteria and long term follow-up are the best for studying the natural history and outcome of a disease but are tedious and time consuming. Even though hospital based study especially those from tertiary care centres cannot be true representatives of the outcome in a population yet they provide the first step in this regard. As yet there are no data from India regarding outcome of JRA.

Patients and Methods

All patients attending the out patient clinic of Department of Clinical Immunology at our institution with JRA (ACR criteria)(1) who had atleast 1-year follow-up with us were included in the study. Case records of all these patients were screened and information regarding the type of disease, course of disease, drugs received, side effects of drugs, outcome and complications of disease was retrieved. Sjogren syndrome was diagnosed based on symptoms and signs of dry eyes and dry mouth. Interstitial lung disease was diagnosed either on chest *X*-ray or high resolution CT scan along with restrictive

pattern on pulmonary function tests. Valvular dysfunction was confirmed on echocardiography and color doppler. Diagnosis of nephropathy was based on kidney biopsy. Amyloidosis was confirmed by rectal biopsy or abdominal fat pad aspiration.

All patients with active disease received non-steroidal anti-inflammatory drugs (NSAIDs). Patients with polyarticular disease refractory to NSAIDs received methotrexate (10-15 mg/m^2/week), D-penicillamine 125-250 mg/day, intramuscular gold (l mg/kg/week to a maximum of 50 mg/week). Low dose prednisolone was used for control of symptoms. Patients with systemic onset disease received prednisolone (0.5-1.0 mg/kg/day) for control of symptoms if disease was refractory to NSAIDs. Patients requiring corticosteroids for more than 3 months were given methotrexate or azathioprine. In patients with mainly joint symptoms other DMARDs were used as for polyarticular disease.

In oligoarticular disease intial management included NSAIDs and intraarticular steroids. In patients with polyarticular course or persistent arthritis, salazopyrine was used at a dose of 40-50 mg/kg/day, or other DMARDs as in polyarticular disease.

Outcome at last visit was assessed as active disease: persistent synovitis despite treatment; stable disease: absence of symptoms but requiring drugs, and inactive disease: absence of symptoms and off drugs for at least 6 months.

Results

There were 214 children with 76 having oligoarticular type, 93 with polyarticular and 45 with systemic onset disease. The detailed demographic data are given in *Table I.*

The median duration of follow-up was 2 years. Among children with pauciarticular disease, ankle (75%) and knee (63%) were the most frequently involved joints, followed by sacroiliac (38%), wrist (28%), hip (26%), cervical spine (10%), elbow and shoulders. Enthesitis was seen in 7 patients whereas uveitis was present in 10 patients. IgA nephropathy, diagnosed on kidney biopsy was present in one patient and valvular heart disease (non rheumatic aortic regurgitation) was seen in 2 patients. Among these 76 patients, 13 had inactive disease, 24 had stable disease and 39 had active disease. Fifty seven continued to have pauciarticular course while 14 of them changed into a polyarticular type and 5 evolved into juvenile ankylosing spondylitis.

In polyarticular disease, the joints involved were knees (87%), ankle (85%), wrist (81%), small joints of hands (69%), elbow (68%), shoulder (57%), hips (22%) and temporomandibular joint (5%). Extra-articular manifestations included Sjogren's syndrome in

TABLE I–*Demographic Data of Patients with JRA*

	Oligoarticular	Polyarticular	Systemic onset
Number	76	93	45
M:F	63:13	46:47	26:19
Age at onset (years)	10 (2-16)	11 (0.5-16)	6 (0.5-16)
Duration of disease (years)	5 (0.25-20)	3 (0.3-26)	3 (0.3-10)
Duration of followup (years)	2 (1-10)	2 (1-11)	2(1-7)
Inactive disease (n)	13	03	12
Stable disease (n)	24	26	8
Active disease (n)	39	64	25

2, small vessel vasculitis in 3, uveitis in 4 and interstitial lung disease in 2 patients. One patient had anterior atlanto-axial dislocation detected on cervical spine radiograph without any neurological deficit. Among these, 31 (33%) had rheumatoid factor and 4 had antinuclear antibodies in their sera. All continued to have polyarticular disease except one patient who developed inflamma-tory bowel disease. Three had inactive disease, 26 had stable disease and 64 had active disease at last follow-up. Patients with active disease had higher baseline ESR value (54.8 mm vs 41.6 mm), longer duration of disease (58.9 months *vs* 33.5 months) and presence of deformities ($p < 0.05$) as compared to those with stable or inactive disease at last follow-up.

In systemic onset type, all patients had fever whereas 24 had skin rash, 40 had lymphadenopathy and 41 had hepato-splenomegaly. The joints involved were wrist (66%), elbow (58%), knee (60%), ankle (50%), small joints of hands (42%). The mean ESR and CRP were 64 and 11.7 mg/dL respectively. Anti-nuclear antibody was not present in any patient. Among 45 children with systemic onset disease, 12 had inactive disease, 8 had stable disease and 25 had active disease. Two children developed proteinuria due to secondary amyloidosis and were treated with cyclophosphamide and prednisolone (*Table II*). Proteinuria improved partly with this treatment.

After a median disease duration of 6 years, 60% of patients continued to have active arthritis, while 27% had stable disease and only 13% had inactive disease.

The incidence of side effects with various agents were as follows: NSAIDs (11%), oral prednisolone (23%), low dose methotrexate (13.5%), intramuscular gold (5%), D-Pencillamine (20%), sulphasalazine (7%), chloroquine (10%). Major side effects were more with D-Penicillamine and intramuscular gold (*Table III*).

Discussion

In our study 87% of patients had active or stable disease after a median disease duration of 6 years. In contrast, in a population based study(3,4) from Sweden 49% of 124 patients had active or stable disease at a median disease duration of 7.1 years. However, that study had a poor representation of cases with systemic and polyarticular disease (3.2% and 29% respectively) while in our study they constituted almost 65% of the study population. Systemic onset and polyarticular disease are associated with higher long- term morbidity(3).

TABLE II–*Drugs Used in Patients of JRA (n)*

	Pauciarticular (76)	Polyarticular (93)	Systemic (45)
Methotrexate	26	59	33
Intramuscular gold	07	13	05
D-Pencillamine	06	14	03
Sulphasalazine	14	09	05
Chloroquine	03	07	04
Azathioprine	0	02	03
Cyclophosphamide	0	01	02
IVIG	0	0	01

Some patients received multiple drugs sequentially

Key Messages

- Two third of patients with JRA, seen at tertiary care hospital continue to have active disease at a median of 6 years after disease onset.
- Polyarticular disease has the worst outcome.
- Methotrexate is a safe disease modifying anti-rheumatoid drug in patients with JRA.

Another study(5) involving 506 consecutive patients with juvenile chronic arthritis and having a median disease duration of 8.8 years at follow-up found that remission rates were 45% for pauciarticular disease, 35% for systemic onset disease and only 20% in the polyarticular group. As our study was not limited to patients with new onset disease, most patients already had persistent disease at the time of presentation to this hospital and would be expected to have a worse prognosis(6).

An overall response rate of 92% with drugs is encouraging even though only 55% had a complete response. The complete response rate was significantly less in polyarticular disease. Polyarticular disease especially seropositive group has the least response to drugs(3). However, we did not find any difference in the seropositive and seronegative group.

Complications like uveitis are thought to have a significant impact on outcome(10) in JRA. Incidence of uveitis was low in our study *i.e.* 2.2% and none of the child had impaired vision due to uveitis. Previous studies from India(1112) and Costa Rica(13) have also reported a low prevalence of uveitis in patients with JRA.

TABLE III–*Major Toxicity of Drugs*

Drug	N	Side effects
Methotrexate	118	Gastritis 5; Anemia 4
		Cytopenia 2; Infection 2
Intramuscular gold	25	Proteinuria 3; Anemia 1
D-Pencillamine	23	Proteinuria 1; Jaundice 1
		Dermatitis 2
Sulphasalazine	28	Rash 3
Chloroquine	14	Rash 2

Due to delay in therapy as well as continued disease activity, 2 patients with systemic onset disease developed secondary amyloidosis. Our incidence of 1% is similar to previously reported low prevalence in USA(14). However, studies from UK, with long term followup and use of radionuclide scans have reported an incidence of 5-9% (10,15). It is most frequent in patients with systemic onset disease as was seen in our patients.

Drug toxicity was minimal with methotrexate but significant with gold and D-penicillamine as has been reported earlier(16). Methotrexate due to its superior efficacy-toxicity ratio has emerged as the single most important DMARD in JRA. The 10% incidence of rash with sulphasalazine in our study was less compared to 23% reported from Western countries(16) and could be related to difference in genetic background.

The limitations of our study are retrospective collection of data, tertiary care hospital source, lack of functional assessment and use of older classification. Older classification has been used as patients diagnosed before 1997 have been analyzed

and retrospective reclassification has its own problems. Still this study serves to reflect that our children with JRA are not receiving optimum care at peripheral level and an early referral is needed to improve the outcome. We also need a long term, population inception cohort based study with use of standardized instruments for measuring outcome including impact on growth and childhood health assessment questionnaire.

Contributors: AA was involved in conception design, analysis, manuscript revision and final approval. VA and DD helped in acquisition of data, analysis, manuscript drafting and final approval. RM helped in design, revision and final approval of manuscript.

Funding: None.

Competing Interests: None stated.

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