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STUDY TO DETERMINE THE LONG-STANDING CONSEQUENCES OF SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS AND PREDICTORS OF BIOLOGIC TREATMENT

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Abstract:

Objective: *The results of systemic juvenile idiopathic arthritis (SJIA) vary from mild disability to mortality. Due to socioeconomic problems, delays in taking certain medications, especially biological agents, can affect the outcome of this disease. This analysis aimed to govern the long-term results and predictors of biological therapy in patients with SJIA.*

Place and Duration: *In the Paediatric unit II of Mayo Hospital Lahore for four-year duration from March 2015 to March 2019.*

Methods: *Patients with SJIA were selected for the study. Data was taken from medical records at the first presentation and during the last clinical visit. The results included disease status, functional impairment and joint damage.*

Results: *Out of 68 SJIA patients, 64 (94%) qualified. Median age at onset (interquartile range) and follow-up were 4.4 (2.9-7.9) and 4.2 (2.3-55.9), respectively. Nine patients (14%) achieved complete remission, while 12 patients (18.8%) survived active disease and 3 died; two of them had macrophage activation syndrome and the other had serious infection. One of the predictors of moderate to severe disability (paediatric health questionnaire ≥ 0.75) was hip involvement (likelihood ratio [OR 27, 95% confidence interval [CI]: 3.20–228.05). In addition, predictors of biological therapy were female (OR 6.4, 95% CI 1.74–23.74), initially at an early age (OR 4.7, 95% CI 1.31–16.66), liver enlargement and spleen (OR 5.9, 95% CI 1.29–27.29) and positive antinuclear antibody (ANA) (OR 6.3, 95% CI 1.19–33.75). In 34.2% of patients, Bone erosion was noted with SJIA.*

Conclusion: *Hip involvement was an important predictor of moderate to severe disability in SJIA, while female gender, younger onset age, liver and spleen enlargement, and positive ANA were predictors of biological therapy.*

Keywords: *Biologic treatment, juvenile idiopathic arthritis, outcomes, predictor, SJIA.*

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INTRODUCTION:

In children, Juvenile idiopathic arthritis (JIA) is the utmost usual cause of chronic arthritis. Its incidence ranges from 0.83 to 23.6 / 100,000 children per year. It is a diverse group of diseases with arthritis of indefinite origin, which begins before the sixteen years of age and persists more than six weeks. JIA was divided into seven subtypes according to the revised criteria of the International Association of Rheumatology (2001). Systemic JIA (SJIA) is the most common JIA subtype in most Asian countries. The course and outcome of SJIA differs from mild disability to mortality due to many factors. In previous studies, persistent systemic traits, early age at baseline, polyarticular pattern, and hip arthritis predictors of poor functional outcomes in JIA. Corticosteroid therapy is the basis for treatment followed by anti-rheumatic drugs (DMARDs) that change the disease. Biological agents have been in our treatment guide for over ten years. However, socioeconomic problems in Pakistan lead to delays in patients receiving the biological agent in a timely manner. Course of the disease and JIA is the utmost usual cause of chronic arthritis in children. Its occurrence ranges from 0.83 to 23.6 / 100,000 children per year. It is a heterogeneous group of disease with arthritis of unknown origin, which begins before the age of 16 and lasts longer than 6 weeks. JIA was divided into seven subtypes according to the revised criteria of the International Association of Rheumatology (2001). Systemic JIA (SJIA) is the most common JIA subtype in most Asian countries.

The long-term consequences of SJIA in Pakistan may differ from those for Asia or other developed countries. Therefore, the aim of this analysis was to govern the long-term results, determinants of biological therapy, and SJIA functional disorders in children in Pakistan.

METHODS:

The study was held in the Paediatric Unit II of Mayo Hospital Lahore for four-year duration from March 2015 to March 2019.

Data collection:

Data were collected from medical records and recent clinical visits at the time of diagnosis. The included parameters were gender, age at onset, time from diagnosis to treatment, joint involvement, rash, hepatosplenomegaly, drugs, mortality and cause of death. Complications, including macrophage activation syndrome (MAS), uveitis, avascular necrosis, interstitial lung disease (ILD), amyloidosis and joint deformities were reported according to the criteria of the Histiocyte Society in 2004. Laboratory data were positive for CBC, ESR, C-reactive protein (CRP), rheumatoid factor, liver function test and antinuclear antibody (ANA).

The guidelines for SJIA treatment depend on the phenotypes of the disease. Nonsteroidal anti-inflammatory drugs and corticosteroids are the basis for treatment in patients with active systemic diseases and varying degrees of synovitis. DMARDs occur in patients with active systemic synovitis. In addition, biological therapy such as tocilizumab, etanercept and infliximab is started when patients with SJIA fail two DMARDs or fail to suspend corticosteroids within 6 months. However, in some patients, due to socioeconomic limitations, biological treatment cannot be started on time. SJIA results were evaluated in three categories: disease state, functional impairment and joint damage. According to the European Union, the disease state can be divided into 4 groups depending on the criteria of rheumatic disease activity: (1) the number of active and increased active joints regardless of drug treatment; (2) number of stable active joints requiring drug treatment; (3) inactive with no evidence of active joint and / or extra-articular feature without drug treatment for <2 years; (4) in remission, there is no evidence of active joint and / or extra-articular symptoms without drug treatment for ≥2 years. Functional impairment was assessed using a child health questionnaire (CHAQ). CHAQ was completed by children ≥ 8 years old or by their parents if the children were younger than 8 years old. Joint damage was assessed by simple radiography of all symptomatic and opposing joints on the last day of observation. Simple radiographs were assessed by a specialist radiologist of the musculoskeletal system according to Dale's radiographic classification system: grade 0, normal joints; Grade 1, osteoporosis and / or swelling of periarticular tissues; Grade 2, no growth anomalies, bone erosion; Grade 3, growth abnormality and marginal bone erosion; Grade 4, deformation and severe erosions; and class 5, severe damage and deformations. Therefore, the radiological classification of Dale 3-5 classes is erosive in nature. After 2 years of observation, the course of the disease was divided into 3 groups; (1) a single-phase active disease event that lasts <2 years during the observation period and continues without a relapse of the active disease; (2) active polycyclic disease followed by inactive disease for any period of time and repetition of the active disease during the observation period; and (3) persistent and active disease, including patients with persistent systemic symptoms and / or persistent symptoms of arthritis ≥ 2 years.

Statistical analysis:
The STATA 13.0 version (StataCorp, College Station, TX, USA) was used for statistical analysis. Categorical variables are expressed as frequency and percentage, and continuous data are shown as median and interquartile range (IQR). A step-by-step multiple logistic regression model was used to determine the prognosis for biological treatment and functional degradation. The significant level was set at 0.05. The results are presented as ratios (OR) with an appropriate 95% confidence interval (CI).

Ethical approval prior to the study, written informed consent and informed consent appropriate to the age were obtained from patients and parents.

RESULTS:
In 64 of 68 patients with SJIA, patients with SJIA qualified for the study and the remaining four patients lost control. There were 30 boys and 34 girls with an average onset age (RIQ) of 4.4 (2.5) years and an observation period of (1.8) years. All patients had high fever, arthritis in 98.4%, polyarthritis in about half, salmon rash in 79.7%, and hepatosplenomegaly in 26.6% and cheeseiness in 10.9%. The most common joints were the wrists (43%), knees (43%) and ankles (37%). The involvement of the hip at the beginning of the disease was about 9%. White blood cell count, platelet count, ESR, CRP and interleukin-6 levels increased at the beginning of the disease and returned to normal levels as shown in Table 1 during the follow-up period.

Table 1: Laboratory data at initial presentation and 4-year follow-up period in 64 systemic juvenile idiopathic arthritis patients

Laboratory data	At disease onset	At follow-up
Neutrophil counts (× 109 cells/L)	10.9 (9.6)	3.9 (2.4)
WBC counts (×109 cells/L)	14.7 (12.1)	8.2 (3.3)
Hematocrit	29.9 (6.1)	37.8 (4.1)
Platelet counts (× 109 cells/L)	516.5 (294.0)	316.0 (103.0)
CRP (mg/dL)*	82.1 (99.1)	0 (1.7)
ESR (mm/h)	92.0 (40.5)	14.0 (18.5)
ANA positive (%)	11 (17.2)	-
IL-6 (pg/mL)**	77.2 (329.5)	3.4 (17.2)
Rheumatoid factor positive (%)	0 (0)	-

Data expressed as median (interquartile range), *CRP was done in 34 patients; **IL-6 levels were measured at disease onset in 11 patients and at follow-up period was done in 52 patients. ANA: Antinuclear antibody, Erythrocyte sedimentation rate, C-reactive protein, WBC: White blood cell, IL-6: Interleukin-6

Systemic corticosteroids were the basis of treatment (87.5%) and most SJIA patients with chronic arthritis required DMARD. 82.8% received methotrexate and 42.2% received both methotrexate and sulfasalazine. Due to socioeconomic problems, patients who have failed two DMARDs are advised to take biological agents. Therefore, sulfasalazine was added after patients could not administer methotrexate. 20% intra-articular steroid injections are provided. Almost half of the patients did not undergo conventional therapy, corticosteroids and DMARD, therefore biological therapy has been indicated. Due to the introduction of tocilizumab and anti-cancer (anti-TNF) agents, no eligibility period for tocilizumab has been granted. Of the 34 patients (53.1%) biologically treated, 29 (85.3%) received the biological substance (26 patients with tocilizumab [89.7%] and 3 patients with etanercept [10.3%]). Five patients (14.7%) received two biological agents, 4 initially received etanercept and the other received infliximab. Not all of them

responded to anti-TNF drugs, so they switched to tocilizumab. Only 37.5% responded to patients receiving anti-TNF medication. Approximately 66.7% of tocilizumab-treated patients achieved a complete response and 33.3% - a partial response. The dose and frequency of tocilizumab treatment was 8 mg / kg every 2 weeks, and the average duration of tocilizumab treatment was 3.1 years (RIC 2.8). There was no immunosuppressant in patients with clinical remission during biological therapy. However, immunosuppressant's, including corticosteroids (14.6%), methotrexate (4.7%), corticosteroids and methotrexate (35.9%), methotrexate and sulfasalazine (4.7%) were prescribed to patients who were not in remission.

In terms of disease activity, nine patients (14.1%) achieved complete remission, eight (12.5%) were clinically inactive, 35 (54.7%) had stable disease, and 12 (18.8%) had persistent active disease. Two patients died of MAS and severe infection, one patient died of severe infection. Therefore, in this study, the most serious complication leading to high mortality in JIA patients was MAS and severe infection. Eleven patients (17.2%) had MAS that developed during the most active diseases. Three out of eleven patients had a partial response to intravenous immunoglobulin and were then treated with systemic corticosteroids. Only 27% responded only to systemic corticosteroids, while other patients needed cyclosporine as additional treatment. Amyloidosis developed around 10 years after JIA in a patient with persistent disease and refractory to treatment. In this study, another patient with MIZ was diagnosed with ILD. General complications of JIA patients during the 4-year follow-up period are shown in Figure 1.

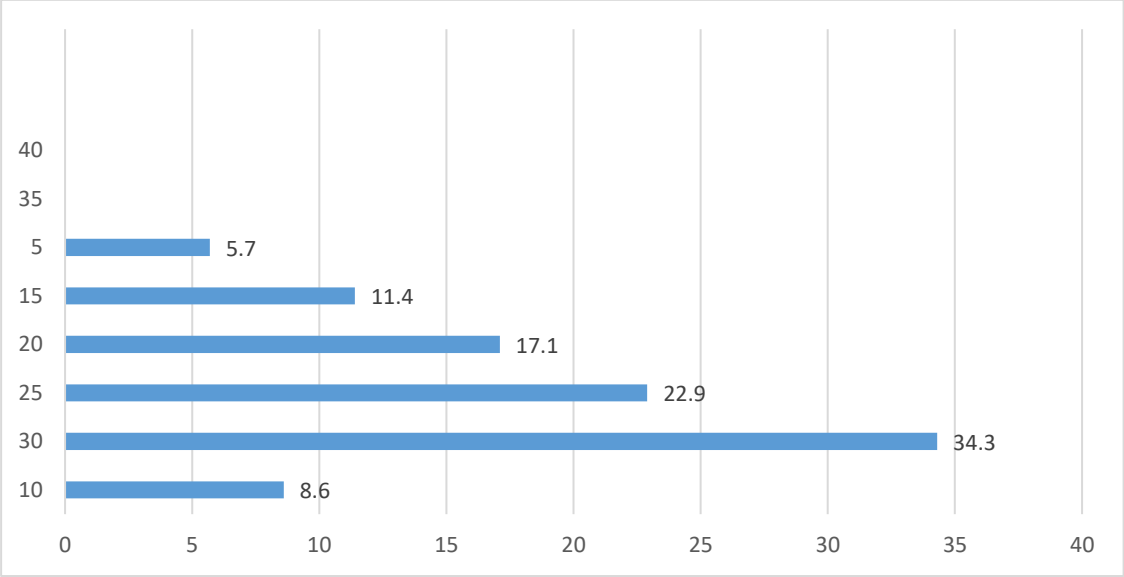

Figure 1: Complications of systemic juvenile idiopathic arthritis patients during 4-year follow-up. *MAS: Macrophage activation syndrome

After using logistic regression analysis, the predictors of biological treatment were female sex, younger onset age, liver and spleen enlargement, and ANA. Positive as shown in Table 2.

Table 2: Predictors of biologic treatment in systemic juvenile idiopathic arthritis patients

Variables	Univariate logistic regression			Multivariate logistic regression		
	OR	**95% CI**	**P**	**OR**	**95% CI**	**P**
Female	3.6	1.3-10.2	0.015	6.4	1.7-23.7	0.005
Age <5.5 years	3.6	1.3-10.2	0.016	4.7	1.3-16.7	0.018
Hip involvement	1.0	0.9-1.0	0.301			
Polyarthritis	1.9	0.7-5.1	0.218			
Hematocrit <30%	1.0	0.9-1.2	0.624			
Hepatosplenomegaly	2.7	0.9-8.6	0.091	5.9	1.3-27.3	0.022
Platelet counts ≥600 (× 109 cells/L)	2.4	0.9-7.0	0.096			
WBC counts ≥20 (× 109 cells/L)	1.8	0.6-5.4	0.299			
ANA positive	3.8	0.9-15.8	0.071	6.3	1.2-33.8	0.031
ESR ≥80 (mm/h)	1.0	0.9-1.0	0.930			

P<0.05, significance, ANA: Antinuclear antibody, ESR, WBC, CI: Confidence interval, OR: Odds Ratio.

About 8% of JIA patients had a moderate to severe degree of disability determined by CHAQ ≥ 0.75. Hip involvement in these patients was the only predictor of moderate or severe disability, with OR 27.0 and 95% CI 3.2-2.2. The median time from onset of disease to radiographic evaluation was 2.7 (IQR 1.7) to assess joint damage in 35 patients. Second class Dale had the highest radiographic classification and the lowest grade, as shown in Figure 2, which is the average grade of the fifth grade. Bone erosion including the Dale Grad 3-5 radiographic classification was 34.2%.

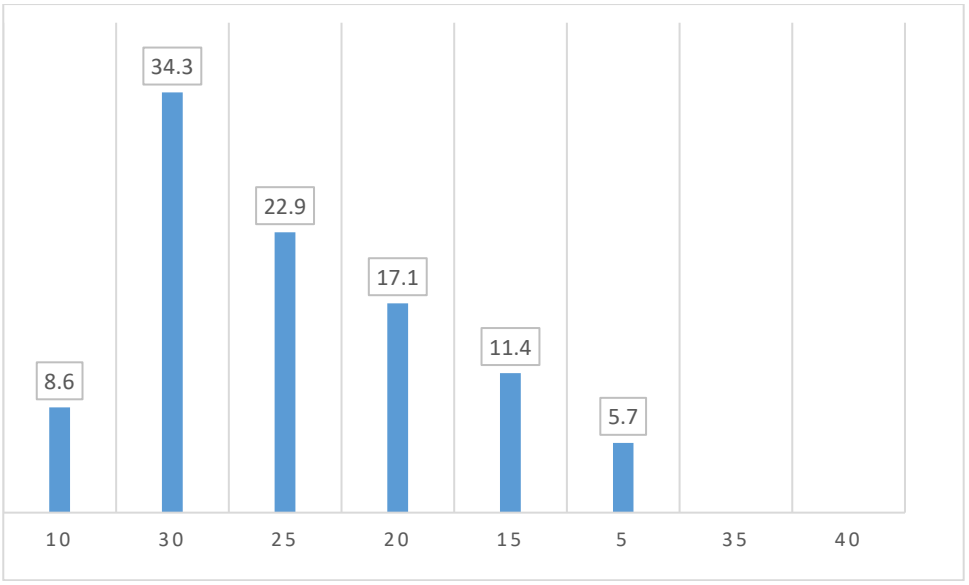

Figure 2: Radiographic abnormalities according to dale radiographic classification system in 35 systemic juvenile idiopathic arthritis patients. *Grade 0, normal joints; Grade 1, juxtaarticular osteoporosis and/or periarticular soft tissue swelling; Grade 2, growth abnormality and bony erosion not present; Grade 3, growth abnormality and marginal bony erosions; Grade 4, deformation and severe erosions; Grade 5, gross destruction and deformity

Most patients (62.5%) had persistent disease, 34.4% had single-phase disease, and only 3.1% had polycyclic disease. The single-phase and polycyclic course of the disease is classified as unstable. Laboratory data and drugs between persistent and unstable disease are shown in Table 3.

Table 3: Laboratory data and medications in systemic juvenile idiopathic arthritis patients between nonpersistent and persistent disease course patterns

Parameters	Nonpersistent (n=22)	Persistent (n=42)	P
Female	10 (45.5)	24 (57.1)	0.373
Age at disease onset, year	6.4 (9.0)	4.2 (4.9)	0.079
WBC counts (× 109 cells/L)	14.9 (14.5)	14.3 (7.9)	0.098
Duration of follow-up, year	2.6 (3.0)	5.1 (4.1)	0.002
Hematocrit	30.3 (4.3)	29.6 (8.0)	0.795
Platelet counts (× 109 cells/L)	572 (413)	508 (245)	0.082
CRP (mg/dL)*	72.2 (114.7)	82.7 (63.7)	0.753
ESR (mm/h)	92.5 (34)	91 (44)	0.662
Stop corticosteroids, if ever	14 (87.5)	24 (60)	0.014
Corticosteroids usage (%)	16 (72.7)	40 (95.2)	0.010
Biologic treatment (%)	9 (40.9)	25 (59.5)	0.156
used (%)			

P<0.05, significance, Data expressed as median (interquartile range), *CRP was done in 34 patients. CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, WBC: White blood cell count

Although 60% of patients with persistent disease underwent biological treatment, persistent disease was not a predictor of biological treatment in this study.

DISCUSSION:

The SJIA is heterogeneous in the course and severity of the disease. Disease results also vary depending on your nationality and treatment strategy. Therefore, this study focuses on clinical features, outcomes, complications, predictors of biological therapy, and functional disorders in patients with JIA. Patients in this study had a number of severities of the disease. Patient demographics in this study differed from previous studies. In addition, at the beginning of the disease was a patient without arthritis. This can be explained by the lack of arthritis in one-third of JIA patients in the initial presentation, and a previous study showed that the average duration of arthritis was 75 days. Among polyarthritis patients, polyarthritis was the same as polyarthritis, which is different from previous reports in which polyarthritis is more common. These findings can be explained by different SJIA phenotypes in different ethnic groups. As a result of the disease, we found that only 14.0% of people had lower clinical remission than others. Tsai et al reported that 28.6% had complete remission, reported incomplete remission in 37.0% of patients in the Russo and Katsicas study. The difference between ethnicity, disease severity, remission criteria and treatment strategies between studies can lead to changes in remission rates. In this study, most patients were treated intensively. None of the 60% of patients specified for biological agents who were unable to receive money on time were in remission, 27.8% developed deformity, and 22.2% had spinal fractures due to prolonged corticosteroid use. In addition, because the study was conducted at a tertiary health centre, patients had worse prognosis. There are many complications at SJIA that require attention. The most serious and life-threatening complication of SJIA is MAS, which is classified as secondary hemophagocytic lymphohistiocytosis (HLH). We found that MAS occurred in approximately 17% of JIA patients, and previous studies ranged from 7% to 15%. When the HLH 2004 criteria are used to diagnose MAS, the incidence of MAS in JIA may be lower because SJIA is a systemic inflammatory disease with a relatively high level of white blood cells and platelets, cut off levels must be different from other HLH aetiologies. MAS' diagnosis criteria should be applied separately from HLH 2004 criteria. Ravelli et al and Davi et al showed preliminary guidelines that MAS in SJIA was stronger than the HLH-2004 criteria, and another common complication in SJIA was destructive arthritis (34.2% with bone erosion). Because the onset of the disease was 2.7 (IQR 1.7) years up to the radiographic evaluation period, some patients had an observation period of over 2 years during the radiographic observation. Therefore, this may explain the high frequency of radiological changes in these patients. Previous studies have shown that approximately 20–40% of JIA patients develop joint damage, which is very similar to this study. Considering those who predicted the severity of the disease, this study revealed that <5.5 years of age is a predictable biological treatment that reflects the severity of the disease and the severity of refractory disease in JIA patients. This finding is very similar to the discovery of Russo et al., Who showed that early-onset SJIA patients showed a more aggressive disease course than late-onset patients.

CONCLUSION:

In conclusion, our study suggests that female gender, earliest age at onset, liver and spleen enlargement, and positive ANA may be important predictors of poor outcomes and refractory disease in patients with increased JIA. The hip is an indicator of moderate to severe disability. These data can be useful to identify high-risk patients and provide early therapeutic intervention to improve outcomes.

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