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Original Article

Outcome predictors in patients with juvenile idiopathic arthritis receiving intra-articular corticosteroid therapy

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Abstract

Background Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in children. It can continue into adulthood and cause severe joint damage, resulting in disability and decreased quality of life.

Objective To determine the predictors of clinical outcomes in JIA patients receiving intra-articular corticosteroid injections (IACS).

Methods We conducted a retrospective cohort study of children with JIA receiving IACS therapy in Dr. Sardjito General Hospital from 1 January 2012 to 31 December 2017 by reviewing data from medical records. The dependent variables were disabilities and early remission time. Independent variables included age at diagnosis, JIA subtype, duration of disease at first diagnosis, timing of IACS, exposure to oral systemic therapy, as well as anti-nuclear antibodies (ANA), rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) test results. External variables were gender and nutritional status.

Results Of 36 patients who received intra-articular corticosteroid injections, 28 (77.8%) experienced remission, and 16 (50%) experienced disabilities. Female subjects (OR 5.296; 95%CI 1.143 to 24.548; P=0.027) and subjects with ESR >26 mm/h (OR 2; 95%CI 1.259 to 3.170; P=0.043) were more likely to have disabilities. Use of oral corticosteroids for ≤3 months and IACS treatment ≤ 3 months after diagnosis were predictors of early remission time (OR 6.897; 95%CI 1.869 to 25 and OR 3.290; 95%CI 1.195 to 9.091, respectively). However, only oral corticosteroid had a significant correlation in multivariate analysis.

Conclusion Female gender and ESR > 26 mm/h predict disabilities in JIA patients receiving IACS. Duration of oral corticosteroid ≤3 months and early IACS within 3 months of diagnosis correlate to earlier remission time. Shorter duration of oral corticosteroid is the only significant predictor for earlier remission time in JIA patients receiving IACS therapy. **[Paediatr Indones. 2019;59:237-43 ; doi: http://dx.doi.org/10.14238/pi59.5.2019.237-43**].

Keywords: *juvenile idiopathic arthritis; intraarticular injection; remission; disability; early remission time*

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in children, causing severe joint damage which results in disability and decreased quality of life.[1] The aims of therapy are to resolve inflammation, prevent further cartilage damage, and maintain joint function. The mainstay of JIA therapy includes a combination of non-steroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs (DMARDs), biological agents, systemic corticosteroids, intra-articular corticosteroid injections (IACS), and physiotherapy.[2,3] The IACS can significantly reduce pain, improve joint function, as well as promote the repair of bone deformity and bone growth.[3-5]

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Of the limited studies on JIA in Indonesia, most are descriptive, and to our knowledge, none have examined JIA patients who received IACS.[6,7] Identifying predictors of outcomes in JIA patients who received IACS can help in therapy selection for patients and education for both patients and families.[1] We aimed to identify possible outcome predictors in JIA patients receiving intra-articular corticosteroid injections (IACS).

Methods

This retrospective cohort study retrieved data from medical records in Dr. Sardjito General Hospital, Yogyakarta. Subjects were children with JIA aged 1-18 years, diagnosed according to *International League of Associations for Rheumatology* (ILAR) criteria (arthritis that occurs under the age of 16 years with duration of illness 6 weeks or more where other causes of arthritis were excluded)[8] and had received intra-articular corticosteroid injections, as outpatients or inpatients between January 2012 and December 2017. Sampling was not performed as all patients who met the inclusion criteria were enrolled as subjects.

Dependent variables were time to remission and disability. Time to remission was calculated since the time of diagnosis to remission and criteria for disability was adapted from *American College of Rheumatology* revised criteria for classification of functional status in rheumatoid arthritis, which subjects who entered class functional 2-4 were defined to have disabilities. Independent variables were age at diagnosis, JIA subtype, duration of disease at the time of diagnosis, timing of IACS, exposure to oral systemic therapy, anti-nuclear antibodies (ANA), rheumatoid factor (RF), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) test results. External variables were gender and nutritional status. Early corticosteroid injection was defined as corticosteroid injections performed ≤ 3 months after JIA diagnosis.[4]

Data were analyzed using *SPSS Statistics version 22.0* software. Normality of data distribution was determined by the Kolmogorov-Smirnov test. Independent variables were analyzed by Chi-square or Fisher's exact tests for categorical variables, followed by multivariate analysis as appropriate. Predictors of early remission time were analyzed using Kaplan-Meier and Cox-regression analyses. The Medical and Health Research Ethics Committee of the Universitas Gadjah Mada and Dr. Sardjito General Hospital approved this study.

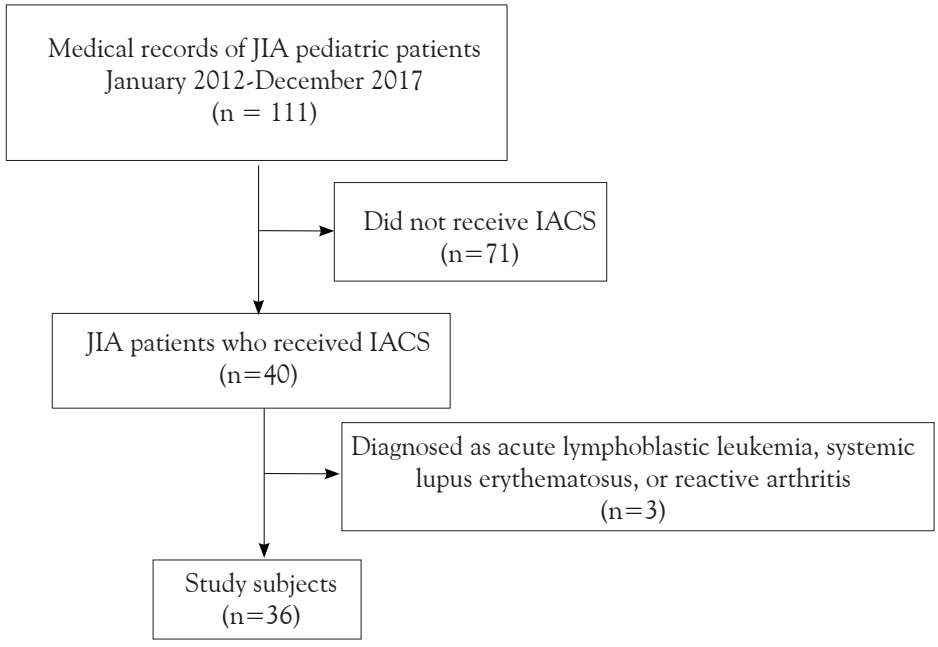

Figure 1. Study subject flow chart

Results

There were 111 JIA patients in RSUP Dr Sardjito from 2012 to 2017, of whom 40 received IACS. We excluded 4 patients due to incomplete medical records or misdiagnosis (**Figure 1**).

Our study included 36 subjects, consisting of 22 girls (61.1%) and 14 boys (38.9%) with a ratio of 1.6:1. Twenty-eight (28) children (77.8%) were in the age group of >6 years. Underweight nutritional status, defined as BMI below 18.5, was found in 22 subjects (61.1%) at the time of enrollment. The most common subtype of JIA was oligoarticular (19 subjects; 52.8%) (**Table 1**).

Table 1. Subjects' characteristics

Characteristics	(N = 36)
Gender	
Female	22
Male	14
Age	
> 6 years	28
≤ 6 years	8
BMI status	
Underweight	22
Normal	13
Overweight	1
Obese	0
Diagnosis	
Oligoarticular	19
Polyarticular RF-	14
Systemic	2
Polyarticular RF+	1

BMI=body mass index; RF+=positive rheumatoid factor; RF-=negative rheumatoid factor

Remission was achieved by 28/36 subjects, with time to achieve remission ranging from 3-37 months after diagnosis (median of 4 months). There were 16 subjects with disabilities (50%). The most common symptoms were joint pain (36/36) and joint swelling (27/36). The ANA was positive in 4 of 21 subjects examined, while RF was positive in 3 of 30 subjects examined. Thirty of 36 subjects received IACS ≤ 3 months after diagnosis (**Table 2**).

Bivariate analysis of predictors for disability is presented in **Table 3**. Female gender (OR 5.296; 95%CI 1.143 to 24.548; P=0.027) and ESR >26 mm/hour (OR 2; 95%CI 1.259 to 3.170; P=0.043) had significantly greater likelihoods for disability in bivariate analysis. However, none of those predictors were significant in multivariate analysis.

Table 2. Clinical and laboratory profiles before IACS therapy

Profiles	(N= 36)
Duration of illness	
≤ 2 months	7
> 2 months	29
Symptoms	
Joint pain	36
Yes	0
No	
Joint swelling	27
Yes	9
No	
Limp	14
Yes	22
No	
Fever	12
Yes	24
No	
Morning stiffness	5
Yes	31
No	
Anti nuclear antibody	
Negative	17
Positive	4
No data	15
Rheumatoid factor	
Negative	27
Positive	3
No data	6
Erythrocyte sedimentation rate	
≤ 26 mm/hour	6
> 26 mm/hour	17
No data	13
C-reactive protein	
≤ 10 mg/dL	11
> 10 mg/dL	11
No data	14
Duration of methotrexate	
≤ 3 months	14
> 3 months	11
Not available	11
Duration of oral corticosteroid	
≤ 3 months	12
> 3 months	12
Not available	12
Timing of IACS after diagnosis	
≤ 3 months	30
> 3 months	6
Disability	
Yes	16
No	20

Table 3. Bivariate and multivariate analysis of predictors for disability

Predictors	Disability (n= 16)	No disability (n= 20)	Bivariate analysis			Multivariate analysis		
			OR	95%CI	P value	OR	95%CI	P value
Gender								
Female	13	9	5.296	1.143 to 24.548	0.027	0.221	0.016 to 2.971	0.255
Male	3	11						
Age								
≤ 6 years	4	4	1.333	0.276 to 6.442	1.000			
> 6 years	12	16						
BMI								
Abnormal	10	12	1.111	0.288 to 4.290	0.878			
Normal	6	8						
Diagnosis								
Oligoarticular	9	10	0.385	0.096 to 1.536	0.171			
Polyarticular RF+	1	1						
Polyarticular RF-	4	9						
Systemic	2	0						
Duration of illness								
> 2 months	12	13	1.615	0.376 to 6.940	0.718			
≤ 2 months	4	7						
Anti nuclear antibody								
Positive	3	1	9.750	0.780 to 121.839	0.490			
Negative	4	13						
Rheumatoid factor								
Negative	12	14	1.714	0.138 to 21.333	1.000			
Positive	1	2						
Erythrocyte sedimentation rate								
> 26 mm/hour	9	9	2.000	1.259 to 3.170	0.043	0.000	0.000 to ~	0.999
≤ 26 mm/hour	0	5						
C-reactive protein								
> 10 mg/dL	5	6	2.222	0.375 to 13.180	0.659			
≤ 10 mg/dL	3	8						
Duration of methotrexate								
≤ 3 months	6	8	0.900	0.183 to 4.415	1.000			
> 3 months	5	6						
Duration of oral corticosteroid								
≤ 3 months	7	5	1.960	0.387 to 9.934	0.414			
> 3 months	5	7						
Timing of IACS after diagnosis								
≤ 3 months	17	14	4.857	0.486 to 48.574	0.338			
> 3 months	1	4						

OR=odds ratio; CI=confidence of interval

Predictors for early remission time were assessed by Cox regression analysis. Shorter duration of oral corticosteroid use and IACS < 3 months after diagnosis (**Table 4**) had greater likelihoods to achieve earlier remission in each time period (HR 6.897; 95%CI 1.869 to 25 and HR 3.290; 95%CI 1.195 to 9.091, respectively). However, only the duration of oral corticosteroid therapy was statistically significant in the multivariate analysis (HR 5.381; 95%CI 1.359 to 21.307 ; P=0.017).

Discussion

There are several indications for intraarticular corticosteroid injection in JIA. This procedure is used as initial therapy for the oligoarticular subtype to relieve synovitis, and/or as additional therapy if the patient does not respond to NSAIDs. The IACS also reduces the need for long-term oral systemic therapy, reduces joint complications including joint contractures and leg length discrepancy, speeds up the

Table 4. Bivariate and multivariate Cox regression analysis for predictors of early remission time

Predictors	Median remission onset, months	Bivariate analysis			Multivariate analysis		
		HR	95%CI	P value	HR	95%CI	P value
Gender							
Female	3.0	1.577	0.710 to 3.401	0.269			
Male	4.0						
Age							
≤ 6 years	3.0	1.582	0.682 to 3.663	0.285			
> 6 years	4.0						
BMI							
Normal	3.0	1.469	0.615 to 3.507	0.386			
Abnormal	3.0						
Diagnosis							
Oligoarticular	3.0	0.634	0.281 to 1.431	0.272			
Polyarticular RF+	1.0						
Polyarticular RF-	4.0						
Duration of illness							
> 2 months	3.0	0.655	0.220 to 1.954	0.448			
≤ 2 months	4.0						
Anti nuclear antibody							
Positive	4.0	1.032	0.292 to 3.648	0.961			
Negative	3.0						
Rheumatic factor							
Positive	1.0	1.624	0.471 to 5.604	0.443			
Negative	3.0						
Erythrocyte sedimentation rate							
> 26 mm/hour	3.0	1.430	0.511 to 4.005	0.496			
≤ 26 mm/hour	4.0						
C reactive protein							
≤ 10 mg/dL	3.0	1.117	0.424 to 2.950	0.822			
> 10 mg/dL	6.0						
Duration of methotrexate							
≤ 3 months	1.0	2.293	0.879 to 5.988	0.090			
> 3 months	8.0						
Duration of oral corticosteroid							
≤ 3 months	1.0	6.897	1.869 to 25	0.004	5.381	1.359 to 21.307	0.017
> 3 months	8.0						
Timing of IACS after diagnosis							
≤ 3 months	3.0	3.290	1.195 to 9.091	0.021	1.781	0.498 to 6.366	0.375
> 3 months	15.0						

HR=hazard ratios

rehabilitation process, improves gait, and reduces pain. Nowadays, intraarticular injection has been applied to the polyarticular subtype as bridging therapy until disease-modifying antirheumatic drugs (DMARDS) therapy starts working effectively, helping to resolve joint deformity and reducing pain.[9]

In our study, females predominated with a female: male ratio of 1.6:1, similar to other studies which reported a predominance of females with JIA (ratios of 1:3 to 1:5, respectively).[6,10] Females might have greater risk for developing autoimmune diseases because of the two copies of the X chromosome and estrogen which plays a role as a promoting factor of the autoimmune processes.[11] Most of our subjects had BMI values lower than normal (61.1%). To our knowledge, there have been no studies that described the nutritional status of JIA patients. Stavropoulos-Kalinoglou *et al.*[12] in 2009 examined the relationship

between nutritional status and disease activity in adult patients with rheumatoid arthritis, and found that subjects with abnormal BMI (thin and obese) had higher CRP values and more severe disabilities.

Most subjects had complaints for more than 2 months (80.6%) before being diagnosed (mean duration of 6 months). Anderson *et al.*[13] noted that the duration of illness has a strong relationship with response to therapy. Patients with longer duration of illness had worse responses to corticosteroid injections. This finding might be caused by the progression of a biological process in the joints over time which causes a reduction in response to therapy.

A diagnosis of arthritis is clinically established by any signs of swelling in the joints or the presence of two of the following joint symptoms: limited joint movement, joint pain, and increased temperature in the joint area. Some studies stated that joint pain was the most common complaint in JIA.[6,7,14,15] This finding was in agreement with our results, as joint pain was the most common complaint (100%), followed by joint swelling (75%).

Increased ANA levels in JIA indicate the role of the humoral immune system in the pathogenesis of JIA.[15] Among the 21 subjects examined, ANA was positive in 4 subjects. Also, RF was positive in 3 of the 30 subjects examined (10%); the RF are often reported in adults with rheumatoid arthritis and usually indicate progressive disease activity, whereas in JIA, RF is only found in 10% of cases, in accordance with our findings.[7]

Examination of ESR and CRP are useful for identifying disease activity.[15] The mean values of ESR and CRP in our study were 48 mm/hour and 34 mg/dL, respectively, indicating that almost all patients were in the acute phase of the disease or the inflammatory process was still ongoing in the patient. Increased ESR accompanied by clinical symptoms are indicative of the ongoing inflammatory process in the joints.[15,16] In our study, ESR >26 mm/hour might be a predictor for disability according to bivariate analysis. This was consistent with a previous study which stated that ESR > 26 mm/hour correlated with longer onset of remission and more severe disease.[17]

Significant predictor for early remission time was duration of oral corticosteroid use. Oral corticosteroids are commonly used in systemic subtypes of JIA. In addition, they are given to JIA polyarticular patients as bridging therapy, or if there is no response to standard therapy. In the systemic JIA protocol used at Dr. Sardjito General Hospital, oral corticosteroids given for 11 weeks are gradually reduced once there is clinical improvement. Our results were in agreement with that of Singh-Grewal *et al.*[17] who showed that patients who no longer needed oral corticosteroid therapy at less than 3 months after diagnosis had earlier remission time (RR 1.95; 95%CI 1.14 to 3.54; P=0.014).

One of the ultimate goals in JIA management is to alter the course of the disease with early therapy. Not only would patients benefit in the short term from faster disease control, but it could translate into longer term benefit by decreasing the occurrence of damage. Early disease control might also impact on the immunological behavior of JIA and alter the long term disease course, a concept called the "window of opportunity".[11,18] Several previous studies focused on the effect of aggressive early systemic therapy, but not on the early corticosteroid injection.[19] There was one study examining the association between early corticosteroid injection and the achievement of remission during the first 2 years after study enrollment, but the results were not significant.[4] Even though early IACS injections could not be proven as a predictor in our study due to study limitation, it is still a promising domain for future studies.

One limitation of this study was the retrospective design using medical records, which has a risk of lost/incomplete data, such as laboratory variables, as well as information bias. Objective measures for patient outcomes such as the *Child Health Assessment Questionnaire* (CHAQ) could not be used because of limited data resources. The small number of subjects also might have diminished the effect of several important and significant predictors from previous studies, which were not statistically significant in our study.

In conclusion, the median time to achieve remission in JIA patients is 4 months, while 50% of subjects suffer from disability during follow up. Female gender and ESR > 26 mm/hour have greater likelihood for disability in JIA patients undergoing corticosteroid injections although they are not significant in multivariate analysis. Shorter duration of oral corticosteroid use is a predictor for early remission time. In view of the increasing use of IACS

in pediatric rheumatology, there is a need for further investigation of JIA outcomes with a well-designed, prospective cohort study.

Conflict of interest

None declared.

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