Factors Affecting the Efficacy of Intraarticular Corticosteroid Injection of Knees in Juvenile Idiopathic Arthritis

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ABSTRACT. ***Objective.*** To determine in a prospective analysis whether baseline demographic, clinical, and laboratory variables predict the outcome of intraarticular corticosteroid (IAC) injection of the knees in children with juvenile idiopathic arthritis (JIA).

Methods. We studied consecutive patients who met the criteria for the diagnosis of JIA and received their initial injection of triamcinolone hexacetonide in one or both knees. Predictor variables included sex, age, age at onset of JIA, onset subtype, disease duration, drug therapy at the time of IAC injection, physician and parent global assessment of disease status, Childhood Health Assessment Questionnaire disability index, erythrocyte sedimentation rate (ESR), C-reactive protein, involvement of other joints besides knees, amount of fluid aspirated, and dose of IAC injected. The primary outcome measure was persistence of complete clinical response at 6 months, i.e., no evidence of synovitis clinically.

Results. Ninety-four patients were available for analysis. At 6 months after the IAC injection, 65 (69%) patients showed a sustained complete clinical response, whereas 29 (31%) had had a recurrence of joint inflammation. Univariate statistical analyses showed that patients who had a sustained clinical response had a significantly higher ESR than those who did not ($p = 0.023$). The ESR was the only variable that remained in the best-fit model from multivariate logistic regression analysis (OR 2.61, $p = 0.049$).

Conclusion. Our findings indicate that patients with JIA who have a higher ESR are more likely to benefit from IAC injection of the knees. (J Rheumatol 2001;28:2100–2)

Key Indexing Terms:
JUVENILE CHRONIC ARTHRITIS
JUVENILE RHEUMATOID ARTHRITIS
INTRAARTICULAR CORTICOSTEROIDS
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Intraarticular corticosteroid (IAC) injections are increasingly used in the management of children with juvenile idiopathic arthritis (JIA) with the aim of producing rapid symptomatic relief of inflammation and functional improvement[1]. However, use of IAC in children is hampered by the fact that most of the information comes from retrospective analyses or, by inference, from studies in adult patients with rheumatoid arthritis.

We investigated in a prospective analysis whether baseline demographic, clinical, and laboratory variables predict the outcome of IAC injection of the knees in children with JIA.

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MATERIALS AND METHODS

Patient selection. All consecutive patients who met the criteria for the diagnosis of JIA[2] and received their initial IAC injection in one or both knees at our department between February 1996 and June 1999 were enrolled in the study. Indication for intraarticular injection therapy included persistent synovitis despite > 3 month treatment with nonsteroidal antiinflammatory drugs and the presence of one of the following: large effusion, severe joint pain, joint deformities such as significant flexion contracture, valgus, or growth disturbances leading to leg length difference, or Baker's cyst. In all patients, the knees were the sole joints injected and no other joint was injected in the subsequent 6 months.

Intraarticular injection procedure. After antiseptic preparation of the skin and local anesthesia with topical EMLA cream (lidocaine + prilocaine), the joint fluid was aspirated and a dose of 1 mg/kg (maximum 40 mg) triamcinolone hexacetonide with 0.5 ml lidocaine (2%) was injected. Younger children (generally aged < 6 yrs) were injected under short-acting inhalation anesthesia. After the IAC, patients were advised to rest the joint for 24 h.

Assessment of predictor variables. The following independent (predictor) variables were recorded at the time of the IAC injection: sex, age, age at onset of JIA, JIA onset subtype, disease duration, drug therapy at the time of the IAC injection, physician and parent global assessments of the disease status, Childhood Health Assessment Questionnaire (CHAQ) disability index[3], erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), involvement of other joints besides knees, amount of fluid aspirated from each knee, and dose of triamcinolone hexacetonide injected.

Evaluation of outcome. The primary outcome measure was persistence of complete clinical response at 6 months, i.e., no evidence of synovitis clinically.

Statistics. Comparison of continuous variables was done with the nonparametric Mann-Whitney U test, whereas differences in frequencies were compared by the chi-square test or Fisher's exact test, as appropriate. A logistic regression procedure was used to identify predictors of the clinical response to IAC injection. All statistical procedures were carried out with the Stata statistical package.

RESULTS

Ninety-four patients with JIA were studied. The disease onset subtype was oligoarticular in 81 (66 with persistently oligoarticular course, 15 with polyarticular course), rheumatoid factor negative polyarticular in 4, and systemic in 5 patients; 4 patients had enthesitis related arthritis. Sixty-six patients received injection in one knee and 28 in both knees. At 6 months after the IAC injection, 65 (69%) patients showed a sustained complete clinical response, whereas 29 (31%) had had a recurrence of signs of synovitis. The only observed adverse event was the development of subcutaneous atrophy at the injection site in one patient (1.1%).

Table 1 shows the patients' main clinical features divided according to outcome at 6 months after IAC injection. Univariate statistical analyses showed that patients who experienced a sustained complete clinical response had a significantly higher ESR than those who experienced a recurrence of joint inflammation (p = 0.023). ESR was the only variable that remained in the best-fit model from multivariate logistic regression analysis for the prediction of complete clinical response to IAC injection (OR 2.61), although the statistical significance level was borderline (p = 0.049) (Table 2).

DISCUSSION

Prediction of outcome of IAC therapy has seldom been attempted among children with JIA. Further, most studies are retrospective or conducted univariate rather than multivariate analyses. Sixty-nine percent of our patients had sustained remission of synovitis in the injected joints after 6 months. This response rate is in the range of that reported in other studies, which varies from 67.6 to 82%[4-7]. Univariate analyses indicated that patients who experienced a complete clinical response had a significantly higher ESR at baseline than those who had a relapse of joint inflammation. ESR was the only variable that proved significant in the best-fit model from multivariate logistic regression analysis.

Previous analyses of predictors of outcome of IAC therapy in children with JIA have provided conflicting results. Breit, *et al*[8] found that the mean duration of remission was longest in early onset JIA and shortest in the

Table 1. Clinical features of patients with juvenile idiopathic arthritis (JIA) divided according to outcome at 6 months after intraarticular corticosteroid (IAC) injection.

	Sustained Remission, n = 65 (%)	Recurrence of Joint Inflammation n = 29 (%)	p
Male/female	21/44	6/23	
Onset age, yrs	5.2 ± 3.8	4.5 ± 3.3	
Onset subtype of JIA			
Systemic	4 (6)	1 (3)	
Polyarticular	2 (3)	2 (7)	
Oligoarticular	57 (88)	24 (83)	
Enthesitis related	2 (3)	2 (7)	
Disease duration, yrs	2.9 ± 3.2	4.2 ± 3.9	
Age at IAC injection, yrs	8.1 ± 4.6	8.9 ± 6.2	
Drug therapy at IAC injection			
None	11 (17)	6 (21)	
NSAID	38 (58)	16 (55)	
NSAID + 2nd line drugs	16 (25)	7 (24)	
Physician global assessment, points*	2.3 ± 0.6	2.1 ± 0.7	
Parent global assessment, points*	1.1 ± 0.7	1.0 ± 0.4	
CHAQ Disability Index, points*	0.6 ± 0.5	0.4 ± 0.4	
Erythrocyte sedimentation rate, mm/h	42 ± 26	30 ± 20	0.023
C-reactive protein, mg/dl	4.0 ± 7.1	1.6 ± 2.2	
Involvement of other joints beside knees (yes)	41 (63)	16 (55)	
Amount of fluid aspirated, ml			
Right knee	16 ± 19	15 ± 22	
Left knee	19 ± 22	18 ± 25	
Dose of TH injected, mg/kg			
Right knee	0.9 ± 0.2	0.9 ± 0.3	
Left knee	0.9 ± 0.2	0.8 ± 0.2	

* 0–3 scale (0 = best, 3 = worst), NSAID: nonsteroidal antiinflammatory drugs, CHAQ: Childhood Health Assessment Questionnaire, TH: tramcinolone hexacetonide.

Table 2. Best predictor model from multivariate logistic regression analysis.

Predictor Variables in the "Best-fit" Model	Odds Ratio	95% CI	p†
ESR (> 20 mm/h)	2.61	0.99–6.89	0.049
Number of knees injected (2 vs one)	2.37	0.72–7.74	
Involvement of other joints beside knees (yes/no)	0.89	0.32–2.49	

† Likelihood ratio test.

systemic onset subtype. Bloom, *et al*[9] also observed a high rate of early relapse in systemic onset JIA. Conversely, Honkanen, *et al*[10] reported that the onset subtype had no predictive value in 79 patients with JIA, though only one had systemic disease, and other investigators found a lower response rate in children with psoriatic arthritis and spondyloarthropathy[4,5]. Allen, *et al*[4] and Hertzberger-ten Cate, *et al*[6] reported a more durable response to IAC injections in patients with shorter disease duration. Allen, *et al*[4] also found a better response pattern in younger patients and boys with JIA. At variance, no correlation of the response rate with age was observed by Honkanen, *et al*[10], and Earley, *et al*[5] could not identify any association with the disease duration or patient age. These discrepancies may depend on differences in study design, patient selection, indications for the IAC therapy, corticosteroid preparation, type of joints injected, time when the injections were performed in the course of the disease, and genetic heterogeneity of patient populations.

We found that a higher ESR was the strongest predictor of sustained complete clinical response to IAC injection of the knees. Differences in cytokine profiles, T cell infiltrate, and T cell clonality have been observed in the synovium of children with JIA, suggesting that different effector mechanisms could be involved in the pathogenesis of synovial inflammation in this disease[11-14]. Our findings suggest that JIA patients who have higher ESR are characterized by a synovial inflammation process that is particularly sensitive to corticosteroid injection.

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