INTRAARTICULAR TRIAMCINOLONE HEXACETONIDE IN THE MANAGEMENT OF CHRONIC ARTHRITIS IN CHILDREN

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The use of intraarticular triamcinolone hexacetonide in the management of persistent arthritis of the knee joint that is unresponsive to nonsteroidal anti-inflammatory drugs was prospectively evaluated in 40 children with chronic arthritis. Of 49 knees that were injected, 63.3% maintained complete resolution of effusion and other signs of inflammation at the 6-month followup. This favorable outcome correlated with a young age, a short disease duration, and a higher dose of triamcinolone hexacetonide. At the 12-month followup, 45% of the injected knees remained in remission.

While it is common practice to use intraarticular corticosteroid medications for the control of inflammatory joint disease in adults, the value of this therapeutic approach in the management of arthritis in children has received little attention. Evidence for the efficacy of such treatment has been based mainly on anecdotal impressions (1–5). We prospectively evaluated the effect of a single intraarticular injection of a corticosteroid preparation, triamcinolone hexacetonide (Aristospan), on the control of chronic inflammatory arthritis of the knee joint in a group of children whose disease had failed to respond in a satisfactory manner to nonsteroidal antiinflammatory drugs (NSAIDs) and physical therapy.

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PATIENTS AND METHODS

Patients. The 40 patients admitted to this study were <16 years of age at the onset of chronic arthritis. Twenty-nine patients fulfilled the American Rheumatism Association revised criteria for the diagnosis of pauciarticular onset juvenile rheumatoid arthritis (JRA) (6). Six patients had psoriatic arthritis (7), 4 had seronegative enthesopathy-arthropathy syndrome (8), and 1 patient had ankylosing spondylitis (9). All patients had pauciarticular onset of arthritis. Two patients (1 with JRA and 1 with psoriatic arthritis) had arthritis in more than 4 joints at the time of study.

All patients were observed at the Pediatric Rheumatology Clinics of the Arthritis Society, Vancouver, and at British Columbia's Children's Hospital. All children had had active arthritis, including involvement in the knee that was to be injected, for at least 4 months. All had received doses of acetylsalicylic acid for inflammation for at least 3 months; 30% had received 1 other NSAID, 22.5% had received 2 other NSAIDs, and 20% had received 3 or more other NSAIDs. Three patients previously had been treated with oral prednisone and 1 patient was receiving hydroxychloroquine. Four patients had received prior injection with a corticosteroid other than triamcinolone hexacetonide and had had unsatisfactory results. Patients were maintained on the same NSAIDs postinjection.

Fifty-three knees, in 40 patients, were injected at least once, with the patients followed for at least 3 months after the injection. There was at least 6-month followup of 49

Table 1. Patient characteristics

Patient group	No. of patients	M/F	Age at onset, years (mean or mean ± SD)	Disease duration, years (mean or mean ± SD)
Juvenile rheumatoid arthritis, pauciarticular onset	29	3/26	5.26 ± 4.5	4.16 ± 3.97
Psoriatic arthritis	6	3/3	8.07 ± 5.39	2.41 ± 1.22
Seronegative enthesopathy-arthropathy syndrome	4	3/1	12.06 ± 1.3	2.50 ± 2.07
Juvenile ankylosing spondylitis	1	1	9.5	5.75

knees (92.5%), 1-year followup of 40 knees (75.5%), and 2-year followup of 31 knees (58.5%). The patient population characteristics are shown in Table 1.

Procedure. After preparation of the skin with antiseptic and infiltration of the subcutaneous tissue with 1% xylocaine without epinephrine, the joint fluid was aspirated and a dose of 20–40 mg of triamcinolone hexacetonide was injected. General anesthesia was administered to those children in whom flexion deformities required casting.

Laboratory evaluations. Tests for antinuclear antibody (ANA) were carried out at a serum dilution of 1:20, using HEp-2 cell substrate. Histocompatibility antigens were determined, as part of another study, by Dr. M-L. Schroeder, University of Manitoba, Winnipeg, using a lymphocytotoxicity assay (10).

Evaluation of outcome. A good response was defined as complete resolution of the signs and symptoms of active inflammation (joint effusion, heat, tenderness), with or without complete correction of deformity. A relapse was defined as a sustained reaccumulation of joint effusion, with or without heat, tenderness, or loss of range of motion. The time of relapse was taken as that point at which the attending physician believed the signs of inflammation had recurred (by physical examination or reliable history, later confirmed by physical examination).

Statistical analysis. Chi-square and Student's *t*-test were used for statistical analysis.

RESULTS

The effects of the injections were evaluated at 6, 12, and 24 months. No immediate complications of intraarticular injections of triamcinolone hexacetonide occurred; however, one patient later developed a small area of subcutaneous atrophy at the injection site.

Minor losses in range of motion had been demonstrated in all knees prior to injection; moreover, 16 knees had flexion contractures which required casting in maximal extension. In all instances, significant (usually complete) restoration of extension was achieved.

Six-month followup. Of 53 knees injected, 49 were followed for a minimum of 6 months. All knees responded well to injection, initially; however, by the 6-month followup, 18 of 49 (36.7%) had relapsed. Of the knees of the children with JRA, 67.6% remained in the good response group; 50% of the knees of children with other types of arthritis remained in the good response group (Table 2). A good response was observed more frequently in male patients than in female patients in both disease groups, although this was significant only in the JRA group ($P < 0.05$) (Table 3).

The mean age (±SD) at injection was significantly greater in the relapse group (14.39 ± 4.45 years) than in the persistent responder group (8.75 ± 4.78 years; $P < 0.005$). The duration of arthritis at the time of injection was 3.5 ± 3.1 years (mean ± SD) in the JRA response group, whereas that of the JRA relapse group was 8.6 ± 4.6 years. This difference was significant ($P < 0.005$).

Table 2. Evaluation of response of 49 knees treated by intra-articular injection of triamicinolone hexacetonide (6-month followup)

Patient group	No. of knees	M/F	No. (%) responded
Juvenile rheumatoid arthritis, pauciarticular onset	37	8/29	25 (67.6)
Other diagnoses	12	7/5	6 (50.0)
Psoriatic arthritis	7	3/4	2
Seronegative enthesopathy-arthropathy syndrome	4	3/1	3
Juvenile ankylosing spondylitis	1	1/0	1

Table 3. Relationship between response to intraarticular injection of triamcinolone hexacetonide and sex of the patient (6-month followup)

Patient group	No.	No. (%) responded
Juvenile rheumatoid arthritis, pauciarticular onset		
Males	8	8 (100)*
Females	29	17 (58.6)
Other diagnoses		
Males	7	4 (57.1)†
Females	5	2 (40)
Total		
Males	15	12 (80)†
Females	34	19 (55.9)

* $P < 0.05$.
† P not significant.

The relationship of drug dose to response was evaluated. The mean drug dose in the JRA response group was 1.08 mg/kg; in the relapse group it was 0.65 mg/kg ($P < 0.01$). In the non-JRA groups, the mean dose was 0.73 mg/kg in the good response group and 0.9 mg/kg in the relapse group (not significant).

Evaluation of the distribution of HLA antigens in 27 children with JRA and in 9 children with other types of arthritis failed to demonstrate any difference in distribution of HLA–A, B, or DR antigens between those who had a continuing good response and those who had relapsed. Twelve patients had both knees injected. Of these, a concordant response was observed in 8 patients and a discordant response in 4, suggesting that genetic factors played a limited role, at most, in determining the response. ANA were present in the sera of 28 of 39 patients studied. These occurred in the same frequency in the good response group and the relapse group.

Table 4. Evaluation of response of 40 knees treated by intraarticular injection of triamcinolone hexacetonide (12-month followup)

Patient group	No. of knees	M/F	No. (%) responded
Juvenile rheumatoid arthritis, pauciarticular onset	30	5/25	5 (50)
Other diagnoses	10	7/3	3 (30)
Psoriatic arthritis	6	3/3	0
Seronegative enthesopathy-arthropathy syndrome	3	3/0	2
Juvenile ankylosing spondylitis	1	1/0	1

Table 5. Evaluation of response of 31 knees treated by intraarticular injection of triamcinolone hexacetonide (2-year followup)

Patient group	No. of knees	M/F	No. (%) responded
Juvenile rheumatoid arthritis, pauciarticular onset	23	3/20	4 (17.4)
Other diagnoses	8	5/3	1 (12.5)
Psoriatic arthritis	6	3/3	0
Seronegative enthesopathy-arthropathy syndrome	2	2/0	1
Juvenile ankylosing spondylitis	0	0/0	0

Late followup. Results of the evaluation of 40 injected knees for which there was followup of at least 12 months after the initial injection are shown in Table 4. In 50% of the knees of children with JRA and 30% of the knees of children with other types of arthritis, a good response was maintained for 12 months. There were no statistically significant differences by disease group, sex, or drug dose in the response rates at this interval.

At 1 year, the effect of age, although still noted, was less pronounced. The mean age in the good response group was 7.99 ± 4.63 years, and in the relapse group it was 12.35 ± 5.27 years ($P < 0.01$). Duration of disease at time of injection was also reflected in the 1-year outcome. In the good response group, the mean duration of disease was 3.73 ± 3.37 years; in the relapse group, it was 7.91 ± 4.58 years ($P < 0.005$).

At the 2-year evaluation of 31 injected knees (Table 5), 16.1% remained in the good response group. There were no significant differences in response rates at this interval by disease group, age, sex, or drug dose.

Evaluation of reinjections. To evaluate the likelihood of a favorable response to reinjection after a relapse, 8 knees which had relapsed were injected a second time and followed for a further 6 months. Of these, only 2 knees relapsed within 3 months of the second injection and another 1 relapsed between 3 and 6 months after injection. Thus, of 8 reinjected knees followed for 6 months, 5 (62.5%) have maintained a good response following the second injection. Two knees were injected a third time. One knee relapsed within 3 months and 1 patient developed locking and pain in her knee 1.4 years after the third injection. As

a result, she had an arthroscopic synovectomy. The single patient who received a fourth knee injection relapsed again, within 3 months. Reinjections were carried out at intervals that ranged from 1–42 months (mean 10.8).

DISCUSSION

This study describes the course of inflammatory knee joint disease in children after intraarticular injection of triamcinolone hexacetonide. A single agent was used in order to eliminate specific drug-related variations in response. Triamcinolone hexacetonide was chosen because of its demonstrated efficacy in adults (11). The incidence of side effects from the procedure was extremely low; only 1 patient developed a small area of subcutaneous fat atrophy at the injection site, a known side effect of corticosteroid injection (12). Gilsan and Bernstein reported periarticular calcification as a complication of intraarticular injection of long-acting insoluble corticosteroids in children with JRA (13). We have not observed this phenomenon, which is apparently almost always asymptomatic, although we have not systematically reevaluated the knees radiographically.

Although our study did not include comparison with a prospectively followed, untreated group, the effectiveness of intraarticular triamcinolone hexacetonide treatment was demonstrated when the patients' disease course was compared with the pretreatment disease course. Only knees in which disease had been uncontrolled despite treatment with adequate trials of at least 1, and usually 2 or more, antiinflammatory medications and with physical therapy were studied. Intraarticular triamcinolone hexacetonide was never used as the initial treatment in any patient. The response rate was highest in young children and in those in whom arthritis had been present for a relatively short period of time. The effect of the dose was somewhat variable, but for the JRA group evaluated at 6 months, the group that responded had received a significantly higher dose of the drug, relative to body weight, than those in the relapse group. Potential predictors of response such as ANA and HLA were not useful. The response to a second injection in a knee which had relapsed following the first injection was encouraging. The effect of the third or fourth injections could not be evaluated because of the small number of knees studied. The risk of repeated intraarticular triamcinalone injections remains undetermined.

In the child with limited joint disease or in whom a small number of joints are particularly unresponsive to oral antiinflammatory agents, the therapeutic options are limited. Nonresponse to aspirin does not preclude a satisfactory response to other NSAIDs; however, the likelihood of a good response to a third or fourth NSAID becomes increasingly small. The potential side effects of gold, penicillamine, or systemic corticosteroids limit their use in children with pauciarticular JRA. Synovectomy may occasionally be necessary, but should not be undertaken without recognition of the potential short- and long-term morbidity. Intraarticular injection of triamcinolone hexacetonide appears to offer an alternative which is rapid in its effect, not attended by significant side effects, and gives clinically worthwhile remission in many patients, particularly when it is administered in young patients who have a short disease duration.

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