A Dose Schedule for Intraarticular Steroids in Juvenile Arthritis

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ABSTRACT. ***Objective.*** To determine whether the intraarticular (IA) dose of triamcinolone hexacetonide (TH) or triamcinolone acetonide (TA) influences time to relapse among patients with juvenile idiopathic arthritis (JIA).

Methods. The primary endpoint variable was the time to relapse of arthritis in the affected joint after an intraarticular (IA) injection. A relapse was defined as the reoccurrence of active arthritis in the injected joint. Analysis was carried out including only the first IA joint injection for each patient. Further analysis was conducted including the first knee injection alone. A separate analysis within the IA corticosteroid groups was performed using the Spearman rank coefficient, to determine if dose of IA steroid affected time to relapse.

Results. Records from 186 patients with JIA (145 females, 41 males) injected with either TH or TA were collected from January 1995 through December 2003. All subjects were followed for a minimum of 15 months from the time of IA injection. Of the 794 joint injections, 422 (53.1%) were injected with TH and 372 (46.9%) with TA. There were 111 first joint injections (all joints) with TH and 70 with TA. There were 89 first joint injections (knee only) with TH and 56 with TA. TH proved more effective than TA with respect to the time to relapse for first injection into all joints (10.47 ± 0.42 mo vs 8.66 ± 0.59 mo; $p < 0.001$), and for first injections into knee only (11.04 ± 0.44 vs 8.99 ± 0.65 mo; $p < 0.001$). IA doses ranged from 0.4 to 4 mg/kg (mean 1.56 ± 0.76) for TH and from 0.5 to 8 mg/kg (mean 2.54 ± 1.74) for TA. There was no correlation between time to relapse and dose of either TH and TA ($r = 0.1$, $p > 0.5$). There was no correlation between time to relapse and sex, duration of illness, age of patient, concurrent medications, or subtype of JIA.

Conclusion. In a larger dataset (794 injections) we have confirmed our previous findings (227 injections) that TH is a more effective IA corticosteroid than TA. In this much larger data analysis, dose of IA corticosteroid in the range we studied did not significantly influence the duration of response. (First Release Dec 1 2011; J Rheumatol 2012;39:374–6; doi:10.3899/jrheum.110125)

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In pediatrics, dosing schedules for many medications are empiric. This is certainly true for intraarticular (IA) steroid use in patients with juvenile idiopathic arthritis (JIA). A review of the literature reveals doses that vary according to age or weight or even vial size[1,2,3,4,5]. For the majority of practitioners their dosage regimen is effective and has stood the test of time. However, there has been a perception that higher dose of IA steroids may provide improved efficacy. We took advantage of the unique dosing schedule we use for IA injections to attempt to answer this question.

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At Cohen Children's Medical Center (formerly Schneider Children's Hospital), the same dose regimen for IA injection is used regardless of the age or weight of the child. Hence when doses of IA steroids are compared at the mg/kg basis there have been a wide variety of doses used. Two studies have suggested that dosage of medication is important for at least 1 of the IA medications — triamcinolone acetonide (TA) — and higher doses may be needed to achieve reasonable efficacy[1,2]. However, we do not currently know the ideal IA steroid dose for treating patients with JIA.

The objectives of our study were to compare patients with JIA injected with either triamcinolone hexacetonide (TH) or TA and to determine whether the per-kilogram dosage of either TH or TA influenced the time to relapse following an IA injection.

MATERIALS AND METHODS

Study design. A retrospective chart review was performed on all children who were diagnosed with JIA according to the American College of Rheumatology revised classification criteria and who received a corticosteroid joint injection with either TH or TA over an 8-year period (January 1995 to December 2003) and in whom duration of response had been ade-

quately documented for a minimum of 15 months of followup[6]. TA had been used exclusively since April 2001 following the unavailability of TH. Some of these patients had been included in an earlier study[1].

IA joint injections were performed using standard techniques, either with topical EMLA cream or under propofol anesthesia. To ensure correct positioning of the needle, aspiration of some joint fluid was attempted prior to injecting the IA steroid. TH was used in a dose of 40 mg for the knee, 30 mg for the ankle and elbow, and 20 mg for the wrist, regardless of the size or age of the patient. Similarly, TA was used in the following doses: 80 mg for the knees, 60 mg for the ankle and elbow, and 40 mg for the wrist. After the joint injection all patients were instructed to minimize their activity for a period of 24 hours.

Statistical analysis. All results are presented as the mean ± SD. Differences between groups were assessed using Spearman rank coefficient or Student t test; P values were considered significant at < 0.05.

Time to relapse was analyzed using the product-limit method (or Kaplan-Meier method). Comparison of the 2 treatment arms was carried out using the log-rank test. A proportional hazards (Cox) regression analysis was carried out to determine whether sex, duration of illness (in years), type of arthritis (poly- vs pauciarticular), and dosage were significantly associated with relapse time.

Analysis was carried out including only the first IA joint injection for each patient (including all types of joints injected). A separate analysis was also conducted including knee joint injections alone.

The sample size was not based on any formal power calculations. The number of subjects in the study was limited to the available data collected during the specified study period.

Procedure. Following a joint injection, patients were reviewed at 2 weeks postinjection and then according to their disease activity, about every 3 months for a minimum of 15 months. Patients were reviewed by the same doctor, who performed both the joint assessment and the joint injection.

The primary endpoint variable for the study was the time to relapse of arthritis in the affected joint after IA injection. A relapse was defined as the reoccurrence of arthritis in the injected joint. If an injected joint did not relapse, then that observation was considered censored at the time of last followup.

RESULTS

Records from 186 patients with JIA (145 females, 41 males) injected with either TH or TA were collected during the period January 1995 through December 2003. There were a total of 794 joint injections; demographic data are provided in Table 1. There were 124 subjects who had TH and 119 who had TA injections during the study period. Injections were given on any of the following 4 joints: knee, ankle, wrist, or elbow. All subjects were followed up to a minimum of 15 months from the time of IA injection.

Analysis was carried out as follows: (1) Each subject's first instance of IA injection (regardless of joint type injected) was included in the analysis. (2) A subgroup analysis including only first knee injections was also carried out.

Comparison of efficacy of TH and TA. There were 111 first joint injections (all joints) with TH and 70 with TA. There were 89 first joint injections (knee only) with TH and 56 with TA. TH proved more effective than TA with respect to the time to relapse for first injection for all joints (10.47 ± 0.42 vs 8.66 ± 0.59 months; $p < 0.001$), and for first injections for knee only (11.04 ± 0.44 vs 8.99 ± 0.65 months; $p < 0.001$). The Cox regression model showed that even after adjustment for sex, duration of illness, or dose of steroid, the time to relapse was still shorter for TA compared to TH ($p < 0.001$).

Table 1. Demographics of all patients who received a corticosteroid joint injection with either triamcinolone hexacetonide (TH) or triamcinolone acetonide (TA). Both groups include the 58 patients who received both TH and TA joint injections.

Characteristic	TH	TA
Patients male/female	124 (26/98)	119 (23/96)
No. joints injected	422	372
Pauciarticular	90	89
Polyarticular	24	25
Systemic disease	10	5
Mean age at joint injection, yrs	9.7 ± 4.8	8.8 ± 4.5
Mean duration of arthritis, yrs	3.1 ± 3.4	3.3 ± 3.3
No. joints injected		
Knees	251	205
Ankles	119	99
Wrists	23	44
Elbows	29	24
No. patients with 2 or more joints injected	66	68
No. patients reinjected	86	6
No. joints that relapsed	249	269
Mean time to relapse, mo ($p < 0.01$)	9.09 ± 3.51	6.82 ± 3.44
Median time to relapse, mo ($p < 0.0001$)	Unestimable	7

IA doses. Analyzing all 794 joint injections, the IA doses ranged from 0.4 to 4 mg/kg (mean 1.56 ± 0.76) for TH and from 0.5 to 8 mg/kg (mean 2.54 ± 1.74) for TA. There was no correlation between time to relapse and dose of TH or TA ($r = 0.1$, $p > 0.5$). There was also no correlation between time to relapse and sex, duration of illness, age of the patient, drug therapy the patient was taking, or subtype of JIA. It should be noted that there was no significant difference in the use of concurrent drugs between the TH and TA groups. There was no statistically significant difference between administration of high-dose (> 1 mg/kg) and low-dose (< 1 mg/kg) IA steroid and use of nonsteroidal antiinflammatory drugs, disease-modifying antirheumatic drugs, or prednisone for either TH or TA. The average length of remission for TH use was 9.09 ± 3.51 months and for TA use 6.82 ± 3.44 months ($p < 0.01$).

Triamcinolone hexacetonide: first injection, all joints. An early relapse was seen in 52.4% (43/82) of the low-dose TH group (< 1 mg/kg) versus 41.4% (12/29) in the high-dose group (> 1 mg/kg) ($p = 0.39$).

TH, first injection, knee joints only. A relapse was seen in 45.2% (28/62) of the low-dose group versus 40.7% (11/27) of the high-dose group ($p = 0.8$).

TH, multiple joint injections, knee joints only. A relapse was seen in 62% (119/192) of the low-dose group versus 37% (22/59) of the high-dose group (statistically significant, $p < 0.001$). However, because of presumed systemic absorption of steroid from the other injected joints, detecting and timing relapse in 1 joint when multiple joints have been injected in the same person is questionable. In other words, when multi-

ple joints are injected a single joint should not be considered an independent variable.

Triamcinolone acetonide: first injection, all joints. A relapse was seen in 73.7% (28/38) of the low-dose group versus 68.8% (22/32) of the high-dose group (p = 0.79).

TA, first injection, knee joints only. A relapse was seen in 71.4% (20/28) of the low-dose group versus 64.3% (18/28) of the high-dose group (p = 0.78).

TA, multiple joint injections, knee joints only. There was no statistical significance between the low-dose and high-dose groups. However, the question of the independence of 1 joint when multiple joints from the same person are injected is disputable.

DISCUSSION

While there have been no controlled studies evaluating effectiveness of joint injections, most published studies have adopted the following dose regimen for IA steroid use in pediatric patients — for large joints such as the knee, a total dose of 1 mg/kg to a maximum of 40 mg for TH has been standard. For smaller joints such as ankles, wrists, and elbows, a lower dose, usually 20–30 mg (roughly 0.5 mg/kg), has been used. An ideal dose schedule for TA has not been clearly determined, but on a mg/kg basis it appears to be less effective as an IA steroid[1,2,4].

Allen, *et al* looked at drug dose and response for knee joint injections. Overall, they had a response rate, defined as no arthritis in the injected joint, of 67.7%, 6 months after the joint injection[3]. The response group and the relapse group were then compared to determine if drug dose was a factor in early relapse. In the responder group the mean drug dosage was 1.08 mg/kg, but in the group that relapsed, mean dose was lower, at 0.65 mg/kg (p < 0.02), suggesting that higher doses of TH may be more effective. We looked at outcomes up to 15 months after joint injection. Although in our original patient cohort[1] there was a trend for higher doses of IA steroids to be more effective, in this larger series of patients there was no statistically significant difference between higher doses of IA steroid and time to relapse of the arthritis.

Only 1 other study has investigated dosage of medication (mg/kg) as an outcome measure for IA steroid use[5]. In that study, however, although it would appear that higher doses of IA steroids (> 1 mg/kg) were more effective, there was no direct comparison between TH and TA. This is important, as TH and TA are not equivalent in terms of efficacy or in dose response. Differences in effectiveness of TH and TA have been studied, and despite a doubling of the dose of TA in comparison to TH there is still a significant difference in efficacy between the 2 medications[2]. Zulian, *et al*[2] speculated that the reason for the failure of increasing dose of TA to provide increasing efficacy was the shorter half-life of TA in the joint. Indeed, in our study there was no increase in efficacy of TA even with doses above 6 mg/kg.

To determine whether there was an ideal dose of either TH or TA on a mg/kg basis, we stratified the 2 IA steroids in 0.5-mg/kg dose ranges and also into high-dose (> 1 mg/kg) and low-dose (< 1 mg/kg) groups. To eliminate the confusion or influence of multiple joint injections, our results were evaluated by examination of the time to relapse for first joint injections only. On this basis there was no statistically significant difference in efficacy between different IA steroid doses for either TH or TA in terms of time to relapse. Our study therefore would support the unofficial dosing guidelines of 1 mg/kg of TH and up to 2 mg/kg of TA in the knee joint as appropriate and effective.

There are limitations to the data presented. Our study was retrospective and all data were collected by chart review. Therefore subtle changes in joint findings and timing as to onset of joint swelling may have been overlooked. There were no formal calculations regarding optimal patient number required to determine statistical significance. It may be that larger patient numbers are required to determine the optimal dose of IA steroid. Additionally, to ensure correct placement of IA steroid within the joint, a study using ultrasound-guided arthrocentesis, especially in the ankles and wrists, would be informative.

Our findings suggest that there is really no ideal dose for IA steroids. The dose regimen that has been in use for years is appropriate. The response of an individual patient to IA steroid injection may have more to do with the joint milieu than the actual dose of steroid.

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