Comparison of the Intraarticular Effectiveness of Triamcinolone Hexacetonide and Triamcinolone Acetonide in Treatment of Juvenile Rheumatoid Arthritis

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ABSTRACT. Objective. To compare patients with juvenile rheumatoid arthritis (JRA) injected with triamcinolone hexacetonide (TH) or triamcinolone acetonide (TA) with respect to time to relapse.

Methods. This was a retrospective chart review of 85 patients: 51 patients with JRA who had received a joint injection with TH during the period June 2000–April 2001 and 48 patients who had received a joint injection with TA during the period May 2001–March 2002 who were followed for a minimum of 15 months, after an intraarticular steroid injection.

Results. The primary endpoint variable for the study was the time to relapse of the arthritis in the affected joint following an intraarticular injection. A total of 227 joints were injected, 114 with TH and 113 with TA. In the TH group the mean time to relapse (± SE) was 10.14 ± 0.49 months compared to the TA group at 7.75 ± 0.49 months (p < 0.0001) using the log-rank test. A proportional hazards (Cox) regression analysis revealed no statistical association between sex, duration of illness, or type of arthritis and relapse time. An analysis was performed on the first intraarticular injection for each patient, with the average time to relapse for all joints injected of 10.36 ± 0.72 months for TH compared to 8.45 ± 0.78 months for TA (p < 0.02). A further analysis of the first knee injections showed a relapse time in the TH group of 11.11 ± 0.81 months compared to 7.95 ± 0.95 months for TA (p < 0.008).

Conclusion. TH offers an advantage to TA, as there is a longer duration of action leading to an improved prolonged response rate in weight-bearing joints, particularly the knees. The results suggest that TH should be the intraarticular steroid of choice, particularly for the knee joint, in patients with JRA. (J Rheumatol 2004;31:2507–12)

Key Indexing Terms:
ARTHRITIS      CHILDHOOD      TREATMENT      INTRAARTICULAR STEROIDS

Intraarticular corticosteroid usage is an important treatment option in children with pauciarticular arthritis and is used as an adjunct in the other forms of juvenile rheumatoid arthritis (JRA). To date, nearly all studies with intraarticular corticosteroids in JRA have been undertaken with triamcinolone hexacetonide (TH), and its effectiveness and safety have been documented1-13. The recent global shortage of TH required a change in practice for many pediatric rheumatologists and necessitated the use of other corticosteroid preparations. Triamcinolone acetonide (TA) differs from TH by an alteration of one side chain, which presumably accounts for the different pharmacologic properties of TA compared to TH. As TH has a lower solubility compared to TA, its absorption from the injected joint is slower, which may account for its enhanced efficacy14. Indeed, anecdotally many rheumatologists have described TA to be a poor substitute for TH, with a shorter time to relapse of the arthritis or in some cases no benefit at all.

In April 2001, TH was no longer available at Schneider Children’s Hospital and TA was substituted as an alternative intraarticular corticosteroid, providing the opportunity for a retrospective study directly comparing the efficacy of these 2 medications in patients with JRA.

MATERIALS AND METHODS

Study design. A retrospective chart review was performed on all children diagnosed with JRA according to the American College of Rheumatology revised classification criteria and who received a corticosteroid joint injection with either TH or TA in the period June 2000 to March 200215 (Table 1). Duration of response was documented for a minimum of 15 months of followup on all patients who received a joint injection, except 4 joints in the TA group and 3 joints in the TH group that were censored at the time of the last clinic visit, and were lost to followup.

Statistical analysis. 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 if sex, duration of illness (in years), and type of arthritis (polyarticular vs pauciarticular) were significantly associated with relapse time.

Analysis was carried out primarily in 2 ways. First, only the initial intraarticular joint injection for each patient was analyzed; and second, a separate analysis was also conducted for initial knee injections alone (Tables 2 and 3).

The sample size for this study was not based on any formal power calculations. The number of patients in the study was limited to the available data collected during the specified study period. Comparison of TH and TA with respect to age and duration of illness was carried out using the Mann-Whitney test. Comparison for sex or type of arthritis was done using Fischer’s exact test.

Methods. Patients were reviewed at 2 weeks after joint injection and then according to their disease activity, about every 3 months for a minimum of 15 months.

Effectiveness of the joint injection was assessed by comparing relapse rates as defined by presence of an active joint as per the attending rheumatologist or a reinjection of a joint within 15-months of the previous injection. Active arthritis was defined as non-bony swelling, and if no swelling was present, limitation of motion with either pain on motion or joint tenderness. A prolonged response rate was defined as no active arthritis in the injected joint for ≥15 months.

Intraarticular 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 intraarticular steroid. TH was used in a dose of 40 mg for the knee, 30 mg for the ankle, 20 mg for the wrist, and 30 mg for the elbow, 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 ankles, 60 mg for the wrist, and 60 mg for the elbow. After joint injection all patients were instructed to minimize their activity for a period of 24 hours.

RESULTS

Charts from 85 patients with JRA (62 female, 23 male) were collected during the period June 2000–March 2002. There were 71 patients injected with either TH or TA and 14 patients who had both TH and TA injections during the study period, providing a total of 51 patients who received a TH injection and 48 who received a TA injection. Injections

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Table 1. Demographic details of all patients who received a corticosteroid joint injection with either TH or TA. Both groups include the 14 patients who received both TH and TA joint injections.

<table>
<thead>
<tr>
<th>TH</th>
<th>TA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n (M/F)</td>
<td>51 (12/39)</td>
</tr>
<tr>
<td>No. of joints injected</td>
<td>114</td>
</tr>
<tr>
<td>Pauciarticular</td>
<td>35</td>
</tr>
<tr>
<td>Polyarticular</td>
<td>13</td>
</tr>
<tr>
<td>Systemic</td>
<td>3</td>
</tr>
<tr>
<td>Mean age at joint injection, yrs</td>
<td>9.7 ± 4.8</td>
</tr>
<tr>
<td>Mean duration of arthritis, yrs</td>
<td>3.1 ± 3.4</td>
</tr>
<tr>
<td>No. of joints injected</td>
<td></td>
</tr>
<tr>
<td>Knees</td>
<td>60</td>
</tr>
<tr>
<td>Ankles</td>
<td>31</td>
</tr>
<tr>
<td>Wrists</td>
<td>11</td>
</tr>
<tr>
<td>Elbows</td>
<td>12</td>
</tr>
<tr>
<td>No. of patients with 2 or more joints injected</td>
<td>31</td>
</tr>
<tr>
<td>No. of patients (joints) reinjected</td>
<td>6 (6)</td>
</tr>
<tr>
<td>No. of joints that relapsed</td>
<td>68</td>
</tr>
<tr>
<td>Mean time to relapse, mo</td>
<td>10.14 ± 0.49</td>
</tr>
<tr>
<td>(p &lt; 0.0001)</td>
<td></td>
</tr>
<tr>
<td>Median time to relapse, mo (p &lt; 0.0001)</td>
<td>12</td>
</tr>
</tbody>
</table>
were analyzed on any of the following 4 joints: knees, ankles, elbows, and wrists. Patients were followed for a minimum of 15 months from the time of the injection. Those patients who did not complete the full 15 months followup were censored at their last clinic visit (Figures 1 and 2).

Among the 85 patients, 28 were injected only once in a single joint, while 12 were injected more than once in at least one joint; 14 patients received both TH and TA injection and the remaining 31 patients had one or more joints injected on the same day. In total, there were 112 (49.6%) knee joint injections, 69 (30%) ankle injections, 24 (10.6%) wrist injections, and 22 (9.7%) elbow injections. Of the 227 joint injections, 114 were with TH and 113 with TA (Table 1). A maximum of 5 joints were injected on any one patient and 15 patients had more than one joint injected (mean 2.6 joints injected) for the TA group, and for the TH group 31 patients had more than one joint injection on the same day (mean 2.75 joints injected). The mean age (± SD) at first instance of any intraarticular injection was 9.4 ± 4.7 years. The mean duration of illness (± SE) at the first instance of any intraarticular injection was 2.8 ± 3.3 years. In the TH group the mean time to relapse was 10.14 ± 0.49 months (median 12 mo), compared to the TA group time to relapse of 7.75 ± 0.49 months (median 6 mo) (p < 0.0001).

Concurrent medication use was similar in the TA and TH groups. As expected, more patients in the TA group were taking the newer disease modifying antirheumatic drugs. Medications were as follows — in the TH group, 33 patients were taking a nonsteroidal antiinflammatory drug (NSAID): 16 were taking methotrexate (MTX), 9 sulfasalazine, 3 were taking combination prednisone plus entanercept, and 14 were taking no medication. In the TA group, 33 patients were taking a NSAID, 12 were taking MTX, 2 sulfasalazine, 4 etanercept, 2 prednisone, 2 leflunomide, and 15 patients were taking no medication.

Data analysis. The analysis was carried out in 2 ways: Each subject’s first instance of intraarticular joint injection (regardless of joint type injected) was included in the analysis. A subgroup analysis including only the knee joint injection was also performed. In other words, this analysis included only the first intraarticular joint injection for each patient (Tables 2 and 3).

![Figure 1](https://example.com/figure1.png)

Figure 1. Comparison of the efficacy of intraarticular TH or TA in patients with JRA as measured by months of remission of the arthritis. Kaplan-Meier analysis of relapse rate after the first injection in all joints.
There were no statistically significant differences between TH and TA with respect to age and duration of illness. There were no statistically significant associations between treatment assignment and sex, type of arthritis, or type of joint injected.

There was a significant difference in the distribution of types of arthritis between treatment groups. There were significantly more of the pauciarticular than systemic types given TH (p < 0.04); more polyarticular than systemic types given TH (p < 0.004); but no difference between polyarticular and pauciarticular types (p < 0.20). For this analysis, the unit of analysis is the joint, not the patient. Therefore, it may not be fair to compare the number of pauciarticular, polyarticular, and systemic types when multiple joints per subject are included.

Analysis of all first intraarticular joint injections (all joints included)

Analysis of time to relapse using Kaplan-Meier method.

Table 2 summarizes the quartile estimates of time to relapse (in months) with respect to the 2 types of intraarticular injections. Based on the log-rank test, there was a difference between TH and TA with respect to the time to relapse (p = 0.023). The Kaplan-Meier estimate of the median time to relapse in the TH group was longer than that for the TA group (13 vs 7 months). On average, the relapse time in the TH group was longer than that of the TA group (10.36 ± 0.72 vs 8.45 ± 0.78 months; Figure 1). This means that subjects injected with TH tended to relapse later than those injected with TA. Table 3 summarizes the results of the Cox regression analysis. The Cox regression model shows that even after adjusting for sex, duration of illness, or type of arthritis, the type of intraarticular injection remains significantly different with respect to relapse time (p = 0.03). The hazard ratio attributed to the injection type was 1.8 (95% CI 1.05, 3.08). This indicates that the hazard is increased, hence relapse time is decreased in the TA group compared to the TH group. The hazard is increased by almost 2-fold (1.8 times).

Analysis of all first intraarticular joint injections (knee joints only)

Analysis of time to relapse using Kaplan-Meier Method (Table 2).

Figure 2. Comparison of the efficacy of intraarticular TH or TA in patients with JRA as measured by months of remission of the arthritis. Kaplan-Meier analysis of relapse rate after the first injection in the knee joint only.
intraarticular injection remains significantly different with respect to relapse time (p < 0.0001). The hazard ratio attributed to the injection type was 1.99 (95% CI 1.43, 2.78). This indicates that the hazard is increased, hence relapse time is decreased in the TA group compared to the TH group. The hazard is increased 2-fold (1.99 times).

**DISCUSSION**

Intraarticular joint injection is becoming the preferred treatment in the management of patients with pauciarticular arthritis and as adjunctive therapy in other subtypes of JRA. Effective treatment ensures rapid resolution of pain and correction of contractures in affected joints, with minimal side effects. Studies show less leg-length discrepancy and a diminished need for physical therapy and splints in patients undergoing intraarticular steroid injections compared to matched subjects who did not undergo injections, suggesting that intraarticular steroid usage is a cost-effective treatment. It is therefore important to determine the effectiveness of the available therapies.

Studies in both pediatric and adult patients have shown the overall effectiveness of TH in terms of longer duration of action and less adrenal suppression in comparison to other intraarticular corticosteroids. Historically, the majority of pediatric rheumatologists have used TH as the steroid of choice and most reports have confirmed its efficacy. This study provides further evidence that TH is a superior intraarticular corticosteroid with a longer duration of action compared to TA.

Comparative studies in pediatric rheumatology are few, but Honkanen, et al compared the effectiveness of TH at a dose of 0.7 mg/kg to methylprednisolone and found a highly significant difference in favor of TH, with a 6-month response rate of 70% for TH compared to 49% for methylprednisolone. From our study we confirm the effectiveness of TH, with a response rate very similar to that reported by Honkanen, et al, at 76% for 6 months; however, in comparison, TA fared better than methylprednisolone in our study, with a 56% response rate for the 6-month period. Recently, Martini, et al compared TH and TA in oligoarticular arthritis of the knee. They found a significant increase in the response rates with TH at 6, 12, and 24 months. While our results for TH administration in the knee joint are almost identical at 6 and 12 months, at 12 months our patients had a response rate of only 21% for TA compared to 36% in Martini’s study. Martini, et al assessed response to therapy through a graded improvement scale; this allowed for some minor arthritis to still be present, which may account for the differences between the 2 studies.

Our study illustrates that both intraarticular steroids have a prolonged duration of action, with over half the children in either group having a sustained response to 6 months when using either TH or TA. However, the effectiveness of TA seems to wane after this period of time, necessitating an additional joint injection in many patients. It has been

**Table 4. Summary of quartile estimates of time to relapse (months) using analysis including all intraarticular (IA) joint injections.**

<table>
<thead>
<tr>
<th>Quartile Estimates</th>
<th>All IA Injections, All Joints Included</th>
<th>TH Estimate (95% CI)</th>
<th>TA Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>75%</td>
<td>15 (8, NE)</td>
<td>10.14 ± 0.49</td>
<td>7.75 ± 0.49</td>
</tr>
<tr>
<td>50% (median time to relapse)</td>
<td>6 (5, 8)</td>
<td>12 (8, NE)</td>
<td>5 (4, 6)</td>
</tr>
<tr>
<td>25%</td>
<td>3 (3, 4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p, log rank test < 0.0001*

* Significant p < 0.05. NE: not estimable.

**Table 5. Summary of Cox regression analysis.**

<table>
<thead>
<tr>
<th>Covariates in The Model</th>
<th>All IA Injections, All Joints Included</th>
<th>Hazard Ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group: TH vs TA</td>
<td>1.995 (1.43, 2.78)</td>
<td>&lt; 0.0001*</td>
<td></td>
</tr>
<tr>
<td>Sex: male vs female</td>
<td>0.81 (0.56, 1.18)</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>Duration of illness, yrs</td>
<td>1.03 (0.98, 1.08)</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>Pauci (pauci, yes/no)</td>
<td>0.68 (0.36, 1.26)</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>Poly (poly, yes/no)</td>
<td>0.89 (0.49, 1.63)</td>
<td>0.70</td>
<td></td>
</tr>
</tbody>
</table>

*p, log rank test < 0.0001*

* Significant p < 0.05.

Based on the log-rank test, there was a difference between TH and TA with respect to the time to relapse (p = 0.007). The Kaplan-Meier estimate of the median time to relapse in the TH group was higher than that of the TA group (15 vs 6.5 months). On average, the relapse time in the TH group was longer than that of the TA group (11.11 ± 0.81 vs 7.95 ± 0.95 months; Figure 2). This means that subjects injected with TH tend to relapse later than those injected with TA.

**Analysis of time to relapse using Cox regression (Table 3).**

The Cox regression model shows that even after adjusting for sex, duration of illness, or type of arthritis, the type of intraarticular injection remains significantly different with a hazard ratio increased by about 2.2 times.

To summarize Table 1, based on the log-rank test there was a difference between TH and TA with respect to time to relapse (p < 0.0001; Table 4). On average, the relapse time in the TH group was longer than in the TA group (10.14 ± 0.49 vs 7.75 ± 0.49 months). This means that subjects injected with TH tended to relapse later than those injected with TA.

**Analysis of time to relapse using Cox regression (Table 5).**

The Cox regression model shows that even after adjusting for sex, duration of illness, or type of arthritis, the type of intraarticular injection remains significantly different with a hazard ratio increased by about 2.2 times.
argued that increasing doses of TA may mitigate this observed shortened efficacy. We have used a standard dose of both TH and TA regardless of the patient’s size or number of joints injected. It should be noted that on prednisone equivalency, twice the dose of TA was used in comparison to TH and still did not achieve equivalency. One consequence of the higher dose is the perceived increased incidence of transient mild facial fullness in the younger children if 2 or more joints are injected. However, we have not stringently studied this question. Indeed our observations are supported by studies showing less adrenal suppression with TH usage in comparison to other intraarticular steroids, including prednisolone acetate17.

Our study confirms the effectiveness of intraarticular corticosteroids in the treatment of children with chronic arthritis. TH is superior to TA as an intraarticular steroid; however, both are effective treatments, with over half the children treated free from arthritis, in the injected joint, at the end of 6 months.

REFERENCES