Triamcinolone acetonide and hexacetonide intra-articular treatment of symmetrical joints in juvenile idiopathic arthritis: a double-blind trial


Objective. Pharmacokinetic studies have shown that the biological effect of triamcinolone acetonide (TA) is equivalent to that of triamcinolone hexacetonide (TH), if used at double the dosage. In this study we compared the efficacy of intra-articular TA at a dose twice that of TH in symmetrically involved joints, in children with juvenile idiopathic arthritis (JIA).

Method. Children with active arthritis and a similar degree of inflammation in two symmetrical joints were enrolled in the study. The symmetry was assessed by both clinical examination and synovial fluid analysis. The dose given was 1 mg/kg up to 40 mg of TH or 2.0 mg/kg up to 80 mg of TA. The identity of injected compound was blinded to the patient and to the physician.

Results. Thirty-seven patients, 30 female, seven male, with JIA, entered the study. A total of 86 joints were injected. Twenty-one (53.8%) of the joints injected with TA relapsed first compared with only six (15.4%) of the joints injected with TH. In three (7.7%) relapse occurred simultaneously. Nine (23%) were still in remission after 24-month follow-up. The percentage of joints with lasting remission was higher with TH than with TA (80 vs 47.5% after 12 months and 63.6 vs 32.4% after 24 months, respectively; log rank test \( P = 0.003 \)).

Conclusion. Even when TA is given at higher doses, TH is more effective and should be considered the drug of choice for intra-articular treatment of JIA.

Key words: Juvenile arthritis, Intra-articular steroids, Triamcinolone.

Intra-articular corticosteroids (IAS) have become an important therapeutic tool for the treatment of juvenile arthritis and are recommended by many authors as a first-line therapy for the oligoarticular type of juvenile idiopathic arthritis (JIA) [1]. Triamcinolone hexacetonide (TH) and triamcinolone acetonide (TA) are the most commonly used long-acting steroids in clinical practice. The choice of the preparation is often arbitrary and depends on where the rheumatologist was trained [2] and on the availability of the drug.

Since pharmacokinetic studies have shown that 40 mg of TA is equivalent to 20 mg of TH with regard to biological effect and that absorption from the joints is slower for TH [3], we compared the efficacy and safety of TH with that of TA, given at double the dosage, in a cohort of children with JIA. In order to minimize the problems of confounding variables in clinical and demographic characteristics of patients, we made this comparison by injecting symmetrically involved joints with the two different compounds.

Patients and methods

The study group consisted of patients managed at the Paediatric Rheumatology Unit of the University of Padua between January 1998 and December 2002. All the patients fulfilled the revised classification criteria for JIA, oligoarticular and polyarticular subtypes [4]. Patients who had a history of any clinically significant adverse reaction to steroids, erosive findings on joint X-ray or who had IAS treatment during the previous 12 months were excluded from the study.

The children entered the study only if they required intra-articular corticosteroid injections in the course of the regular treatment plan and the degree and duration of inflammation was comparable in two symmetrical joints.

Clinical evaluation

Clinical assessment of synovitis was performed at baseline, before treatment, and 3, 6, 9, 12, 18 and 24 months after the procedure or in case of relapse.

On each observation four variables were recorded: swelling on inspection, limitation of range of motion, pain on passive movement and warmth to touch, as proposed as part of the preliminary core set of outcome measures developed at the Consensus Conference held at Marco Island (Florida, USA) [5]. For each joint, a score ranging from 0 to 3 was attributed to each variable: 0 normal, 1 mild, 2 moderate, 3 severe. The articular score was then obtained by summing the scores of each variable. To avoid inter-observer variability, a single examiner undertook the pre- and post-injection assessments for each child.

To enter the study the child needed to have active arthritis with at least two symmetrical joints with an identical score and a difference in duration of arthritis in each joint of less than 6 months. Ethical committee approval and informed consent by the parents were obtained before the enrolment.

Submitted 16 April 2004; revised version accepted 15 June 2004.

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Synovial fluid analysis

Besides the clinical assessment, the symmetry of joint involvement was established by synovial fluid (SF) analysis which included both mononuclear cell (MNC) count and cytokine analysis. After joint aspiration, SF samples from paired joints were immediately analysed for physical aspect, viscosity and MNC count, expressed as number of cells × 10^3/ml. The remaining part of the SF sample was centrifuged to remove cells and debris and stored at −70 °C.

Cytokine analysis included the measurement of both pro-inflammatory cytokines [interleukin (IL)-1β, IL-6, tumour necrosis factor-α (TNFα) and IL-2 soluble receptor (IL-2r)] and immunosuppressive cytokines (IL-10), and was performed by an Immulite Analyzer (Diagnostic Product Corporation, Los Angeles, CA) by using a chemiluminescent method [6].

Procedure

After clinical and SF assessment of the degree of inflammation, each joint was injected with either TH or TA. A randomization procedure was followed to assign each compound to the right or to the left joint. Children under the age of 6 yr and very anxious older children were sedated in an intermediate setting of the paediatric intensive care unit using a combination of a low dosage of ketamine (Ketalar®), 0.5 mg/kg and propofol (Diprivan®), 2 mg/kg. The dose of IAS administered was 1.0 mg/kg of body weight up to 40 mg of TH (Lederspan® or Hexatrinone®) or 2.0 mg/kg of body weight up to 80 mg of TA (Kenacort A Retard®) for the knee joint, or half of this dose for ankle and wrist. Resting of the joints for 3 days was recommended.

Since the drug concentration in the products commercially available is 20 mg/ml for TH and 40 mg/ml for TA, the injected volume was the same for each compound but the weight of TH was half that of injected TA. The identity of the compounds was unknown to the physician performing the injection and to the patients and their parents until the end of the study when analysis of the therapeutic responses was completed.

Response to treatment was defined as absence of synovitis or as a decrease in joint inflammation leading to a reduction of the articular score of greater than 60% from baseline. Relapse was defined as reappearance of active arthritis after a period of response to treatment, defined as above. Remission was defined as absence of synovitis and of any medical treatment for more than 2 yr.

In case of relapse the patient was withdrawn from the study and the time to relapse was recorded. Any change in oral medication, adverse events and significant trauma to the joints causing swelling were also recorded and, if necessary, the patient was withdrawn from the study.

Data analysis

Since the two drugs were administered concurrently in the same patient and under the same conditions, the two treatment groups were identical for age at the time of treatment, age at disease onset, disease duration, sex, type of joint injected, articular score before the procedure, antinuclear antibodies (ANA), (tested on HEp2 cell line, positive ≥1:80, according to our laboratory standards), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) values at baseline and concomitant therapy.

The primary outcome variable was defined according to the articular score at 3, 6, 12, 18 and 24 months after the procedure. The efficacy of the treatment was expressed as percentage of positive results in each group. The difference between groups was expressed as incidence rate ratio (IRR) of relapse. The 95% confidence interval (CI) defined the degree of significance and the accuracy of the estimate.

The data obtained both in the clinical and laboratory evaluations were compared by using the χ² test, Student’s t-test or Fisher’s exact test as appropriate. The analysis of time to flare, in each treatment group, was undertaken according to the Kaplan–Meier procedure and compared by the log-rank test. The Stata statistical package was used for data evaluation.

Results

The clinical characteristics of the patients are summarized in Table 1.

Thirty-seven patients entered the study, 30 (81.1%) were females and seven (18.9%) were males. The average age at disease onset was 4.9 yr, ranging from 1.1 to 14.8 yr. The disease duration, at the time of treatment, was 2.6 yr (range 0.3–9 yr). Twenty-two patients (59.5%) had persistent oligoarticular JIA, 10 patients (27%) had extended oligoarticular JIA and 5 (13.5%) had polyarticular JIA. ANA was positive in 26 patients (70.3%), while HLA-B27 was positive in one (2.7%).

Eighty-six joints (43 joint pairs) were injected: 68 knees, 16 ankles and two wrists. In six patients two joint sets were injected at the same time. Three patients (four joint pairs) were excluded from the analysis: two for having been treated with methotrexate (MTX) due to the spreading of the disease to other joints and one because of patient withdrawal. No significant differences were recorded between the pre- and post-treatment regimen except for the introduction of MTX therapy in two patients who were excluded from the final analysis. All 34 patients completed the 24-month follow-up.

SF analysis was performed in 25 patients (56 joints). In the remaining 12 patients (30 joints) it was not possible to obtain SF from one or both joints. Results of analysis of paired SF samples are summarized in Table 2. There was a difference of less than 30% in MNC count between the two joints and cytokine concentrations...
Intra-articular steroid treatment was safe in our population: only 2 patients, one in each group (2.3% of treated joints), developed side-effects similar in the two treated joints as proven by the Student’s t-test for paired samples.

All 39 joint pairs injected with TA and TH initially improved. However, after a period varying from 2 to 24 months, 21 joints (53.8%) injected with TA relapsed compared with only six (15.4%) injected with TH. In three (7.7%) relapse was simultaneous and nine joint pairs (23.1%) were still in remission after 24 months of follow-up.

The rate of persisting or sustained response was significantly higher with TH than with TA [at 6 months, 89.7 vs 61.5% (P = 0.008), at 12 months, 84.6 vs 48.7% (P = 0.001), and at 24 months, 76.9 vs 38.5% (P = 0.001) respectively].

The ‘survival’ curves, regarding the analysis of the time to disease flare, are shown in Fig. 1. The Kaplan–Meier estimate of incidence rate of arthritis flare was 1.6/100 months of follow-up for the TH group and 4.3/100 months for the TA group (incidence rate ratio 2.7, 95% CI 1.2–6.5).

The log-rank test showed that the probability of achieving joint remission was higher with TH than with TA (80 and 47.5% after 12 months and 63.6 and 32.4% after 24 months respectively; P = 0.003).

**Side-effects**

Intra-articular steroid treatment was safe in our population: only two patients, one in each group (2.3% of treated joints), developed skin atrophy at the injection site. No other known complications, such as joint infections or chemical synovitis, were noted.

**Discussion**

Intra-articular steroids have been shown to be an effective therapy for adults and children with inflammatory joint disease [7–12]. Even when given during a period of growth, they not only benefit the child but also improve and prevent limb length discrepancy, do not interfere with the integrity of the cartilage and, sometimes, induce disappearance of pannus [7, 8, 12–15].

A number of different corticosteroid compounds have been used for intra-articular joint injections. Currently in Europe and the USA the long-acting steroids most commonly used in JIA for intra-articular treatment are TH and TA. TH has been used in Britain and the USA for intra-articular injections since 1967 [16]. TH is not marketed in Italy or in other European countries and Australia, and for this reason it is rarely used and must be imported by individual users.

TA is a synthetic glucocorticoid. TA (molecular weight 434.49) is presented as 40 mg/ml vials and TH (molecular weight 332.66) is presented as 20 mg/ml vials. Previous pharmacokinetic studies showed that 40 mg of TA are equivalent in potency to 20 mg of TH with regard to biological effect and that absorption from the joints is slower for TH, due to its lower solubility [3, 17]. This issue has never been verified in children, nor it has been demonstrated if, by doubling the dosage of TA, safety and efficacy are comparable. Indeed, TH is not commercially available in many countries, including Italy, and in others there is often shortage of the drug necessitating the use of TA as an alternative preparation.

For all these reasons we decided to investigate if intra-articular TA, used at double dosage, can be equally effective as TH for the treatment of JIA by directly comparing the efficacy of these two medications in symmetrical joints.

The results obtained in the present study clearly show that TH is more effective than TA even if administered at higher doses (twice that of TH). Among 78 symmetrical joints analysed, 53.8% relapsed on TA, 15.4% relapsed on TH and 7.7% relapsed simultaneously. The rate of response, significantly higher with TH than with TA at 6 months, was sustained during the 24-month follow-up.

The log-rank test showed that the probability of achieving joint remission was significantly higher with TH than with TA, being 80 and 47.5% after 12 months and 63.6 and 32.4% after 24 months, respectively.

These results confirm what has been previously suggested by retrospective studies both in adults and in children. In a study of 270 adults with RA comparing hydrocortisone succinate (HC), TA and TH, the authors found that TH was significantly more effective than HC and TA in reducing pain and joint inflammation in the first 12 weeks after injection [18]. Similar results were achieved in a comparative retrospective study between betamethasone and TH [19] and TA and TH in children with oligoarticular JIA [20].

In a prospective study comparing TH and TA used at the same dosage in different joints, we have recently shown that TH was much more effective than TA, at comparable dose, both in short- and long-term follow-up [21].

In trying to explain the reasons for the better efficacy of TH, previous pharmacokinetic studies showed that, although there was no significant difference in the amount of triamcinolone absorbed into the circulation after intra-articular injection of TH and TA, the log-rank test showed that the probability of achieving joint remission was significantly higher with TH than with TA, being 80 and 47.5% after 12 months and 63.6 and 32.4% after 24 months, respectively.

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In trying to explain the reasons for the better efficacy of TH, previous pharmacokinetic studies showed that, although there was no significant difference in the amount of triamcinolone absorbed into the circulation after intra-articular injection of TH and TA,
the mean residence time in the joint was calculated to be 6 days for TH and 3.2–4.3 days for TA [3]. This is considered to be due to the slower release of TH, which in turn is related to its lower solubility. This characteristic of the drug may explain its long-lasting efficacy that was not reached even by doubling the TA dosage.

It is worth pointing out that in our study population no major side-effects were observed. In two patients (2.3%), one in each group, skin atrophy at the injection site was reported. This incidence rate is lower than previously reported (8.3%) [22] but similar to what has been reported more recently by other authors [10, 13, 21]. It is interesting to note that the larger amount of TA injected did not increase the prevalence of side-effects, confirming that these are related more to the injection technique than to the different type or dosage of drug utilized.

Another aspect of this study to be underlined is the methodological approach that has been followed. We have compared the efficacy of the two compounds in symmetrically involved joints in the same patient given at the same time. In this way, we eliminated most of the confounding variables that influence the effects of therapy in controlled clinical trials. In fact, the two treatment groups were absolutely comparable for all the usual confounders such as age at disease onset, disease duration, sex, type of joint injected, articular score before the procedure, ANA, ESR, CRP values at baseline and concomitant therapy. Indeed, the symmetry of joint involvement was not only assessed clinically but also confirmed by the identical inflammatory pattern of SF, making the comparison between two paired joints, even more reliable.

In conclusion, this study shows that TH is much more powerful than TA for the intra-articular treatment of juvenile arthritis, both in short- and long-term follow-up, even if the latter is used at double the dosage. This clearly confirms that TH is the ideal intra-articular steroid preparation for the treatment of JIA and underlines the need to solve the relevant issue of the poor or even absent availability of the drug in many countries.

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<td>• In symmetrically involved joints, intra-articular triamcinolone hexacetonide was shown to be more effective than triamcinolone acetonide, even if given at double the dose, for the treatment of juvenile idiopathic arthritis.</td>
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Acknowledgements

We thank Balu H. Athreya (Jefferson University, Philadelphia) for reading the manuscript and for helpful suggestions and Diego Faggian (Department of Laboratory Medicine, University Hospital of Padua) for technical assistance.

The authors have declared no conflicts of interest.

References