Probability of remission of juvenile idiopathic arthritis following treatment with steroid joint injection

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Abstract

Objective

Steroid joint injection is indicated as starting treatment for juvenile idiopathic arthritis, but its effect as single treatment has not been explored. Our aim was to estimate arthritis remission probability after single or repeated injections.

Methods

Conduct a retrospective analysis of inactive arthritis status, remission on medication and remission off medication, estimating cumulative probability and mean time to survival, from the first joint injection session to the last follow-up visit or disease-modifying anti-rheumatic drugs initiation. Remission and time to achieve remission status after single or repeated injections were compared.

Results

Seventy-seven patients with 4-year medium follow-up and 254 treated joints, were reviewed. Eighty-three percent of the individuals had oligoarticular subtype and 57% had persistent oligoarticular course. Overall, 26% achieved remission off medication status, 4% remission on medication and 38% initiated disease-modifying anti-rheumatic drugs. Survival analysis resulted in mean time of achieving inactive disease status, remission on medication and off medication of 8, 11 and 56 months, respectively. The cumulative probability of remission off medication was 2% at 12 months, 8% at 24 months and 18% at 36 months. Frequency of inactive disease, remission on medication and remission off medication status decreased proportionally following repeated joint injections in comparison with the frequency of the same status for those receiving single treatment.

Conclusion

The dropout rates due to anti-rheumatic drugs initiation indicated limited long-term benefits of intra-articular steroids for juvenile idiopathic arthritis.

Key words

juvenile idiopathic arthritis, remission, triamcinolone hexacetonide.

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Introduction

Juvenile idiopathic arthritis in patients with limited arthritis, affecting less than five joints during the whole disease course, presents greater probability of achieving inactive disease status and remission, regardless of treatment (1-3). In practice, intra-articular steroids are recommended as the initial treatment.

Although intra-articular steroid injections are widely used to control arthritis in daily practice (4-6), the duration of the effect is unknown. Steroid joint injections are recommended, either as a single treatment or concomitantly with anti-inflammatory or disease-modifying anti-rheumatic drugs. The procedure can involve a single or multiple active joints injected at the same time (7). This practice varies among paediatric rheumatologists (8). Repeated injections are indicated within a 4 to 6 month interval, in cases of relapse. The injections are most often performed by unguided puncture, but they can also be guided by ultrasound or magnetic resonance imaging (9, 10), particularly for joints that are difficult to access, such as the hip, subtalar (11), temporomandibular joints (12) or for tendon sheets injection (13). Performing unguided puncture is a standard practice among rheumatologists and adverse events are rarely described. However, the probability of remission or the duration of the effects following single or repeated joint injection remain unknown**.** Therefore, the aims of the study were estimate the frequency and probability of inactive arthritis, remission on and off medication, by retrospective analysis of juvenile idiopathic arthritis cases treated by steroid joint injection associated only with oral non-steroidal anti-inflammatory drugs.

Method

Subjects

A comprehensive review of consecutive cases of JIA, diagnosed between 1997 and 2011, was conducted. The cases were classified according to the International League of Associations for Rheumatology (ILAR) criteria (14). Patients treated with steroid joint injection, in association with only non-steroidal anti-rheumatic drugs, were selected. Data were recorded in a protocol for all cases with regular clinic attendance, from the first joint injection to the last visit or until the prescription of disease-modifying anti-rheumatic drugs or biological treatment. During the observation period, arthritis symptoms and relapse were recorded.Cases with missing notes or lost during follow-up were excluded. The protocol was approved by the institution's research ethics committee, under no. 3992/2011.

Joint injection procedure

The most frequent indications for steroid joint injection were: the presence of synovitis in up to four joints with pain, joint contracture and/or functional impairment, regardless of JIA classification. The patients were submitted to conscious sedation, using intravenous midazolan associated with fentanyl, under close surveillance for oxygen saturation. Joint injections by unguided puncture were performed by trained physicians using aseptic technique, in outpatient theatre setting. Sedation antagonists, intravenous flumazenil and naloxone, were used to reverse sedation upon completion of the procedure. Topical skin or subcutaneous anaesthetics were used as alternative to conscious sedation. Synovial fluid aspiration was systematically attempted. Aspiration of synovial fluid was performed to assist needle placement in the joint space. In some cases, the joint was distended by saline injection to ensure intra-articular steroid delivery (13). Triamcinolone hexacetonide was the most frequently used drug, though when it was unavailable, triamcinolone acetonide was used as an alternative. For both drugs, the prescribed dose was 0.5 to 1 mg/kg of body weight for the knee, 0.25–0.5 mg/kg of body weight for the ankle, up to 50 mg maximum dosis. Following the procedure, the patient was observed in day-clinic, and then discharged with a recommendation of 48 hours restricted activity. Joint rest was recommended, achieved by limiting physical activity to avoid stress in the treated joints.

Outcome assessment

Medical records revision was guided by a standardised protocol, conducted

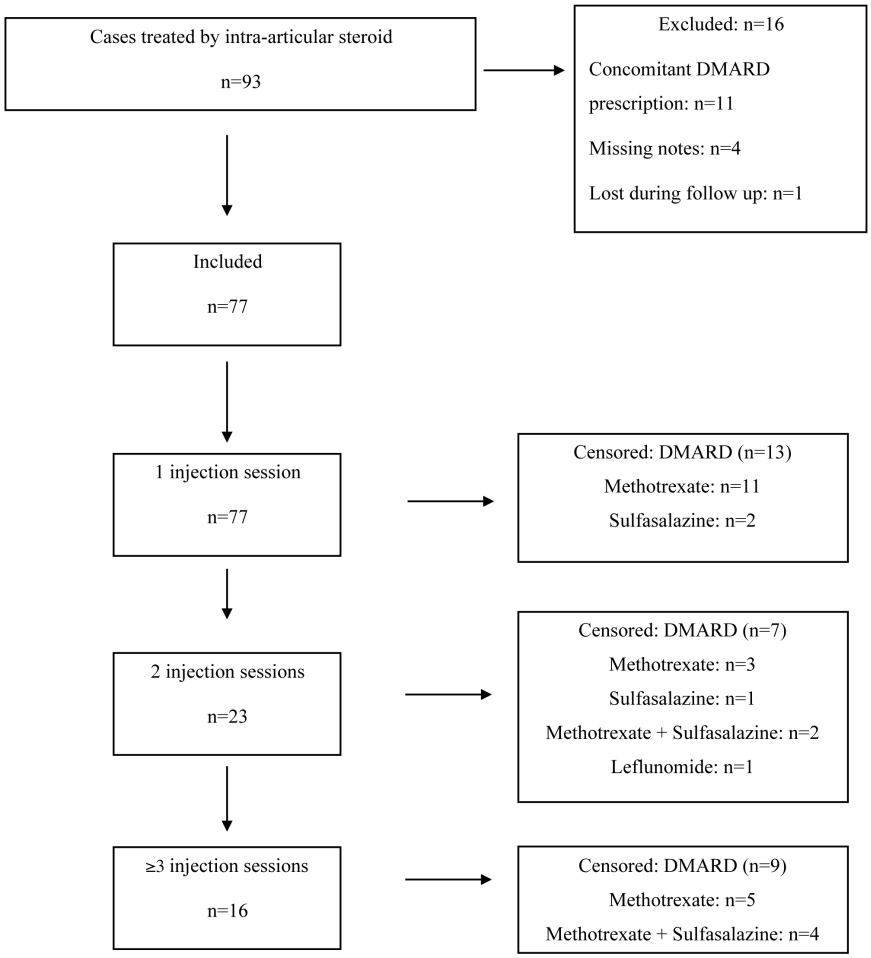

Fig. 1. Cases selection by inclusion and exclusion criteria.

by expert physicians to define active or inactive status, during each of the visits. Activity status was defined according to the Wallace criteria (15), for inactive disease, remission on and off medication. These criteria comprise clinical assessment and standardised joint assessment with full joint count examined during standard care. Joint count should indicate no active arthritis. Global assessment of disease activity is scored by the attending physician, based on a scale ranging from 0 to 10, in which 0 means no activity at all, absence of any systemic signs and symptoms, absence of uveitis, normal range of either the erythrocyte sedimentation rate or C-reactive protein or both, if they are tested together. The patient is classified as having inactive arthritis when all these criteria are present, at some time point, regardless of the episode duration. The patient is categorised as in remission on medication when inactive arthritis status persists for six month while the patient is under medication of any type. Similarly, the patient is categorised as in remission off medication when inactive arthritis status persists for 12 consecutive months without any medication.

In our protocol, due to the retrospective design, the physician's global assessment using a visual analogue scale was omitted. Instead, the physician who reviewed the medical records categorised the patient as in active or inactive status based on joint assessment and patient complaints, scoring all remaining items of the Wallace criteria, including uveitis status by regular ophthalmologic exams. We considered the patient to be on medication if any additional treatment was prescribed, besides intra-articular steroids.

The respective dates patients achieved the status of inactive arthritis, remission on and off medication, were recorded. Clinical and demographic data were also recorded: sex, date of birth, current age, arthritis onset date, joint injection procedure dates, arthritis classification, antinuclear antibody, rheumatoid factor and HLA-B27 tests, date of the first visit, arthritis duration and prescribed treatment. Data related to the procedure were also reviewed and recorded in the protocol: sedation and analgesics prescribed, category and number of joints treated, aspirated synovial fluid, steroid preparation, doses per kg of body weight for each injected joint and reported adverse events. The visits made before the procedure were also examined to identify the decision to treat, up to the first joint injection. From that point onwards, in case of arthritis relapse, the active joints were recorded independently whether previously treated or not.

Statistical analysis

Categorical variables were presented as absolute frequency and percentage. Continuous variables were presented by median and inter-quartile range (IQR). The Chi square test was performed to compare categorical variables and the non-parametric Mann-Whitney test was performed to compare continuous variables.

Survival analysis and Kaplan-Meier curves were calculated considering remission off medication as the main event, including only patients with more than one year follow-up. Individuals who never achieved the status of remission off medication were censored. Cumulative probability of remission off medication was calculated with the complementary values (1-p) obtained in the survival curve, where *p* was the probability of not achieving remission off medication status at a given time. Stratified survival curves comparing survival in relation to the number of repeated injections procedure and also comparing survival related to persistent or extended oligoarticular subtype, were analysed by log-rank test.

For all tests, the level of statistic significance was 5%, with correspondent bi-caudal *p*-value, calculated by the software SAS for Windows, version 9.2, and plotted by Statistica for Windows, version 10.0.

Results

Subjects

Ninety-three patients were treated with at least one steroid joint injection. Sixteen were excluded, being four due to missing notes, one who did not complete follow-up and 11 had a prescription of anti-rheumatic drug concomitant with the first injection (Fig. 1). Thus, 77 cases were included. Their clinical and demographic descriptors are presented in Table 1. Median age of arthritis onset was 8 (IQR 4.2–11) years. Median follow-up time was 4.3 (IQR 2.7–6.1) years.

JIA classification is presented in Table I. The number and frequency of cases studied were: 44 (57.1%) persistent oligoarticular, 20 (26%) extended oligoarticular, 6 (7.8%) enthesitis related arthritis, 5 (6.5%) undifferentiated arthritis, 1 (1.3%) psoriatic arthritis and 1 (1.3%) rheumatoid factor positive polyarthritis. Positive antinuclear antibody test was found in 34 (44.2%) cases. The latex test for rheumatoid factor was performed in 73 cases, with positive results in 6 (7.8%). The HLA-B27 test was performed in 10 cases, with positive results in 3 (3.9%).

All the patients received at least one prescription of an oral non-steroidal anti-inflammatory.

Steroid joint injection procedure

Seventy-seven patients were submitted to 116 joint injection sessions, with at least one treated joint. Twenty-three (29.9%) were submitted to one repeated session, 12 (15.6%) were submitted to two repeated joint injection sessions, three (3.9%) were submitted to three repeated sessions, and only one (1.3%) to more than three repeated sessions (Fig. 1). The number of treated joints was 254. The knees were treated in 55 sessions (47.4%), knees and ankles in 44 (37.9%), and only ankles in 17 (14.7%). The steroid preparation was triamcinolone hexacetonide in 101 sessions (87.1%) and triamcinolone acetonide in 15 (12.9%). The median (IQR) steroid doses in each joint was 1.5 (IQR1.0–2.4) mg/kg of body weight. Collection of drained synovial fluid was recorded in 17 (19.5%) sessions, however low volume effusions were not aspirated.

Table I. Demographic and clinical descriptors of 77 patients treated by steroid joint injection, according to remission status.

	Total n=77	Remission on and off medication n=23	Without remission n=54	p^*
Sex. n (%) Female	51 (66.2)	15 (65.2)	36 (66.7)	NS
Persistent oligoarticular n (%)	44 (57.1)	18 (78.3)	26 (48.1)	0.03*
Extended oligoarticular n (%)	20 (26.0)	2 (8.7)	18 (33.3)	0.05*
Enthesitis related arthritis n (%)	6 (7.8)	0 (0)	6 (11.1)	NS
Undifferentiated† n (%)	5 (6.5)	2 (8.7)	3 (5.6)	NS
Psoriatic arthritis n (%)	1 (1.3)	1 (4.3)	0 (0)	NS
Polyarticular n (%)	1 (1.3)	0 (0)	1 (1.9)	NS
Anti-nuclear antibodies n (%)§	34 (44.2)	9 (39.1)	25 (46.3)	NS
Positive rheumatoid fator n (%)††	6 (7.8)	2 (8.7)	4 (7.4)	NS
Positive HLA-B27 n (%)†††	3 (3.9)	0 (0)	3 (5.6)	NS
Biologic therapy n (%)	3 (3.9)	0 (0)	3 (5.6)	NS
DMARDS n (%)	29 (37.7)	0 (0)	29 (53.7)	<0.001
Prednisone or Prednisolone n (%)	9 (11.7)	1 (4.3)	8 (14.8)	NS
Non-steroid anti-inflammatory n (%)	77 (100)	23 (100)	54 (100)	NS
Arthritis onset years#	8.0 (4.2–11.0)	8 (6.0–11.8)	8 (4.0–10.7)	NS
Age at the first injection years#	10.1 (7.0–13.0)	10.1 (5.8–13.1)	10.1 (7.8–13.0)	NS
Follow-up duration years#	4.3 (2.7–6.1)	4.3 (3.6–5.6)	4.2 (2.2–6.3)	NS

*chi-square test for categorical variables and Mann-Whitney test for continue variables
†Undifferentiated: oligoarthritis with positive rheumatoid factor; §Positive antinuclear antibody test by Hep2 cell immunofluorescence and titres higher than 1:80. ††Rheumatoid Factor (available in 73); †††HLA-B27 (available in 10); #median (interquartile range); NS: not significant; DMARDS: disease-modifying anti-rheumatic drugs.

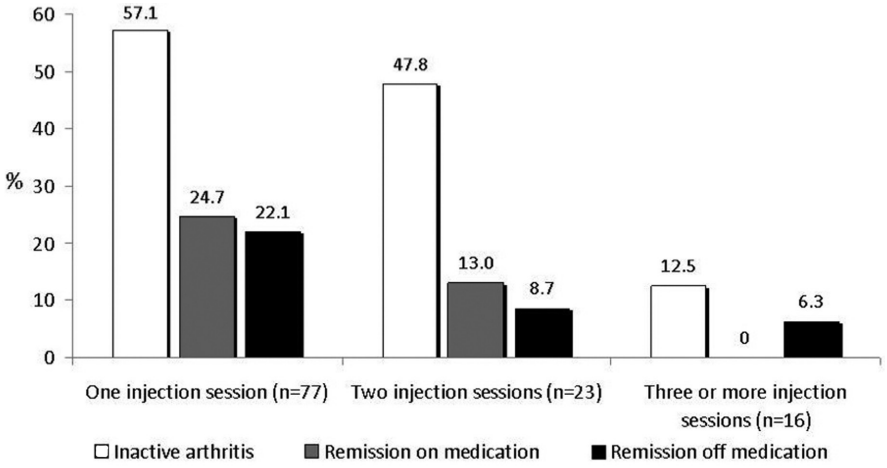

Fig. 2. Frequency of inactive arthritis (white), remission on medication (grey) and remission off medication (black), after single and repeated joint injection

The majority of the sessions were conducted under conscious sedation with analgesic association, using midazolan and fentanyl in 62 (80.5%), 14 (18.2%) received topical anaesthetics and only one (1.3%) was submitted to inhaled anaesthetics. Adverse events related to sedation, in particular low oxygen saturation, were observed in 5 (7.9%) cases. One developed urticarial rash over the joint surface at the injection site, but it is not known whether this was caused by the steroid injection itself or topical antiseptics used to clean the skin area of the injection. All adverse events resolved within a few hours and no serious adverse events were reported.

Frequency of inactive arthritis and remission

Figure 2 presents the frequency of inactive arthritis, remission on medication and remission off medication, after a single session of joint injection or two or more repeated sessions. Higher frequency of inactive arthritis, remission on and off medication was observed after a single injection session. Forty-

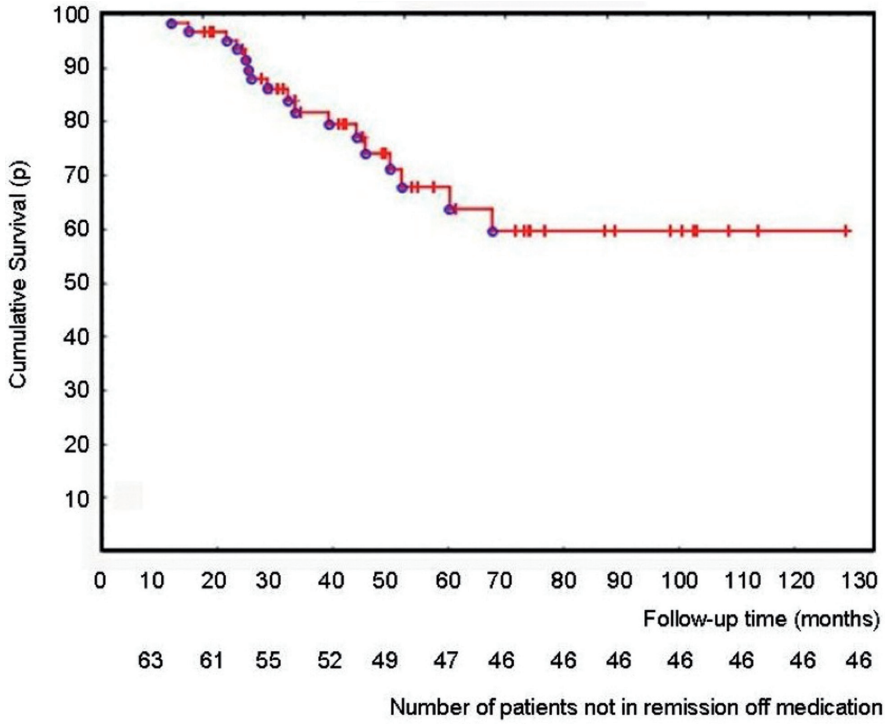

Fig. 3. Cumulative survival probability of remission status after the first steroid injection. Circles represent patients in remission off medication over time, bars represent patients censored, who never achieved remission.

four (57.1%) patients achieved inactive arthritis status, at some time point. Of those, 19 (24.7%) achieved remission on medication and 17 (22.1%) achieved remission off medication. Repeated injections resulted in remission off medication in only two (8.7%) cases, after the two injections session and one (6.3%) after three or more injection sessions. Prescription of disease-modifying anti-rheumatic drugs after the first injection session was observed in 13 cases, which were excluded from further observation. The remaining 64 patients continued to participate in the study. Of those, 7 received anti-rheumatic treatment after the second session of joint injection and 9 after the third or subsequent sessions. Repeated sessions varied from 1 to 5, including both repeated injection in the same joint or in newly affected joints.

Taking into account all patients who were submitted to at least one session, the outcome at the last recorded visit was remission off medication in 20 (26%), remission on medication in 3 (3.9%), inactive disease in 15 (19.5%), disease-modifying anti-rheumatic drug prescription in 26 (33.8%), combination of disease-modifying anti-rheumatic drug and biological therapy prescription in 3 (3.9%), and active disease in 10 (13%).

Survival analysis

Survival analysis and the number of patients not in remission off medication during follow-up are presented in Figure 3. Mean time of achieving inactive disease status, remission on medication and off medication was 8, 11 and 56 months, respectively. The cumulative probability of remission off medication was 2% in 12 months, 8% in 24 months and 18% in 36 months. Stratified survival analysis comparing remission according to single or repeated injection sessions resulted not significant by log rank test comparison ($p>0.05$). Likewise, stratified survival curve comparing persistent oligoarticular and extended oligoarticular JIA subtypes was not significant by log rank test ($p>0.05$).

Discussion

These results about JIA cumulative probability of remission seem to reflect the late effects of intra-articular depot steroids because only non-steroidal anti-inflammatory drugs were used concomitantly. Remission rates were lower than remission rates in oligoarticular JIA reported by Wallace *et al*. (2) and Fernandes *et al*. (3).

Most of the intra articular steroid treatment reports were conducted during standard care, the main outcome was control of the treated joint, but controlled studies are scarce (5-7). Standardised remission outcomes have not been reported to date, therefore comparison was not possible. Besides this specific distinction, reported studies also contain important variations in JIA classification, number of treated joints in a single session, concomitant systemic treatment and time to achieve response to treatment.

Frequency of favourable response in previous studies varied from 27 to 82% in 12 months and from 16 to 64% in 24 months (6); however, the outcome discussed was the treated joint, not the overall disease status. Zulian *et al*. (16), who defined remission as complete absence of synovitis off medication for more than two years, reported remission rates of 23% in 24 month. Our data indicated lower probability of remission in two years after the first injection. The probability decreased even more after repeated joint injections. Stratified survival curves comparison failed to show significant difference in patients submitted to two or more treatment sessions, possibly due to reduced numbers of cases on follow up. A recent longitudinal study addressing the optimum steroid dosis and the time to relapse following treatment did not show evidence of any relationship between these factors (17). The time required for response to treatment and the time up to relapse remain unpredictable.

Reported predictors of response to intra-articular steroids are: recent arthritis onset, a single injection, knee injection or methotrexate use (18). Among all those related factors, only methotrexate use was not a selection criterion in our work, where the selection reflected the predominance of oligoarticular subtype and restricted treatment to the most commonly affected joints,

the knees and ankles. The American College of Rheumatology (4) recommends repeating steroid joint injection as single or combined treatment, as needed within a 4- to 6-month interval. In our series, repeated injections were required in 29% of cases and further treatment in 38%. It is important to highlight that progression to structural damage was observed in 38.7% of cases of oligoarticular juvenile idiopathic arthritis in the same population (19).

Adverse events reported were mostly related to the sedation procedure. Late adverse events, such as scars, skin atrophy and hypopigmentation over the injection site, needle track calcification or the systemic effects of steroids were not systematically recorded due to limitations of retrospective assessment. Skin atrophy and hypopigmentation were observed in 8% of cases in the same population by scoring the Juvenile Arthritis Damage Index (JADI) (19).

Other limitations of our study are the small sample size and the retrospective design. On the other hand, controlled studies involving intra-articular steroids are rare and difficult to conduct. Triamcinolone hexacetonide and triamcinolone acetonide were used in the same dosage in a few patients. In spite of the common view of increasing the dose of triamcinolone acetonide in order to obtain longer effect (16, 17), the use of equivalent dosage might potentially have influenced the response, but it was used only in small proportion of cases, when the triamcinolone hexacetonide was unavailable.

In spite of these limitations, comparison of the effects and estimates of effect duration is important and necessary. The need for repeated injections and the relatively high dropout rates due to disease-modifying anti-rheumatic drug treatment indicate that nearly half the cases could not be fully controlled by steroid joint injection as a single treatment.

Continued observation of treatment variables allowed estimation of remission status and the period of remission. Although rapid response to treatment occurs, reflecting positively on patient satisfaction, improving function and quality of life (5-7), the concept of treatment effectiveness is not supported by the long-term benefits of intra-articular steroids.

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