Review

A reappraisal of intra-articular corticosteroid therapy in juvenile idiopathic arthritis

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ABSTRACT

Intraarticular corticosteroid (IAC) injection is a safe and rapidly effective treatment for synovitis in children with juvenile idiopathic arthritis (JIA). This procedure can be performed in an ambulatory care setting using local anaesthesia, with or without conscious sedation. Younger children, or those candidate to multiple injections, require general anaesthesia. Triamcinolone hexacetonide is the optimal corticosteroid preparation. However, for smaller joints or joints that are not easy to assess clinically, use of a more soluble corticosteroid drug is advised. Imaging guidance may facilitate accurate placement of the needle within the joint space. Use of ultrasound for this purpose has gained increasing popularity in the recent years. IAC injections are used most frequently to treat oligoarthritis, but the strategy of performing multiple IAC injections to induce disease remission, while simultaneously initiating therapy with second-line or biologic agents, has been proposed also for children with polyarticular JIA. However, the current place of IAC therapy in the management of children with JIA is uncertain due to the lack of controlled studies. Furthermore, it is still unknown whether this therapy has a disease-modifying effect over the long-term. This review summarises the present information about the use of IAC therapy in children with JIA.

Introduction

Intra-articular corticosteroid (IAC) injections are widely used in the management of children with juvenile idiopathic arthritis (JIA) to induce short-term relief of inflammation symptoms and functional improvement, and to obviate the need for regular systemic therapy (1). The use of IACs in adults with arthritis was first reported in 1951 (2). Although this therapeutic modality in childhood arthritis was presumably adopted from as early as the sixties, the first study of IAC administration in paediatric patients was published only in 1984 (3). In spite of its long use in paediatric rheumatology practice, much of the evidence supporting IAC therapy remains anecdotal or based on open, non-controlled studies. Furthermore, wide disparities likely exist in the indications for IACs, injection technique, and protocols for sedation and post-injection management across different centres. This article provides a brief summary of the experience gained so far on the use of IAC in childhood arthritis, highlighting in greater detail the most recent advances.

Indications

Traditionally, IAC injections have been used in children with JIA after failure of first-line treatment with nonsteroidal anti-inflammatory drug (NSAID) therapy. Malleson and Petty were probably the first, in an editorial published in 1990 (4), to emphasise the potential advantages of IACs over prolonged NSAID therapy in children with JIA. Taking into account the increasing doubt about the ratio of risk to benefit of NSAID therapy and considering their personal satisfactory experience, in terms of both efficacy and safety, of IAC injections in single and multiple joints, they suggested including IAC therapy at the base of the treatment pyramid of JIA. Nowadays, it is thought that many paediatric rheumatologists are using IACs as their first approach in oligoarticular JIA (5, 6). However, a recent survey of paediatric rheumatologists in the United States and Canada has shown considerable variation in the initial treatment of knee

monoarthritis in children with JIA (7). Only 27% of 129 respondents recommended initial IAC injection at disease presentation. The majority of respondents (63%) advised a trial of NSAID, followed by IAC injection in cases of NSAID failure, whereas the remainder (10%) preferred initial NSAID administration, followed by methotrexate or sulfasalazine instead of IACs. This disparity clearly reflects the lack of evidence-based information to guide the therapeutic approach to children with oligoarticular JIA.

The same authors of the above survey subsequently sought to identify the optimal treatment strategy for knee monoarthritis in JIA using a decision analysis approach with direct evaluation of parent's preferences (8). Of the 12 parents who completed the preference assessment task, 92% chose the initial IAC injection strategy over the NSAID-only strategy and the strategy that involved a 2-month NSAID trial followed by IAC injection if arthritis was not resolved after 2 months. Interestingly, most parents (75%) felt that having their child undergo the discomfort of IAC injection was preferable to 0.5 months or more of active arthritis. Since the parents' sample included in this study is small, it is unknown whether the observed preferences are generalisable to all parents of children with JIA. However, understanding parents' (and children's) preferences may help establish whether initial IAC injection is the optimal treatment strategy for monoarthritis or oligoarthritis.

Although potentially effective on all subtypes of JIA, IAC injections are used most frequently to treat oligoarthritis. Unlike NSAIDs, IAC therapy is able to prevent some important musculoskeletal abnormalities in this JIA subset (Table I). It breaks the vicious circle that leads to deformities (*e.g.* valgus knee) secondary to joint contractures. When used precociously after diagnosis, and if necessary repeatedly, it may prevent development of leg-length discrepancy (9). IAC therapy has been proven to be able to facilitate discontinuation of oral medications, correct joint contractures, resolve Baker's cysts, and improve tenosynovitis (10). Importantly, there is no point in giving local corticosteroid injection into a Baker cyst (11). The cyst gradually disappears if the disease in the knees clears or if fluid formation is suppressed by IAC injection into the knee cavity. However, the strategy of performing multiple IAC injections is used by some paediatric rheumatologists in children with polyarticular JIA to induce prompt remission of synovitis, while simultaneously initiating therapy with disease-modifying drugs (DMARDs) and/or biologic agents (12). This approach is regarded as an alternative to systemic corticosteroids to pursue the so-called "bridge" effect, that is, to achieve a quick control of inflammatory symptoms while awaiting the full therapeutic effect of a DMARD or biologic medication. Multiple IAC injections have the potential advantage of avoiding many side effects of systemic corticosteroids and of targeting selectively the inflamed joints. A recent survey among paediatric rheumatologists in the United States and Canada has shown that 15% had performed greater than 10 IAC injections in a single paediatric patient at one time (13). However, to date there have been no controlled trials on IACs in children with polyarticular JIA.

Choice of corticosteroid preparation

It is well known that the duration of response to IACs is dependent on the corticosteroid used, with less soluble preparations providing a longer duration of response. Triamcinolone hexacetonide (TH), the least soluble agent, is universally recognised among paediatric rheumatologists as the medication of choice for intra-articular administration in JIA. In earlier comparative studies, TH was shown to be superior to both bethametasone and methylprednisolone (14, 15). TH is also thought to be more advantageous over triamcinolone acetonide (TA). The two compounds differ from one another by an alteration of one side chain, which gives TH a much lower solubility. Recently, a randomised controlled trial comparing TH and TA, used at similar doses, in oligoarthritis found a significant greater response rate in the TH group at 6 months (81.4% *vs*. 53.3%; p=0.001), which was maintained at 2 years of follow-up (60% *vs*. 33.3%; p=0.002) (16). Based on pharmacokinetic studies showing that the biological effect of TA is equivalent to that of TH, if used at double dose (17), the same group of investigators subsequently compared the efficacy of TH and TA, given at twice the dose of TH, by injecting symmetrically involved joints with the 2 different compounds. By log-rank test, the probability of achieving remission was higher in joints injected with TH than in those injected with TA (80% *vs*. 47.5% at 12 months and 63.6% *vs*. 32.4% at 24 months; p=0.003). These findings led the authors to conclude that TH remains more effective than TA even when the latter drug is given at higher doses (18). Similar results were obtained by Eberhard *et al*. (19), who found that TH induced a more prolonged response rate than did TA in weight-bearing joints, particularly the knees. The dosage regimen of IAC injections currently used in the corresponding author's centre is reported in Table I.

Anaesthetic procedures

Because IAC injections are painful, a pain-free method increases the comfort for the patient and facilitates successful placement of the steroid within the joint. To lessen anxiety and pain, IAC therapy may be performed under local anaesthesia, conscious sedation, or general anaesthesia. Older children, who are deemed able to cooperate, may be just given a local anaesthetic before needle insertion. The eutectic mixture of lidocaine/prilocaine cream 5% (EMLA®) containing 2.5% of each drug has been proven to induce surface anaesthesia when applied topically under occlusion. The efficacy of lidocaine/prilocaine cream in reducing the pain associated with IAC injection was evaluated in 31 children with JIA scheduled for IAC injection into a knee in the context of a randomised, placebo-controlled trial. No significant difference was found in the pain reported after needle insertion or steroid injection between the lidocaine/prilocaine cream group and the placebo group (20). In spite of the disappointing results of this trial, EMLA® cream remains widely used

as local anaesthetic in many paediatric rheumatology centres. However, a recent survey among paediatric rheumatologists in North America has revealed a wide variability in the methods used to deliver local anaesthesia, with no accepted standard of care (21).

Conscious sedation may be achieved with benzodiazepines, such as midazolam. This medication has the advantage of inducing an amnesic effect, but has no analgesic properties. This means that it may need to be associated with an opioid medication or ketamine, which may have a negative impact on the safety profile. Midazolam can be administered intravenously, orally or rectally. The distress resulting from insertion of the intravenous cannula often makes the former route of administration unsatisfactory. Furthermore, the potential for respiratory depression means that this method should only be used when adequate facilities for paediatric resuscitation are available. The oral or rectal routes are more accepted by children and families, but have the disadvantage of an erratic absorption. A recent study has described the use of intranasal midazolam (22).

Young children, or those candidate to multiple injections, may require general anaesthesia. With modern anaesthesia techniques, most children can receive their joint injection in the anaesthetic room under a short general anaesthetic, and can be treated as day cases. The use of an inhaled mixture of nitrous oxide and oxygen to facilitate painful procedures, including IAC injections, in children has been recently proposed (23-25). This procedure has the advantage of allowing a short stay in hospital and avoiding the risks associated with either intravenous sedation or general anaesthesia. It does require a degree of cooperation from the patient, however, which limits its applicability in younger children

Injection technique

A telephone survey of paediatric rheumatologists in the UK has revealed a wide variation in individual practice with respect to IAC injections (26). There was no consensus of opinion over issues such as flushing of the needle track with saline or local anaesthetic, mixing the corticosteroid preparation with local anaesthetic, and "pulsing" (administration by several small increments into an individual joint) of injections, especially into small joints, to minimise the risk of steroid leakage and subcutaneous atrophy. Surprisingly, only 9.8% of respondents to this postal survey reported the routine use of surgical gloves to reduce the risk of infection.

Aspiration of as much of synovial fluid as possible prior to IAC injection is advised to provide immediate relief of symptoms. In addition, it is assumed that removal of excess synovial fluid increases the efficacy of treatment because it leaves a smaller fluid volume for the corticosteroid to distribute in. Complete aspiration of synovial fluid before injecting IAC has been found to reduce the risk of relapse in adult patients with rheumatoid arthritis (27). The potential benefit of nonarthroscopic joint lavage followed by IAC injection to treat knee arthritis refractory to conventional IAC injections has been described (28).

To increase the chance of success of IAC therapy and minimise the risk of local side effects, namely subcutaneous atrophy (see below), accurate placement of the needle within the joint space is fundamental. However, this can be difficult for certain joints that are not easy to assess clinically, such as the hip, the subtalar joint, or the temporomandibular joint. A high rate of inaccurate placement of the needle within the joint space has been reported in adult patients with arthritis (29). Aspiration of synovial fluid before injection of a corticosteroid is one method that may allow for improved accuracy. Image guidance with the aid of ultrasound or fluoroscopy has gained increasing popularity in recent years. Ultrasound is the most valuable tool as it does not involve radiation exposure and can be done by the rheumatologists themselves. It has been suggested that practitioners, after trying a few US-guided needle placements, would gain accuracy in subsequent blind placements and, ultimately, achieve better results (30). The technique of injection in specific joints has been reviewed recently (31).

Post-injection management

A wide inconsistency in practice regarding post-injection rest, splinting, and physiotherapy regimens has been reported (5). It is postulated that limiting movement in the joint diminishes the extent of clearance of the medication from the joint space and re-absorption. Policies about the rest period have varied from non-weight bearing for 24 hours to 24 hours of strict bed rest, to 24 hours of light activity, to 48 hours of minimal weight bearing. The use of splints was also variable, with some therapists not using splints, others only using them for the joints with flexion contractures, and some applying them following every injection. The follow-up physiotherapy was quite variable as well, with some children attending therapy for 48 hours following injection

Table I. Type and dose of corticosteroids currently used for intra-articular corticosteroid injections at the corresponding author's centre.

Joint	Corticosteroid	Dose
Shoulder	TH	1 mg/kg (max 40 mg)
Elbow	TH	0.75 mg/kg (max 30 mg)
Wrist	TH	0.25–0.5 mg/kg§ (max 20 mg)
Hand metacarpophalangeal and interphalangeal	MP	5–10 mg§
Hip	TH	1 mg/kg (max 40 mg)
Knee	TH	1 mg/kg (max 40 mg)
Ankle	TH	0.75 mg/kg (max 30 mg)
Subtalar and intertarsal	MP	20–40 mg§
Foot metatarsophalangeal and interphalangeal	MP	5–10 mg§
Tendon sheats	MP	20–40 mg§

TH: triamcinolone hexacetonide; MP: methylprednisolone acetate.
§Depending on the child's size.

and others being treated for 1-2 weeks or according to therapist's availability. It is the authors' policy to prescribe a non-weight bearing period of 24 hours. In our experience, as in that of others (5), splinting is rarely necessary to correct contractures due to the efficacy of the IAC therapy. However, in children with contractures, valgus deformity, or muscle hypotrophy an intensive and individually tailored physiotherapy program post-injection is advised.

Outcome and predictors of outcome

Overall, remission rates range from 22% to 70% at 6 months, from 22% to 77% at 12 months, and from 16.7 % to 55% at 2 years (6). However, reported studies on the efficacy of IAC injections in JIA are difficult to compare and interpret due to differences in the disease subtypes included, type and number of joints injected, definitions of improvement used, concomitant systemic therapy, and timeframe adopted to assess treatment response or failure. The same applies to the analyses of outcome predictors.

In case of relapse of synovitis, reinjection is commonly performed. Although there are no established guidelines for this practice, most rheumatologists will limit the frequency of reinjections to 3 times per year, with repeated procedures being performed at least 3 months apart (6, 32). Newer joint imaging techniques, such as MRI and ultrasound, may play an important role in the evaluation of IAC injection, particularly in establishing whether clinically-defined remission parallels resolution of synovitis on imaging studies (33-35). Although the short-term efficacy of IAC injections is well established, it is still unclear whether this treatment influences the natural history of JIA, particularly in terms of prevention of structural damage. Recently, the benefit of IAC injection was demonstrated by three dimensional-gait analysis in both injected and uninjected joints (36).

A number of predictors of the efficacy of IAC therapy have been reported, sometimes with conflicting results (Table II). The effect has been found to be best after the first injection into an individual joint, and the duration of the effect has been shown to be longest in patients with oligoarthritis and shortest in patients with systemic arthritis (37). Response rate and duration of effect have been found to be greater in the knee than in the hips. Other predictors of favourable response include shorter disease duration and younger age at the time of the IAC injection, male gender, and higher ESR (6, 38). A higher count of synovial fluid polymorphonuclear leukocytes was associated with a higher relapse rate (15). A recent retrospective chart review of 60 JIA patients who received 202 IAC injections over a 5-year period showed that remission was longer in the joints of the upper extremities (wrist and finger joints) and knees, in patients who were given concomitant treatment with methotrexate, and when injection was performed under general anaesthesia (39). Vivarelli and co-workers (40) reported that the -173 G/C single nucleotide polymorphism of macrophage migration inhibitory factor (MIF) was significantly associated with duration of response to IAC injection in children with JIA, with carriers of a MIF -173*C allele being significantly more likely to relapse within 3 months. The authors noted that this finding was consistent with the ability of MIF to counteract the anti-inflammatory effect of corticosteroids. A study of biomarkers concentration in synovial fluid of JIA patients who underwent an IAC injection showed that higher levels of matrix metalloproteinase (MMP)-3 and, possibly, interleukin (IL)-6 and IL-10 predicted better outcome at 6 months (41).

Table II. Predictors of outcome of IAC therapy.

Predictors of favourable response
First injection
Oligoarthritis
Shorter disease duration
Younger age
Male sex
Injection in the knee
Injection in upper extremity joints
Higher erythrocyte sedimentation rate
Concurrent methotrexate therapy
Injection under general anaesthesia
Higher levels of matrix metalloproteinase (MMP)-3 in the synovial fluid
Predictors of poor response
Systemic arthritis
Injection in the hip
Higher synovial polymorphonuclear leukocyte count
-173*C allele of macrophage migration inhibitory factor (MIF)

Side effects

The most common adverse effect of IAC injections is subcutaneous atrophy, with reported incidence ranges from 1.5 to 8.3% (3, 6, 42). It is caused by extravasation of the injected medication from the joint space. Subcutaneous atrophy may resolve with time in most patients, but persists in some. The risk of this complication is minimised by following a careful injection technique and by ensuring accuracy of needle placement in the joint space. Corticosteroid preparations with higher potency and duration of action, namely TH, carry the greatest risk of subcutaneous atrophy. The risk is higher in smaller joints.

There has been concern that IAC injections may damage intra-articular structures. In a 13-month follow-up study, Huppertz *et al*. (43) demonstrated by means of MRI scans pre and post-procedure that cartilage integrity was well preserved in all injected joints. More long-term studies and studies in children who receive repeated injections in the same joints are needed to further investigate the safety of IAC procedures. The potential role of IAC injections in causing avascular necrosis of the femoral head is discussed below.

It has been warned that following multiple IAC injections there could be sufficient systemic absorption of corticosteroids to produce a Cushingoid appearance. Huppertz and Pfüller (44) reported transient suppression of cortisol release detected by a low morning peak value of salivary cortisol. In all 22 cases studied, the cortisol values returned to normal within a median of 16 days and no adverse events were recorded secondary to this transient adrenal suppression. However, one case of Cushingoid syndrome and severe adrenal suppression following local corticosteroid use was recently reported (45). This patient, who had received 36 injections of TH over 4 years, developed florid

Cushingoid symptoms, associated with reduced growth velocity for 11 months and undetectable cortisol levels for 6 months. In another study, prominent Cushingoid features were reported in 9/180 (5%) children with JIA who had received TA (46). This side effect seemed to be independent from the corticosteroid dose used or the number of steroid administrations. Although these symptoms were described as being distressing for both children and parents, spontaneous resolution within a few months occurred in all cases. Altogether, these finding suggest that although systemic absorption of corticosteroids may cause significant adrenal suppression and transient clinical manifestations ranging from minor cosmetic changes to overt Cushingoid syndrome, it is not associated with long-term adverse effects and is short-lived.

Another known complication of IAC injections is the development of periarticular calcifications. The majority of these abnormalities are asymptomatic and are detected coincidentally on radiological follow-up. However, in one case, surgical removal from the infrapatellar fat pad was necessary (3).

Septic arthritis of the ankle 48 hours after an IAC injection in a knee in a child with respiratory infection has been reported (47). This report suggests that the procedure should be postponed if the child has signs of an intercurrent infection. Rigorous aseptic measures, including a careful no-touch technique, should always be adopted to prevent such serious complication.

Injected corticosteroids may cause a crystal-induced synovitis, which may present with post-injection erythema and pain. This is thought to result from phagocytosis of corticosteroid crystals in the joint, leading to the release of inflammatory mediators (48). These symptoms usually subside spontaneously or with local ice application within a few days. Acute anaphylaxis following intraarticular injection of a mixture of methylprednisolone and local anaesthetic has been described in adult patients (49), but has never been reported in children.

The main side effects of IACs are presented in Table III.

Table III. Main side effects of IAC therapy.

Subcutaneous atrophy
Periarticular calcification
Crystal-induced synovitis
Avascular necrosis of bone
Cushingoid syndrome
Septic arthritis
Anaphylactic reaction

IAC injection in specific joints

– Hip joint

The hip is one of the joints less frequently treated with IAC injections due to the complexity of the procedure. Furthermore, there is concern that corticosteroid injection into the hip joint could induce avascular necrosis (AVN) of the femoral head. Recently, Neidel *et al*. (50) followed prospectively 48 children with JIA who received IAC injection in 67 hips under ultrasound guidance. Each hip was injected with TH at a dose of 1 mg/kg, not exceeding 40 mg/joint. A post injection rest of 3 days was prescribed. Remission of coxitis, assessed both clinically and with ultrasound/MRI, was achieved at 2 years in 76% of the hips after single or repeated injections. Two patients developed AVN of the femoral head. Both these children were receiving long-term systemic corticosteroids. Overall, the AVN rate was not found to increase after IAC therapy compared with the AVN rate between the onset of JIA and the IAC treatment. Furthermore, all cases of AVN seen in the authors' series occurred among children who received long-term corticosteroids, while no AVN was seen in children who did not receive such treatment. Tinjala *et al*. (51) reported the results of ultrasound-guided IAC treatment of 20 hips in 13 JIA patients. At 12 months, the frequency of response, defined as absence of synovitis clinically and the lack of effusion on ultrasound, was 50%. No side effects due to the IAC injection were observed during the follow-up time. Altogether, these studies suggest that IAC therapy of hip synovitis is effective and safe, with the risk of AVN of the femoral head being small and probably increased by the simultaneous administration of systemic corticosteroids. However, nowadays most JIA patients with hip disease are more likely to be treated precociously and aggressively with DMARDs and biologic medications, often in combination.

– Temporomandibular joint

Use of IAC injection into the temporomandibular joint (TMJ) has been advocated with the aim of controlling synovial inflammation and potentially preventing mandibular growth alterations, leading to micrognathia and jaw deviation. The latter indication has been inferred from the proven benefit of IAC treatment in the prevention of leg-length discrepancy in children with oligoarticular JIA (see above). However, until recently use of this procedure among paediatric rheumatologists has been hampered by reports of corticosteroid-induced chondrolysis in adults with TMJ pain (52). Arabshashi *et al*. (53) followed prospectively 23 JIA patients who underwent computer-tomography (CT)-guided IAC injections into the TMJ by experienced paediatric interventional radiologists. Injected medication was TA (40 mg) or TH (20 mg). The majority of patients who had jaw pain before the procedure experienced complete resolution of pain. Maximal incisal opening improved significantly in 43% of patients. Resolution of joint effusions was observed in 48% of patients who had follow-up MRI studies. In the majority of patients, no side effects from IAC injection were seen. Two patients experienced facial swelling, which was transient and was not accompanied by any cutaneous atrophy or pain. Ringold *et al*. (54) reported a retrospective chart review of 25 JIA patients who underwent 74 IAC injections on 47 separate occasions. The injections were performed by an experienced oral and maxillofacial surgeon. Each TMJ was injected with 20-40 mg of TA or 10-20 mg of TH. Over the study period, patients experienced, on average, significant improvement in maximal incisal opening. At the last study visit, 84% of patients did not report symptoms related to TMJ involvement and 72% of patients had no documented abnormalities on TMJ examination. Three of 5 patients had resolution of jaw deviation during follow-up. One patient developed subcutaneous atrophy at the injection site. Two

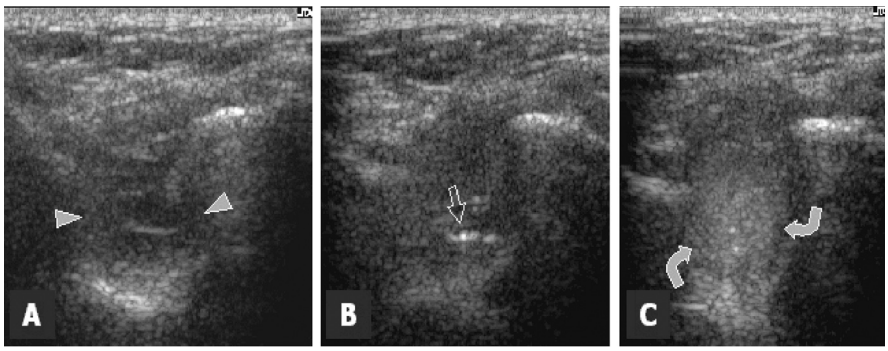

Fig. 1. Ultrasound-guided IAC injection into a subtalar joint in a child with JIA. **A.** localisation of joint space; **B.** identification of the needle tip within the joint space; **C.** flow of the corticosteroid preparation within the joint.

patients developed small, asymptomatic intraarticular calcifications. Altogether, these studies suggest that IAC injection is a useful procedure for the prevention and treatment of morbidities associated with TMJ arthritis in JIA.

– Subtalar and tarsal joints

In spite of the frequent occurrence of arthritis in the subtalar joint (*i.e.* posterior talo-calcaneal joint), this joint is not commonly injected, possibly due to technical difficulty or lack of recognition. A chart review of 38 JIA patients who underwent 55 subtalar IAC injections was recently described (55). Indication for injection was the presence of qualitatively decreased foot inversion or eversion on physical examination. Injection was performed under fluoroscopic guidance and the corticosteroid preparation was TH (20 mg/joint). Improvement, defined by enhanced foot inversion and eversion, was documented in 82% of the initial injections, with the mean duration of improvement being 1.2 years. Forty-four percent of patients had complete recovery of subtalar arthritis following injection. However, 53% of patients developed skin hypopigmentation or subcutaneous atrophy. The authors hypothesised that these complications were related to the dose of injected corticosteroids and possibly the accuracy of needle placement. Tynjala *et al*. (51) described their experience with injection of joints and tendon sheaths in the swollen tarsal region in 19 patients with JIA who received 22 injections. Before the IAC injection, inflamed areas in the swollen ankles/feet were targeted with MRI. The corticosteroid preparation used was methylprednisolone, whose dose varied from 4 to 40 mg according to the size of the joint or the tendon sheath, the total number of injection sites, and the size of the patient. The response rate was 82% at 1 month, 59% at 3 months, 41% at 6 months, and 32% at 12 months. No local side effects, including subcutaneous tissue atrophy, were observed during follow-up time. The authors concluded that targeting the synovitis site by radiological imaging optimises the treatment of tarsal synovitis in JIA.

In general, the assessment of the localisation and extent of the inflammatory process in the ankle by clinical examination is often challenging. When a patient presents with ankle swelling, it is frequently difficult to establish whether this is predominantly due to synovitis in the tibio-talar joint, subtalar joint, or both, or whether the main cause is prominent tenosynovitis. This translates into difficulties in identifying the area that needs to be targeted with a local corticosteroid injection.

As synovitis in the ankle is often associated with active disease in the tarsal joints, namely the talo-navicular, anterior talo-calcaneal, or calcaneo-cuboid joints, this may affect improvement of pain and ankle movements, namely inversion and eversion, following local injection therapy. Concomitant tarsal arthritis may explain the relatively low rate of complete resolution observed in some studies of IAC therapy in the ankle or subtalar joints.

Overall, these issues underscore the low reliability of clinical examination and the importance of imaging studies in the precise localisation of the inflammatory process in the ankle and mid-foot areas (34, 35). Furthermore, because blind injection of the subtalar and tarsal joints and tendon sheaths is technically challenging, even in experienced hands, the efficacy of injection in these structures can be improved and the risk of local side effects minimised using imaging guidance, namely with ultrasound (Fig. 1).

Intraarticular injection of biologic medications

In recent years, based on the favourable therapeutic results obtained with the systemic administration of the anti-tumour necrosis factor agents in several inflammatory arthritides, these medications have been injected intraarticularly with encouraging results in patients with persistent monoarthritis resistant to other therapeutic options, including IACs (56-59). However, more information is necessary before this approach can be considered for use in children with JIA.

Conclusion

IAC injection remains an important therapeutic option for children with JIA, even in the biologic era. However, the current place of IAC therapy in the management of children with JIA is still uncertain due to the lack of controlled studies. Systematic and prospective studies and controlled trials are needed to define the optimal role of IACs in the management of children with JIA and to establish whether this treatment has the ability to prevent the development of structural joint damage. Furthermore, there is a need to support training of paediatric rheumatologists on the technique of IAC injection in the joints that are more difficult to access, and on ultrasound-guided procedures.

References

1. RAVELLI A, MARTINI A: Juvenile idiopathic arthritis. *Lancet* 2007; 369: 767-78.
2. HOLLANDER JL, BROWN EM JR, JESSAR RA, BROWN CY: Hydrocortisone and cortisone injected into arthritic joints; comparative effects of and use of hydrocortisone as a local antiarthritic agent. *J Am Med Assoc* 1951; 147: 1629-35.
3. GILSANZ V, BERNSTEIN BH: Joint calcification following intra-articular corticosteroid

therapy. *Radiology* 1984; 151: 647-9.
4. MALLESON PN, PETTY RE: Remodelling the pyramid--a pediatric prospective. *J Rheumatol* 1990; 17: 867-8.
5. DENT PB, WALKER N: Intra-articular corticosteroids in the treatment of juvenile rheumatoid arthritis. *Curr Opin Rheumatol* 1998; 10: 475-80.
6. CLEARY AG, MURPHY HD, DAVIDSON JE: Intra-articular corticosteroid injections in juvenile idiopathic arthritis. *Arch Dis Child* 2003; 88: 192-6.
7. BEUKELMAN T, GUEVARA JP, ALBERT DA, SHERRY DD, BURNHAM JM: Variation in the initial treatment of knee monoarthritis in juvenile idiopathic arthritis: A survey of pediatric rheumatologists in the United states and Canada. *J Rheumatol* 2007; 34: 1918-24.
8. BEUKELMAN T, GUEVARA JP, ALBERT DA: Optimal treatment of knee monarthritis in juvenile idiopathic arthritis: A decision analysis. *Arthritis Rheum* 2008; 59: 1580-8.
9. SHERRY DD, STEIN LD, REED AM, SCHANBERG LE, KREDICH DW: Prevention of leg length discrepancy in young children with pauciarticular juvenile rheumatoid arthritis by treatment with intraarticular steroids. *Arthritis Rheum* 1999; 42: 2330-4.
10. PADEH S, PASSWELL JH: Intraarticular corticosteroid injection in the management of children with chronic arthritis. *Arthritis Rheum* 1998; 41: 1210-4.
11. DIXON ASTJ, GRABER J: *Local injection therapy in rheumatic diseases*. 2nd ed. Basel: Eular Publishers, 1983
12. SOUTHWOOD TR: Report from a symposium on corticosteroid therapy in juvenile chronic arthritis. *Clin Exp Rheumatol* 1993; 11: 91-4.
13. BEUKELMAN T, GUEVARA JP, ALBERT DA, SHERRY DD, BURNHAM JM: Usage of intra-articular corticosteroid injections for the treatment of juvenile idiopathic arthritis: a survey of pediatric rheumatologists in the United States and Canada. *Clin Exp Rheumatol* 2008; 26: 700-3.
14. BALOGH Z, RUZSONYI E: Triamcinolone hexacetonide versus betamethasone. A double-blind comparative study of the long-term effects of intra-articular steroids in patients with juvenile chronic arthritis. *Scand J Rheumatol Suppl* 1987; 67: 80-2.
15. HONKANEN VE, RAUTONEN JK, PELKONEN PM: Intra-articular glucocorticoids in early juvenile chronic arthritis. *Acta Paediatr* 1993; 82: 1072-4.
16. ZULIAN F, MARTINI G, GOBBER D, AGOSTO C, GIGANTE C, ZACCHELLO F: Comparison of intra-articular triamcinolone hexacetonide and triamcinolone acetonide in oligoarticular juvenile idiopathic arthritis. *Rheumatology* 2003; 42: 1254-9.
17. DERENDORF H, MOLLMANN H, GRUNER A, HAACK D, GYSELBY G: Pharmacokinetics and pharmacodynamics of glucocorticoid suspensions after intra-articular administration. Clin Pharmacol Ther 1986; 39: 313-7.
18. ZULIAN F, MARTINI G, GOBBER D, PLEBANI M, ZACCHELLO F, MANNERS P: Triamcinolone acetonide and hexacetonide intra-articular treatment of symmetrical joints in juvenile idiopathic arthritis: A double-blind trial. *Rheumatology* 2004; 43: 1288-91.
19. EBERHARD BA, SISON MC, GOTTLIEB BS, ILOWITE NT: Comparison of the intraarticular effectiveness of triamcinolone hexacetonide and triamcinolone acetonide in treatment of juvenile rheumatoid arthritis. *J Rheumatol* 2004; 31: 2507-12.
20. UZIEL Y, BERKOVITCH M, GAZARIAN M, KOREN G, SILVERMAN ED, SCHNEIDER R *et al*.: Evaluation of eutectic lidocaine/prilocaine cream (EMLA) for steroid joint injection in children with juvenile rheumatoid arthritis: A double blind, randomized, placebo controlled trial. *J Rheumatol* 2003; 30: 594-6.
21. WEISS JE, URIBE AG, MALLESON PN, KIMURA Y: Anesthesis for intra-articular corticosteroid injections in juvenile idiopathic arthritis: a survey of pediatric rheumatologists. *Pediatr Rheumatol* 2010; 8: 3.
22. LANE RD, SCHUNK JE: Atomized intranasal midazolam use for minor procedures in the pediatric emergency department. *Pediatr Emerg Care* 2008; 24: 300-3.
23. ANNEQUIN D, FIEZ N: The use of a mixture of an equimolecular mixture of oxygen protoxide of nitrogen in pediatrics. *Rev Infirm* 2000; 65: 28-33.
24. CLEARY AG, RAMANAN AV, BAILDAM E, BIRCH A, SILLS JA, DAVIDSON JE: Nitrous oxide analgesia during intra-articular injection for juvenile idiopathic arthritis. *Arch Dis Child* 2002; 86: 416-8.
25. UZIEL Y, CHAPNICK G, ROTHSCHILD M *et al*.: Nitrous oxide sedation for intra-articular injection in juvenile idiopathic arthritis. *Pediatr Rheumatol Online J* 2008; 6: 1.
26. HASLOCK I, MACFARLANE D, SPEED C: Intra-articular and soft tissue injections: A survey of current practice. *Br J Rheumatol* 1995; 34: 449-52.
27. WEITOFT T, UDDENFELDT P: Importance of synovial fluid aspiration when injecting intra-articular corticosteroids. *Ann Rheum Dis* 2000; 59: 233-5.
28. SORNAY-SOARES C, JOB-DESLANDRE C, KAHAN A: Joint lavage for treating recurrent knee involvement in patients with juvenile idiopathic arthritis. *Joint Bone Spine* 2004; 71: 296-9.
29. JONES A, REGAN M, LEDINGHAM J, PATTRICK M, MANHIRE A, DOHERTY M: Importance of placement of intra-articular steroid injections. *BMJ* 1993; 307: 1329-30.
30. CANOSO JJ: Ultrasound imaging: A rheumatologist's dream. *J Rheumatol* 2000; 27: 2063-4.
31. COURTNEY P, DOHERTY M: Joint aspiration and injection. *Best Pract Res Clin Rheumatol* 2005; 19: 345-69.
32. EARLEY A, CUTTICA RJ, MCCULLOUGH C, ANSELL BM: Triamcinolone into the knee joint in juvenile chronic arthritis. *Clin Exp Rheumatol* 1988; 6: 153-5.
33. HUPPERTZ HI, GOHLKE F, HORWITZ AE: Intra-articular steroid therapy in treatment of chronic arthritis in childhood and adolescence. *Monatsschr Kinderheilkd* 1993; 141: 883-7.
34. MAGNI-MANZONI S, EPIS O, RAVELLI A *et al*.: Comparison of clinical versus ultrasound-determined synovitis in juvenile idiopathic arthritis. *Arthritis Rheum* 2009; 61: 1497-504.
35. ROONEY ME, MCALLISTER C, BURNS JF: Ankle disease in juvenile idiopathic arthritis: Ultrasound findings in clinically swollen ankles. *J Rheumatol* 2009; 36: 1725-9.
36. BROSTROM E, HAGELBERG S, HAGLUND-AKERLIND Y: Effect of joint injections in children with juvenile idiopathic arthritis: Evaluation by 3D-gait analysis. *Acta Paediatr* 2004; 93: 906-10.
37. BREIT W, FROSCH M, MEYER U, HEINECKE A, GANSER G: A subgroup-specific evaluation of the efficacy of intraarticular triamcinolone hexacetonide in juvenile chronic arthritis. *J Rheumatol* 2000; 27: 2696-702.
38. RAVELLI A, MAGNI MANZONI S, VIOLA S, PISTORIO A, RUPERTO N, MARTINI A: Factors affecting the efficacy of intraarticular corticosteroid injection of knees in juvenile idiopathic arthritis. *J Rheumatol* 2001; 28: 2100-2.
39. MARTI P, MOLINARI L, BOLT IB, SEGER R, SAURENMANN RK: Factors influencing the efficacy of intra-articular steroid injections in patients with juvenile idiopathic arthritis. *Eur J Pediatr* 2008; 167: 425-30.
40. VIVARELLI M, D'URBANO LE, INSALACO A *et al*.: Macrophage migration inhibitory factor (MIF) and oligoarticular juvenile idiopathic arthritis (o-JIA): Association of MIF promoter polymorphisms with response to intra-articular glucocorticoids. *Clin Exp Rheumatol* 2007; 25: 775-81.
41. CATTALINI M, MADUSKUIE V, FAWCETT PT, BRESCIA AM, ROSE CD: Predicting duration of beneficial effect of joint injection among children with chronic arthritis by measuring biomarkers concentration in synovial fluid at the time of injection. *Clin Exp Rheumatol* 2008; 26: 1153-60.
42. SPARLING M, MALLESON P, WOOD B, PETTY R: Radiographic followup of joints injected with triamcinolone hexacetonide for the management of childhood arthritis. *Arthritis Rheum* 1990; 33: 821-6.
43. HUPPERTZ HI, TSCHAMMLER A, HORWITZ AE, SCHWAB KO: Intraarticular corticosteroids for chronic arthritis in children: Efficacy and effects on cartilage and growth. *J Pediatr* 1995; 127: 317-21.
44. HUPPERTZ HI, PFULLER H: Transient suppression of endogenous cortisol production after intraarticular steroid therapy for chronic arthritis in children. *J Rheumatol* 1997; 24: 1833-7.
45. HAMEED R, ZACHARIN MR: Cushing syndrome, adrenal suppression and local corticosteroid use. *J Paediatr Child Health* 2006; 42: 392-4.
46. GONDWE JS, DAVIDSON JE, DEELEY S, SILLS J, CLEARY AG: Secondary Cushing's syndrome in children with juvenile idiopathic arthritis following intra-articular triamcinolone acetonide administration. *Rheumatology* 2005; 44: 1457-8.
47. SHORE A, RUSH PJ: Possible danger of intra-articular steroid injection in children with respiratory tract infections. *Br J Rheumatol* 1987; 26: 73.
48. HERTZBERGER-TEN CATE R, DE VRIES-VAN DER VLUGT BC, VAN SUIJLEKOM-SMIT LW, CATS A: Intra-articular steroids in pauciarticular juvenile chronic arthritis, type 1. *Eur J Pediatr* 1991; 150: 170-2.

49. HOPPER JM, CARTER SR: Anaphylaxis after intra-articular injection of bupivacaine and methylprednisolone. *J Bone Joint Surg Br* 1993; 75: 505-6.
50. NEIDEL J, BOEHNKE M, KUSTER RM: The efficacy and safety of intraarticular corticosteroid therapy for coxitis in juvenile rheumatoid arthritis. *Arthritis Rheum* 2002; 46: 1620-8.
51. TYNJALA P, HONKANEN V, LAHDENNE P: Intra-articular steroids in radiologically confirmed tarsal and hip synovitis of juvenile idiopathic arthritis. *Clin Exp Rheumatol* 2004; 22: 643-8.
52. HADDAD IK: Temporomandibular joint osteoarthrosis. histopathological study of the effects of intra-articular injection of triamcinolone acetonide. *Saudi Med J* 2000; 21: 675-9.
53. ARABSHAHI B, DEWITT EM, CAHILL AM *et al*.: Utility of corticosteroid injection for temporomandibular arthritis in children with juvenile idiopathic arthritis. *Arthritis Rheum* 2005; 52: 3563-9.
54. RINGOLD S, TORGERSON TR, EGBERT MA, WALLACE CA: Intraarticular corticosteroid injections of the temporomandibular joint in juvenile idiopathic arthritis. *J Rheumatol* 2008; 35: 1157-64.
55. BEUKELMAN T, ARABSHAHI B, CAHILL AM, KAYE RD, CRON RQ: Benefit of intraarticular corticosteroid injection under fluoroscopic guidance for subtalar arthritis in juvenile idiopathic arthritis. *J Rheumatol* 2006; 33: 2330-6.
56. BLIDDAL H, TERSLEV L, QVISTGAARD E *et al*.: A randomized, controlled study of a single intra-articular injection of etanercept or glucocorticosteroids in patients with rheumatoid arthritis. *Scand J Rheumatol* 2006; 35: 341-5.
57. BLIDDAL H, TERSLEV L, QVISTGAARD E *et al*.: Safety of intra-articular injection of etanercept in small-joint arthritis: An uncontrolled, pilot-study with independent imaging assessment. *Joint Bone Spine* 2006; 73: 714-7.
58. CONTI F, CECCARELLI F, PRIORI R, IAGNOCCO A, SIGNORE A, VALESINI G: Intra-articular infliximab in patients with rheumatoid arthritis and psoriatic arthritis with monoarthritis resistant to local glucocorticoids. clinical efficacy extended to patients on systemic anti-tumour necrosis factor alpha. *Ann Rheum Dis* 2008; 67: 1787-90.
59. NIKAS SN, TEMEKONIDIS TI, ZIKOU AK, ARGYROPOULOU MI, EFREMIDIS S, DROSOS AA: Treatment of resistant rheumatoid arthritis by intra-articular infliximab injections: A pilot study. *Ann Rheum Dis* 2004; 63: 102-3.