

Intra-articular corticosteroids in the treatment of juvenile idiopathic arthritis: Safety, efficacy, and features affecting outcome.

A comprehensive review of the literature

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Abstract: Intra-articular corticosteroid injection (IACI) has been used in the treatment of inflammatory arthritis in adults for over fifty years. Over the last two decades, IACI has become an important tool in the management of juvenile idiopathic arthritis (JIA), particularly in the oligoarthritis subset of JIA. Many factors may affect the efficacy of this treatment modality, although the majority of evidence on this topic is anecdotal, nonconvincing, or conflicting. The review examines the rationale, efficacy, safety, and application of the use of IACI in the treatment of JIA, focusing on factors that affect the outcome following IACI.

Keywords: juvenile idiopathic arthritis, juvenile rheumatoid arthritis, glucocorticoids, treatment, children

Introduction

Juvenile idiopathic arthritis (JIA) describes a heterogeneous collection of chronic inflammatory conditions which have in common arthritis of unknown etiology, of at least six weeks duration, and with onset before the 16th birthday. More homogeneous categories of JIA have been delineated by the International League of Associations for Rheumatology (ILAR) classification based upon predominant clinical and laboratory features.¹ Intra-articular corticosteroid injection (IACI) is a frequently used therapeutic modality in the management of JIA, particularly in the subset of JIA patients with oligoarthritis, defined by ILAR as arthritis affecting less than five joints during the first six months of disease. The safety and efficacy of IACI to improve pain, mobility, and morning stiffness in adults with rheumatoid arthritis (RA) have been confirmed in a recent systematic review of placebo-controlled randomized trials,² however no such placebo-controlled randomized trials exist in children with JIA. The use of IACI in JIA has been previously reviewed by Dent and Walker,³ See,⁴ Cleary and colleagues,⁵ and Hashkes and Laxer.⁶ This article serves to expand upon these previous reports and to review the current literature regarding the rationale, efficacy, safety, and application of the use of IACI in the treatment of JIA, focusing on factors that affect the outcome following IACI.

Historical aspects

The use of IACI for the treatment of inflammatory arthritis in adults was initially reported by Hollander in 1951.⁷ The use of IACI in children was first noted anecdotally

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in 1979,⁸ and the first prospective evaluation of IACI in the management of chronic arthritis in children was reported by Allen and colleagues in 1986.⁹ Since that time, IACI has become a common and accepted tool in the management of JIA, with 44% of children with juvenile rheumatoid arthritis (JRA) receiving IACI as part of the therapy.¹⁰ IACI use is particularly common in the management of the oligoarthritis subtype of JIA, with only non-steroidal anti-inflammatory drugs (NSAIDs) utilized more frequently.¹¹ In a recent survey of the treatment preferences of United States and Canadian pediatric rheumatologists, 90% of respondents recommended IACI as a treatment strategy for uncomplicated monoarthritis of the knee in oligoarticular JIA, and 27% of respondents recommended IACI as the initial therapy in this setting.¹²

Rationale for use

Glucocorticoids have a wide range of anti-inflammatory and immunosuppressive effects, including increased transcription of anti-inflammatory genes; inhibition of expression of multiple inflammatory genes including cytokines, enzymes, receptors, and adhesion molecules; and inhibition of T-lymphocyte activation, proliferation, and survival.¹³ However, the systemic use of glucocorticoids is associated with substantial toxicity, limiting its role in the treatment of chronic disorders such as JIA. Targeting glucocorticoids to the joint greatly reduces these systemic adverse effects while still attaining local anti-inflammatory benefits.¹⁴ Transient decreases in the serum inflammatory cytokines Interleukin (IL)-2, IL-4, IL-6, IL-7, IL-17, and tumor necrosis factor- α (TNF- α) have been demonstrated following IACI in a patient with RA, suggesting that local corticosteroid treatment also has systemic effects on key inflammatory regulators.¹⁵

Indications for IACI

Pediatric rheumatologists employ IACI to attain various goals. In the management of oligoarthritis, IACIs can be used to resolve synovitis, either as the initial and sole therapy or as a contingency therapy should NSAIDs prove ineffective.¹² IACIs are also utilized to avoid or decrease systemic therapy,¹⁶ to prevent or treat leg length discrepancies and joint contractures,^{16,17} to facilitate physical therapy and rehabilitation,¹⁸ to effect positive changes in gait,¹⁹ and to relieve pain. Additionally, IACI can have a role in the management of polyarticular disease, either administered as multiple simultaneous IACIs or as IACIs targeted to a few problematic joints, serving as a bridge while disease-modifying antirheumatic (DMARD) therapy becomes effective, as well as treating joint deformities and providing pain relief.⁴

Efficacy

Direct comparison of studies evaluating the efficacy of IACI in JIA is difficult due to the significant variability that exists in the study design; patient population; type, dose, and frequency of corticosteroid used; outcome measure employed; and length of follow-up reported. More than 15 investigations have been reported in the English language regarding the efficacy of IACI in the treatment of JIA, the vast majority of which are either retrospective chart reviews or open label studies (see Table 1). Only three studies have been reported which employed some form of randomization and blinding,²⁰⁻²² all of which compared various corticosteroid preparations. No comparison exists between a corticosteroid and placebo injection.

Complete resolution of arthritis

The most stringent primary outcome reported in studies evaluating the efficacy of IACI in JIA is that of complete resolution of all signs and symptoms of inflammation, specifically, joint effusion, heat and tenderness. This was the outcome used by Allen and colleagues in the initial prospective report of the efficacy of IACI, a noncontrolled, nonblinded study of IACI in 49 knees of 40 children with various types of chronic arthritis (including 29 children with pauciarticular JRA, a condition equivalent to oligoarthritis under the current nomenclature scheme) who had failed at least three months of aspirin treatment with or without other NSAIDs.⁹ Complete resolution of signs and symptoms of inflammation occurred in 63.3% of knees injected with 20 to 40 mg of triamcinolone hexacetonide (TH) at six months post-injection, 45% of knees at 12 months, and 16.1% of knees at 24 months.

Slightly better response rates ranging from 67% to 82% were found in subsequent studies that also evaluated for complete resolution of arthritis at six months post-IACI. In a retrospective review of 27 knees injected with 10-20 mg triamcinolone acetate (TA) in 21 patients with type 1 pauciarticular juvenile chronic arthritis (JCA), Hertzberger-Cate and colleagues reported a response rate of 70% at six months post-injection.²³ In an open label study, Ravelli and colleagues reported resolution of arthritis at six months in 69% of 94 children with JIA (including 81 patients with oligoarthritis, either persistent or extended) who had either one or both knees injected with 1 mg/kg TH, up to 40 mg.²⁴ In a smaller open label report of 35 children with oligoarthritis of the knee and two children with enthesitis-related arthritis of the knee, Lepore and colleagues found 68% of children injected with 1 mg/kg TH (maximum 40 mg) had

Table I Summary of clinical studies of IACI in JIA

Author, year	N	Study design	Steroid used	Outcome measures	Results
Allen 1986 ⁹	40	Open label	TH, 20–40 mg/joint	CCR	63.3% response at six months
Balogh 1987 ²²	23	Randomized, double-blinded	TH vs BM	Difference in knee circumference	TH: –1.7 cm BM: +1 cm
Earley 1988 ²⁷	60	Open label	TH	Reduction in inflammation	“Excellent” or “good” response in 77% at one year
Hertzberger-ten Cate 1991 ²³	21	Retrospective review	TA 10–20 mg/joint	CCR	70% response at six months
Honkanen 1993 ²⁶	79	Retrospective review	MP 1.5 mg/kg vs TH 0.7 mg/kg	Reduction in inflammation	75% response at six months
Padeh 1998 ¹⁶	71	Open label	TH 10–40 mg/joint	CCR	82% response at six months
Sherry 1999 ¹⁷	30	Open label	TH 20 mg/joint vs no IACI	LLD, thigh circumference discrepancy	IACI: no LLD, No IACI: 7 with LLD
Breit 2000 ²⁸	194	Retrospective review	TH, variable dose	Duration of improvement	Depends on subgroup of disease
Ravelli 2001 ²⁴	94	Open label	TH, 1 mg/kg	CCR	69% response at six months
Neidel 2002 ³⁹	48	Open label	TH, 1 mg/kg	CCR and radiographic remission	76% response at two years
Lepore 2002 ²⁵	37	Open label	TH, 1 mg/kg	CCR	68% response at six months
Zulian 2003 ²⁰	85	Randomized by drug availability	TH, 1 mg/kg vs TA, 1 mg/kg	Decrease in articular score $\geq 60\%$	TH: 81.4% TA: 53.3% response at six months
Zulian 2004 ²¹	37	Randomized, double-blinded	TH, 1 mg/kg vs TA, 2 mg/kg	Decrease in articular score $\geq 60\%$	TH: 89.7% TA: 61.5% response at six months
Eberhard 2004 ²⁹	85	Open label	TH 20–40 mg/joint vs TA 60–80 mg/joint	Time to relapse	TH: 10.14 mo TA: 7.75 mo

Abbreviations: BM, betamethasone; CCR, complete clinical resolution of arthritis; IACI, intra-articular corticosteroid injection; JIA, juvenile idiopathic arthritis; LLD, leg length discrepancy; MP, methylprednisolone; TA, triamcinolone acetate; TH, triamcinolone hexacetoide.

disappearance of clinical signs of inflammation of at least six months duration.²⁵ The highest rate of complete resolution of joint inflammation was reported by Padeh and Passwell in an open-label, nonrandomized evaluation, who found complete remission at six months post-IACI with 10–40 mg of TH in 82% of 300 injected joints in 71 children with chronic arthritis (including 43 children with pauciarticular JRA).¹⁶

Improvement in arthritis

Additional investigations have evaluated the efficacy of IACI based on improvement in physical signs and symptoms of arthritis without requiring complete resolution of these features. In an early retrospective review of 34 children with JCA injected with 0.7 mg/kg of TH in a knee (a lower dose than used in other studies), Honkanen and colleagues defined remission in such a way that allowed for minimal signs of inflammation to still be present.²⁶ In this study, the

more liberal definition of response did not result in significant variation from response rates reported elsewhere, with a remission rate of approximately 75% at six months from injection and approximately 60% at 12 months from injection reported. Also using an outcome definition that permitted a mild degree of abnormality to be present yet still be classified as a good response, Earley and colleagues reported higher rates of response in their experience of 83 TH injections to the knee in 60 children with pauciarticular JCA less than 10 years old, finding either an “excellent” (absence of swelling, limitation, or deformity) or “good” (slight swelling or deformity in a well-functioning knee) response in 77% of knees at one year post-injection.²⁷

Further impressive response rates were reported by Zulian and colleagues in 2003²⁰ and again in 2004,²¹ who defined response to treatment as either absence of synovitis or decrease in joint inflammation leading to a reduction of the articular

score by more than 60% from baseline. The articular score was obtained by scoring each of four variables (swelling, limitation of range of motion, pain on passive movement, and warmth) on a scale of zero to three (three being most severe), then summing the scores for each variable. In the 2003 report, 42 joints of children with oligoarticular JIA were injected with 1 mg/kg of TH (maximum 40 mg), and response rates of 81.4% at six months, 67.1% at 12 months and 60% at 24 months were reported. Of note, subjects were excluded if they had ongoing chronic disease, radiographic erosions, or had received an IACI in the preceding 12 months, potentially selecting out children with more severe disease and thus introducing a selection bias. In the 2004 report, 37 children with JIA (32 with oligoarthritis, either persistent or extended) who had symmetrical arthritis underwent injection of one joint of the symmetrical joint pair with 1 mg/kg (maximum 40 mg) of TH and injection of the other joint in the pair with 2 mg/kg (maximum 80 mg) of TA in a double-blinded fashion. Of the joints injected with TH, 89.7% were in remission at six months, 84.6% at 12 months, and 76.9% at 24 months. In this more recent report, the presence of radiographic erosions or IACI in the preceding 12 months were again exclusion criteria, however, ongoing chronic disease was not, lessening any selection bias that may have been present in the 2003 report.

Duration of response

Additional data has been gathered concerning the duration of response obtained after IACI. In the largest retrospective review of children with JCA treated with IACI, Breit and colleagues reported the experience of 194 children who received 1,439 TH injections and found a mean duration of improvement of 74 weeks.²⁸ Improvement was defined more liberally than in other studies, defined as a reduction in the inflammation score (derived from the presence or absence of six clinical variables) of at least 50% from the inflammation score prior to treatment with IACI. The duration of response differed significantly between subgroups of JCA: children with early-onset pauciarticular JCA type 1 had the longest duration of improvement at 121 weeks, while children with systemic JCA had the shortest duration of improvement at 36 weeks. Using a more stringent definition of remission (defined as complete disappearance of clinical signs of inflammation, as opposed to the definition of improvement utilized by Breit and colleagues), Lepore and colleagues reported a much shorter duration of remission of 13.9 months in a study of 37 children with oligoarticular JIA involving the knees.²⁵ In a 2004 retrospective chart review comparing time

to relapse following TH injection to time to relapse following TA injection in 85 children with all subtypes of JRA who underwent 227 IACIs, Eberhard and colleagues reported a mean time to relapse (defined as presence of an active joint as per the attending rheumatologist) of 10.14 ± 0.49 months in the group injected with TH and a mean time to relapse of 7.75 ± 0.49 months in the group injected with TA.²⁹ More recently, Marti and colleagues found a longer than previously reported median duration of remission of 23.1 months in a retrospective chart review of 60 children with various onset types of JIA who underwent IACI with either TH or TA.³⁰

Prevention of long-term sequelae

Leg length discrepancy is a well-recognized potential consequence of asymmetrical arthritis involving the lower extremities, and is thought to be due to hyperemia to the growth plates in an inflamed joint.³¹ Given that arthritis is frequently asymmetrical in oligoarthritis/pauciarticular JRA, leg length discrepancy is a particular concern in this condition. Sherry and colleagues demonstrated that early (within two months of diagnosis) and repeated IACI is associated with less leg length discrepancy.¹⁷ In this retrospective study, a group of 16 children with asymmetric pauciarticular JRA involving the lower extremity who had been managed with early and repeated IACI had no instances of unequal leg lengths, whereas seven out of 14 children from a different center who were not treated with IACI had unequal leg lengths, with a mean (\pm SD) difference between leg lengths of 1.0 ± 1.4 centimeters.

Additional cases of resolution of joint deformities with IACI have been reported. In the open label study previously discussed by Padeh and Passwell, improvement in the discordance of leg lengths in seven children with leg length discrepancy prior to treatment with IACI was demonstrated, with the average difference in leg lengths improving from 1.5 cm to 0.8 cm over the follow-up period.¹⁶ Additionally, Padeh and Passwell reported the correction of joint contractures in 55 joints of 42 children, with corrections of contractures at the knees, wrists, elbows, and fingers noted. Further, all 11 children with Baker's cysts in this study experienced complete resolution after IACI to the knee, and two children had correction of trigger fingers with IACI.

Radiographic improvement

Attempts at radiographic documentation of efficacy of IACI have at times yielded conflicting results. Two studies have used gadolinium enhanced magnetic resonance imaging (MRI) pre- and post-IACI in children with chronic arthritis

to evaluate response. In the initial study, Eich and colleagues performed MRI of 11 affected knees in eight consecutive children with oligoarticular JCA before and one month after IACI (steroid preparation and dose not given).³² Effusion and pannus were present in all knees prior to treatment; effusion resolved in seven knees and pannus in four knees following IACI. Three children had popliteal cysts present prior to IACI; the cysts resolved in two of the children after IACI, but persisted in one child whose cyst had ruptured. One child had apparent replacement of the articular cartilage with enhancing pannus at the lateral and medial femoral condyles before treatment that resolved almost completely one month after IACI. Four hips were also injected and evaluated in two patients (one with polyarticular JCA and one with systemic JCA) in this same report, with less efficacious response. Pannus persisted in three of the four hips injected, and the two hips with evidence of destruction of articular cartilage prior to IACI showed no improvement at one month post-IACI.

In a similar study, Huppertz et al showed better, but not complete, responses to IACI.³³ Radiographic improvement in the extent of articular inflammation following IACI was demonstrated in a prospective evaluation of 21 consecutive children with chronic arthritis who underwent MRI prior to intra-articular injection of 1 mg/kg TH (maximum 60 mg) and at approximately seven weeks and 13 months after IACI. The MRI appearance of all joints examined was improved both at seven weeks and 13 months post-injection, with completely normal MRI studies in 11 joints at seven weeks but in only two joints at 13 months. Eight joints had residual effusion and eight joints had residual synovial enhancement at seven weeks. At 13 months after injection, six joints had slight effusions, 11 joints had synovial enhancement, and two joints had pannus, however, all joints were noted to be better than before the injection.

Magnetic resonance imaging (MRI) studies in adults with RA have documented less consistent improvements after IACI. In one study, although synovial enhancement and the median volume of synovial effusion was significantly decreased one week after injection with TA, the synovial pannus was not affected significantly, and the synovial volume actually increased in two patients.³⁴ In a second study in adults with RA, two out of six subjects had reduction in pannus width and decrease in total synovial fluid volume following IACI to the knee, while the other four subjects had minimal changes in fluid and synovium over the four week follow-up period.³⁵ More recently, Boesen and colleagues demonstrated no improvement by either ultrasound or MRI four weeks after intra-articular injection of the wrist with

40 mg methylprednisolone in 12 patients with wrist disease resistant to DMARD therapy.³⁶ It may be possible that the absence of response seen was related to the use of an inferior steroid preparation for intra-articular deposition, however, the systemic nature of the disease may also have contributed to the poor response seen to localized therapy.

Other benefits

Additional anecdotal benefits of IACI have been reported. In the report by Padeh and Passwell, 60% of children were able to discontinue all oral medications following IACI, limiting potential toxicity and inconvenience.¹⁶ A transient remission of systemic manifestations following intra-articular TH injection was reported in a boy with systemic-onset JIA.³⁷ Positive effects have also been reported in joints that were not injected in patients that underwent IACI at other sites, including improvement in gait pattern at uninjected joints.¹⁹ Presumably these more distant effects are secondary to systemic actions of the steroid. Further, although the majority of reports of the use of IACI in the treatment of JIA focus on injections of the knee, IACIs have been shown to be useful in the treatment of arthritis of other joints, including the hip,³⁸⁻⁴⁰ subtalar joints,⁴⁰⁻⁴³ wrist,⁴⁴ and temporomandibular joints.^{45,46}

Factors affecting outcome

Technical aspects

One of the most important technical factors affecting the success of an IACI is the corticosteroid preparation used, with excellent evidence supporting the use of TH as the preparation of choice (Table 2). In the 1970s, investigations comparing various steroid preparations were carried out in adults with RA. Bird and colleagues reported a double-blinded comparison of prednisolone t-butyl acetate, methyl prednisolone acetate, and TH used to treat adult RA patients with synovitis of the knee and found that TH injection resulted in significantly greater initial improvement and more durable improvement in joint inflammation as assessed by thermogram than the other steroid preparations.⁴⁷ In the first double-blinded comparison of steroid preparation reported in children, TH was superior to betamethasone in reducing knee swelling and stiffness in children with oligoarticular disease.²² Honkanen and colleagues compared the results of 45 children with various types of JCA injected at the knee with 1.5 mg/kg methylprednisolone to 34 children injected with 0.7 mg/kg of TH and found the overall probability of a patient staying in remission was considerably higher in the TH group.²⁶ More recently, Zulian and colleagues reported

Table 2 Summary of features possibly affecting outcome after IACI

I. Technical aspects
A. Steroid preparation used
B. Dose of steroid
C. Radiographic guidance
D. Adequate anesthesia
E. Post-injection care
II. Patient and disease characteristics
A. Disease subtype
B. Specific joint injected
C. Patient sex*
D. Patient age*
E. Disease duration*
F. Higher ESR*
G. % PMNs in synovial fluid*
H. Higher level synovial fluid macrophage inhibitory factor
I. ANA status*
J. Concomitant medications
K. Initial treatment vs. re-treatment*

Note: *Conflicting data amongst studies.

Abbreviations: ANA, anti-nuclear antibodies; ESR, erythrocyte sedimentation rate; IACI, intra-articular corticosteroid injection; PMNs, polymorphonuclear leukocytes.

better response rates with TH than TA in 85 children with oligoarticular JIA injected with the preparation available for use at the time of treatment.²⁰ Response rates at 6, 12, and 24 months were 81.4%, 67.1%, and 60% when TH was used, compared to 53.3%, 43.3%, and 33.3% with TA, respectively. Further, in the double-blinded study comparing TA at twice the dose of TH in children with symmetrical arthritis (one joint of the joint pair injected with TH, the second joint in the pair injected with TA at twice the dose), Zulian and colleagues found that TH remained superior to TA even when the TA dose was doubled.²¹ In this report, the joint injected with TA relapsed first in 53.8% of the joints injected, whereas only six (15.4%) of the joints injected with TH relapsed first. Eberhard and colleagues reported longer time to relapse with TH when compared to TA in a retrospective chart review of 227 joints injected, finding a mean time to relapse (\pm SE) of 10.14 ± 0.49 months in the TH group versus 7.75 ± 0.49 months in the TA group.²⁹ Marti and colleagues also confirmed the superiority of TH over TA for IACI of the knees in a retrospective review.³⁰ The greater efficacy of TH in intra-articular injections can likely be explained by its lower solubility and slower absorption compared to TA, thus maintaining synovial levels for a longer time and creating lower systemic corticoid levels.⁴⁸

Other than the comparison of TA at twice the dose to TH, no studies have prospectively evaluated different dosing

regimens in children. In the study by Allen, dosing of TH was not specified but ranged from 20–40 mg per knee; a dose-dependent relationship to response was reported, with a higher mean dose in the response group (1.08 mg/kg) compared to the relapse group (0.65 mg/kg).⁹ In general, the accepted doses used for TH are 1 mg/kg for large joints (knees, hips, and shoulders), 0.5 mg/kg for smaller joints (ankles, wrists, and elbows), 1–2 mg/joint for metacarpophalangeal joints and metatarsophalangeal joints, and 0.6–1 mg/joint for proximal interphalangeal joints.⁵

Undoubtedly, the specific technique and procedures utilized during the administration of an IACI have a large impact on the success of the therapy; however this is a very difficult aspect to assess due to the large variations in technique that occur in individual practices.⁴⁹ In an interesting evaluation performed with adult providers in which radiographic contrast medium was mixed with the steroid preparation and a plain radiograph was taken following the IACI to document the location of the injected material, only 56 of 108 joint injections (52%) were documented to result in accurate intra-articular placement of the steroid.⁵⁰ Although similar provider-specific practices have not been assessed expressly in pediatric providers, it is conceivable that similar rates of inaccuracy would apply. Radiographic guidance has been shown to improve the accuracy of IACI, particularly in less visually accessible joints, such as the

subtalar and temporomandibular joints. In a report of 11 consecutive JCA patients that underwent clinical and MRI evaluation of the tibiotalar and subtalar joints, MRI-guided IACI resulted in at least six months remission in 6 of 9 ankles injected, compared to 1 of 10 ankles which had been previously treated with unguided IACI.⁴³ Additionally, a retrospective review of 38 children with all subtypes of JIA who underwent 55 fluoroscopically-guided IACIs of the subtalar joints demonstrated improvement after 89% of the injections with a mean duration of improvement of 1.2 years.⁴² Adequate relaxation and anesthesia are also essential to obtaining an accurate IACI,⁵ and multiple methods of sedation for younger children, including use of local anesthetics, benzodiazepines,⁴ ketamine and propofol,⁵¹ nitrous oxide,⁵² and general anesthesia have been employed. In fact, the use of general anesthesia has been associated with a longer duration of IACI-induced remission than other types of anesthesia or no anesthesia in a subgroup analysis of knee IACI in children with JIA.³⁰

As with the specific injection procedures, considerable practice variation exists regarding post-IACI care and activity recommendations. Various recommendations that have been suggested include complete bed rest, nonweight bearing, full-time splint use, and return to usual activities. This topic has been the subject of a systematic review,² however, no controlled studies of rest or splints have been pursued in children. In fact, many of the previously discussed studies regarding the use of IACI in JIA do not report what post-IACI care was utilized. In the adult literature, a randomized controlled trial of bed rest versus no bed rest following IACI of the knee in 91 adults with inflammatory arthritis found that the rested group had significant improvement in pain, stiffness, knee circumference and walking time over the nonrested group.⁵³ Resting of the wrist post-IACI, however, does not appear to be beneficial. In a randomized controlled trial of rest versus no rest in 117 adults with RA who underwent IACI of the wrist, the relapse rate was higher in the rested group, and there was no difference between the two groups in terms of pain, joint circumference, wrist function, grip strength, or range of motion.⁵⁴

Patient and disease characteristics

Several of the studies of the efficacy of JIA discussed above included post hoc analyses attempting to identify demographic, clinical, or laboratory features that were associated with response to IACI; the majority of these analyses have yielded conflicting results, likely due to small sample sizes. A single prospective study of 94 patients

reported by Ravelli and colleagues used logistic regression to identify predictors of the clinical response to IACI of the knees in children with JIA, and found that children with a higher erythrocyte sedimentation rate (ESR) were more likely to have a sustained response to IACI.²⁴ In general, data associating patient and disease characteristics with the outcome of IACI are scarce and insufficient to support any definitive conclusions.

Demographic characteristics have not been shown to have a replicable association with IACI outcome. Allen and colleagues found a statistically significant more frequent good response in males with JRA,⁹ however, Breit and colleagues reported a better response to IACI in girls (median duration of effect 78 weeks) than in boys (median duration of effect 54 weeks);²⁸ additional studies found no relationship between patient sex and response to IACI.^{20,23} Patient age at disease onset has not been found to be a predictive feature.^{20,23,25,26} Younger patient age at time of treatment was associated with good response in the study by Allen, with a mean age (\pm SD) of 8.75 ± 4.78 years in the response group versus 14.39 ± 4.45 years in the relapse group;⁹ no association between response and age at time of treatment was identified in other studies.^{20,26,27} No studies have evaluated the effect of race or ethnicity on response to IACI.

The onset type of JIA has been convincingly demonstrated to have an important impact on the duration of efficacy of IACI in children with JCA. In the large retrospective chart review of 1,439 TH injections in 194 children with all subtypes of JCA reported by Breit and colleagues, duration of improvement after IACI was significantly different between arthritis subgroups.²⁸ While all subgroups showed some degree of efficacy, early-onset pauciarticular (EOPA) JCA type I patients had the longest duration of improvement at 121 weeks, followed by rheumatoid factor (RF) negative polyarticular JCA patients at 105 weeks, then RF-positive polyarticular JCA patients at 63 weeks, then late-onset pauciarticular JCA patients at 47 weeks, and, finally, systemic JCA patients with the shortest duration of improvement at 36 weeks. However, these results were not confirmed in the retrospective chart review by Marti and colleagues, who found a longer duration of response in children with enthesitis-related arthritis (ERA), although only four children with ERA were included in the study.³⁰ Further, Honkanen and colleagues did not find onset type to be predictive of length of remission after IACI, however, in his group of 79 study subjects, only one child had systemic JCA, making it unlikely that such an association would be found.²⁶

Duration of disease and initial treatment versus treatment of relapse have both been demonstrated to have associated with IACI outcome in some reports, but not confirmed by others. Lepore and colleagues found that children treated within six months of disease onset were more likely to experience an IACI-induced remission than those patients with more long standing disease.²⁵ Both Allen and colleagues and Hertzberger-ten Cate also found a shorter duration of disease to be associated with better response to IACI,^{9,23} however, Zulian and Honkanen found no such relationship.^{20,26} Likewise, the data regarding whether an IACI given as a first injection versus a re-treatment impacts the efficacy of the IACI are conflicting. Zulian and Allen found no difference in response whether the IACI was an initial treatment or re-treatment,^{9,20} yet Breit and colleagues found that efficacy (as determined by duration of improvement) decreased with each subsequent re-injection.²⁸

Although the majority of studies of the efficacy of IACI in JIA concern injections to the knees in particular, reports that include injections of other joints suggest that the specific joint injected appears to impact the efficacy of the IACI. Breit and colleagues reported that the duration of improvement following IACI depended on which joint was injected, with the duration of effect for each joint again varying significantly among onset type of JCA.²⁸ In patients with EOPA JCA, knees had the longest duration of improvement; in all other types of JCA, hands and feet joints had the longest duration of improvement. Specifically within the EOPA group, knees had the longest median duration of response (120 weeks), followed by hand joints (>77 weeks), then ankles (72 weeks), feet (>68 weeks), elbows (>67 weeks), wrists (>55 weeks), shoulders (>52 weeks), and hips (>48 weeks). However, no significant difference in median duration of effect in joints of the upper extremity compared to those of the lower extremity was found. This contrasts to the report by Marti and colleagues, in which injection of joints of the upper extremity had a longer duration of remission.³⁰ In the 2003 report by Zulian and colleagues in which either knees or ankles were injected in children with oligoarthritis, ankles showed a significantly worse response than knees at all time points evaluated.²⁰

Investigations have been pursued with the goal of identifying laboratory parameters at the time of treatment that predict response to IACI. Of these, only the report by Ravelli and colleagues described above investigated this aim in a prospective manner, using logistic regression to identify higher ESR as the only factor evaluated associated with a sustained clinical response.²⁴ The authors suggested that JIA patients who had higher ESR had a synovial inflammatory

process that was more sensitive to IACI than children with lower ESR. Patients with a high proportion of polymorphonuclear leukocytes (PMNs) in the synovial fluid were found to have significantly shorter remissions than patients with lower proportions of PMNs in the synovial fluid in the report by Honkanen and colleagues.²⁶ Conversely, Padeh and Passwell found no significant differences in the ESR, synovial and peripheral white blood cell counts and percentage of PMNs between the IACI responder and nonresponder groups.¹⁶

Immunologic and genetic features have also been investigated with regards to possible associations with IACI response. Macrophage migration inhibitory factor (MIF), an immunostimulatory and pro-inflammatory cytokine, has been demonstrated to be functionally relevant in regards to response to IACI, with higher synovial fluid levels of MIF inversely correlated with duration of response to IACI in patients with oligoarticular and systemic-onset JIA;⁵⁵ further, the presence of the MIF-173*C polymorphism in children with systemic-onset JIA was associated with a significantly shorter duration of response to TH injection (and with other surrogates of poor outcome) than in systemic-onset JIA patients without the allele.⁵⁶ The absence of anti-nuclear antibodies (ANA) was found to be associated with a better response in children with oligoarthritis/EOPA by both Lepore and Breit,^{25,28} leading to speculation that the presence of ANA signifies more immunologically active disease that is less responsive to IACI; other studies found no association with ANA status and response to IACI.^{9,20,23} Further, no difference in the distribution of human leukocyte antigen (HLA)-A, -B, or -DR antigens between IACI responders and nonresponders was found by Allen and colleagues,⁹ although Breit and colleagues found that HLA-B27 negative children responded better to IACI than those children with HLA-B27.²⁸

It is reasonable to assume that the use of concomitant medications would influence the outcome to IACI, unfortunately, the majority of published studies do not account for this variable. However, a recently published retrospective review did analyze this covariate, and, in fact, found concomitant use of methotrexate to be the strongest predictive factor in the study and highly significantly associated with a longer duration of remission to IACI.³⁰

Safety

Early animal studies demonstrating decreased synthesis of collagen and proteoglycans with the development of fissures and cysts leading to destruction of rabbit articular cartilage following IACI of hydrocortisone acetate in a dose-dependent manner initially gave reason to question

the safety of using IACI as a treatment approach (Table 3).⁵⁷ However, subsequent experiments evaluating the effect of IACI with methylprednisolone on primate cartilage (Macaca irus monkeys) found no change in the joints injected with corticosteroids compared to joints that received control injections.⁵⁸ Since these early animal studies, radiographic studies have not demonstrated deleterious effects of IACI on human cartilage. In the report by Eich and colleagues, MRI and ultrasonography performed in children with JRA prior to IACI and one week and one month post-IACI demonstrated no evidence of destruction of ligaments, avascular necrosis, or other cartilage damage post-IACI.³² Further, Huppertz and colleagues confirmed these results, finding no evidence of toxic effects of IACI on cartilage in 21 children with JRA who underwent MRI before and seven weeks after IACI.³³

Radiographic studies have also demonstrated other, generally clinically insignificant, findings after IACI. In a blinded retrospective review of 39 children with JRA who received 92 IACI, joint calcifications were found to be a potential consequence of IACI, with 20 children exhibiting joint calcifications by plain radiographs. All of the calcifications were incidental findings and were asymptomatic except for one calcium deposit in a 16-year-old girl's knee that had broken into the joint as a loose body, causing pain and locking in the knee and requiring surgical excision.⁵⁹ The location of the calcifications was related to the site of the needle perforation, and the calcifications were more likely to occur periarticularly or in the joint capsule, rather than intra-articularly. Job-Deslandre and Menkes reported the rate of intra-articular calcifications to be 4.9% in their series of 48 children with JRA or HLA-B27 associated arthritis treated with IACI.⁶⁰ In a retrospective review of radiographs of 145 joints of 55 children with chronic arthritis treated with intra-articular TH by Sparling and colleagues, the rate of possible deleterious effects was low, noted in 16 joints of 11 children, including nine joints with periarticular calcifications.⁶¹ Other possible radiographic effects of IACI reported in this study

included small patella (two joints), patellar osteochondritis dissecans (one joint), intra-articular tibial bone spur (one joint), avascular necrosis (AVN) of the distal radial epiphysis (two joints), and AVN of the proximal femoral epiphysis (one joint); only the case of femoral AVN was symptomatic and radiographic abnormalities were present prior to the IACI. The authors concluded that the use of IACI was not associated with any significant joint damage, with many of the radiographic findings consequences of chronic arthritis that could also be seen in children who had not received IACI.

The most well-recognized and common adverse effect seen after IACI is that of subcutaneous atrophy with or without hypopigmentation at the injection site. The reported rates of subcutaneous atrophy vary depending on the series, ranging from 0%²⁶ to 10%,²⁵ with the majority of series reporting a rate of subcutaneous atrophy between 1%–4%. In an early report of severe cutaneous atrophy at the site of IACI in eight adult patients with RA compared to results obtained after injecting the same corticosteroid preparations into the skin of rabbits, higher potency, concentration, and volume of injected corticosteroid were related to the development of atrophy.⁶² Injection techniques that allowed leakage of the steroid into the subcutaneous tissues and injection of small joints with less extra-articular tissues were also related to the development of atrophy. This knowledge has led some practitioners to use more soluble steroid preparations, such as betamethasone or methylprednisolone, in place of TH when injecting small joints of the hands and feet. This complication appears late, often six months or later after the IACI,²⁸ and frequently undergoes spontaneous resolution,^{16,25,62} although persistent atrophy of up to four years duration have been reported.⁶⁰

Potential complications that are inherent to all types of injections and are not particular to IACI have been reported, primarily in adults, and include injection site bleeding, injection site pain, and syncope proximate to the timing of the injection.⁶³ These potential complications are readily manageable, and, in fact, are often preventable if proper technique and adequate anesthesia are employed.

An inflammatory reaction characterized by acute increase in pain, swelling and redness occurring in the first 24 hours after an IACI is a rare, but well-documented adverse reaction to IACI. It is likely due to the intra-articular formation of corticosteroid crystals that incite a reactive synovitis, and is thus termed "crystal synovitis."⁶⁴ Also referred to as "steroid flare," intra- and extra-cellular rod-shaped crystals have been demonstrated in the synovial fluid post-IACI by compensated polarized microscopy, and increased synovial

Table 3 Adverse events related to IACI reported in children

1. Peri-articular calcifications
2. Subcutaneous atrophy at injection site
3. Hypopigmentation at injection site
4. "Crystal synovitis"
5. Transient suppression of endogenous cortisol production/exogenous hypercortisolism
6. Avascular necrosis of the femoral head
7. Difficulty maintaining glucose control in diabetic children

Abbreviation: IACI, intra-articular corticosteroid injection.

white blood cell counts (predominantly PMNs) post-IACI are well-documented.⁶⁵ Post-IACI inflammatory flare is reported in approximately 1%–2% of adult patients,⁶⁶ and is felt to be more common with earlier steroid preparations, such as hydrocortisone acetate, but has also been reported with TH. Crystal synovitis has also been reported in children,^{16,23} and is self-limited with resolution in three to five days with supportive care, including NSAIDs and rest.

Intra-articularly administered TH has been documented to be detectable in the sera of adults for up to three weeks post-IACI⁶⁷ and intra-articularly administered TA has been demonstrated in the plasma and urine of children 4–5 months post-IACI,⁶⁸ prompting concern for the potential of systemic adverse effects. In fact, symptomatic suppression of the hypothalamic–pituitary–adrenal axis in an adult with RA following long-term use of IACI every eight weeks for an eight year time period has been reported.⁶⁹ Transient suppression of endogenous cortisol production following single IACI treatment was documented by Huppertz and Pfuller in 22 children with chronic arthritis, all of whom had morning cortisol levels that were depressed below the lower limit of normal by salivary samples obtained shortly after IACI.⁷⁰ All of the cortisol levels returned to normal within seven weeks of the IACI, and in the 11 children for whom data were available, the median time to return to normal cortisol levels was 16 days. No adverse effects related to steroid withdrawal or excess were reported. Although no symptoms related to hypercortisolism were reported in this series, the use of multiple (>10) IACI has been associated with Cushingoid features in children with polyarticular disease due to increase systemic steroid absorption,⁷¹ and Kumar and colleagues reported the case of a 9-year-old girl who developed fullness and flushing of the face, a dorsocervical hump, striae and weight gain after multiple IACI (total dose 120 mg TA) lasting for five months.⁶⁸ Systemic effects of hypercortisolism have also been reported after a single IACI, including facial flushing, increased appetite, mood changes, weight gain, striae, and easy bruising.^{30,68} It is likely that the effects of IACI on adrenal suppression and cortisol excess are decreased when TH is the steroid preparation used instead of TA. Suppression of endogenous cortisol suppression at four weeks post-IACI was least marked with TH in comparison to other corticosteroid preparations,⁴⁷ likely due to its increased intra-articular residence (and thus decreased systemic absorption). Further, in a retrospective review of 195 children who received IACI with either TA or TH, 5% of children who received TA had visibly prominent Cushing's syndrome, while no children who were injected

with TH had Cushingoid features, even when multiple joints were injected.⁷²

Other potential systemic effects of intra-articularly administered corticosteroids should be considered. Children with type 1 diabetes mellitus may potentially experience transient difficulty maintaining blood glucose control if multiple IACIs are administered.⁷³ Allergic reactions, ranging from mild hives to anaphylactic shock, have been reported in adults immediately after treatment with IACI, with skin prick and intradermal testing confirmatory of allergy to the corticosteroid preparation and not to co-administered vehicles or anesthetics;^{74,75} no such allergic reactions have been reported to date in children. Although transient (less than 1–2 weeks) suppressive effects on leg growth measured by knemometry have been anecdotally reported,⁷⁶ no cases of growth suppression due to IACI therapy have been reported. In fact, in the 1995 report by Huppertz, after one year of follow-up post-knee IACI, there was no effect on statural growth.³³

Intra-articular infection perhaps remains one of the most worrisome theoretical complications of IACI, but to date, there have been no cases of septic arthritis reported in children post-IACI. The reported risk of septic arthritis post-IACI in adults is 0.002% (out of 100,000 procedures),¹⁴ but nonetheless, strict aseptic procedure must be a priority to prevent this serious complication. Anecdotally, a case of a septic ankle developing 48 hours after an IACI to the knee in a child with an intercurrent respiratory infection has been reported.⁷⁷

Mechanical consequences of IACI have also been reported, most commonly after hip injections. AVN of the femoral head following IACI was reported in two children in a series of 48 children with JRA treated with IACI for coxitis.³⁹ Both children had long-standing disease (systemic JRA and RF-negative polyarthritis) requiring systemic corticosteroid therapy and repeated IACI who developed AVN 44 and 21 months after the last hip injection. The first child also developed necrosis of the humeral head which was not injected, so it is likely that the AVN was due to chronic synovitis or systemic steroid use rather than the IACI, as AVN of the femoral head is a well-recognized complication of arthritis of the hip in the absence of IACI treatment. Breit and colleagues also reported a single episode of AVN of the hip three months post-IACI in a child with systemic JCA and pre-existing osteoarthritis.²⁸ This child was unable to walk prior to the IACI, and the authors suggested that it was the return of her ability to walk with increased physical activity post-IACI that led to the progressive joint destruction

following the IACI. In a different series of intra-articular hip injections in children with JCA, no cases of AVN were reported in the 37 hips with at least 12 months of follow-up or in the 20 hips with at least 24 months of follow-up.³⁸ An interesting anecdotal case of bilateral shoulder subluxations in a 14-year-old girl with RF-positive polyarticular JCA that occurred 2 days after bilateral shoulder IACI has been reported.²⁸ This child also had long-standing arthritis with radiographic changes noted in the shoulders prior to receiving IACI; the authors speculated that the reduction of joint inflammation with decreased synovial thickening and intra-articular effusion lead to joint instability and the subluxation.

Finally, although it has not been studied in a controlled fashion, the use of repeated injections to an individual joint appears to be safe and has not been associated with adverse outcomes.⁶ Repeated IACI are used by some in clinical practice, and in the report by Sherry and colleagues comparing leg length discrepancies in children treated with IACI to those who did not receive IACI, almost all children in the IACI group received subsequent injections; the maximum time any individual joint was injected was 4. No adverse events related to multiple IACI were reported.¹⁷ In a small report of three children with oligoarticular JCA who required repeated IACI (ranging from 11–14 IACI per child), MRI performed 6–13 years after treatment revealed no deleterious effects.⁷⁸ Occasional reports of clinical and radiographic changes similar to those seen in Charcot-like (neuropathic) arthropathies have been reported in adults after repeated IACI relieved pain and facilitated overuse of a joint, leading to trauma to the joint;⁷⁹ this phenomenon has not been reported in children.

Conclusions

IACI is a safe and effective treatment option in the management of JIA, particularly in the management of oligoarthritides. It has been well-demonstrated that use of IACI can control disease activity and induce resolution of synovitis, decrease the presence of joint and limb deformities, improve function, provide pain relief, and serve as an adjunct to minimize more toxic treatments. Various technical aspects, patient characteristics, and disease features impact the efficacy of IACI, although conclusive data that elucidates these factors are scarce. Extensive data regarding the incidence of adverse effects related to IACI support the assertion that IACI is a safe treatment option, with the majority of reported adverse effects being of minimal clinical significance. Definitive studies are needed to identify factors associated with response

to IACI so that this treatment modality may be utilized to optimum effectiveness.

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