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The impact of early intra-articular corticosteroid injections on the outcome of oligoarticular juvenile idiopathic arthritis

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The impact of early intra-articular corticosteroid injections on the outcome of oligoarticular
juvenile idiopathic arthritis

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Résumé

Contexte Un objectif important de la prise en charge de l'arthrite juvénile oligoarticulaire serait d'altérer le cours de la maladie à l'aide d'une thérapie hâtive. Nous avons étudié l'effet des injections intra-articulaires de corticostéroïdes hâtives sur les chances d'atteindre un décompte d'articulation active de zéro et une maladie inactive.

Méthode Les données démographiques, cliniques et thérapeutiques des patients avec oligoarthrite juvénile enrôlés dans une étude prospective longitudinale pancanadienne ont été collectées pendant 2 ans. Une injection hâtive était définie comme étant reçue dans les 3 premiers mois suivant le diagnostic. Les équations d'estimation généralisées ont été utilisées pour l'analyse statistique.

Résultats Trois cent dix patients ont été inclus. Cent onze (35.8%) ont reçu une injection hâtive. Ces derniers avaient une maladie plus active lors de l'entrée dans l'étude. Les patients exposés à une injection hâtive avaient une chance similaire d'obtenir un décompte d'articulation active de zéro, OR 1.52 (IC95% 0.68-3.37), p=0.306 mais étaient significativement moins à risque d'avoir une maladie inactive, OR 0.35 (IC95% 0.14-0.88), p=0.026.

Interprétation Dans cette cohorte de 310 patients avec oligoarthrite juvénile, les injections hâtives de corticostéroïdes n'ont pas mené à une probabilité plus élevée d'atteindre un décompte d'articulation active de zéro ou une maladie inactive. Des problématiques méthodologiques intrinsèques à l'utilisation de données observationnelles pour fins d'estimation d'effets thérapeutiques auraient pu biaiser les résultats. Nous ne pouvons affirmer avec certitude que les injections hâtives n'améliorent pas le décours de la maladie. Des études prospectives adressant les limitations soulevées seront requises pour clarifier la question.

Mots-clés : Arthrite juvénile idiopathique, oligoarticulaire, injection intra-articulaire de corticostéroïdes, traitement hâtif, décompte d'articulation active de zéro, maladie inactive, pronostic.

Abstract

Background One of the goals in oligoarticular juvenile idiopathic arthritis would be to alter the disease course with early therapy. We examined the association between early intra-articular corticosteroid injections and the achievement of an active joint count of zero and inactive disease during the first two years after study enrollment.

Methods We included oligoarticular juvenile idiopathic arthritis patients enrolled into a prospective longitudinal cohort across Canada. Demographic, clinical and treatment-related information were collected. Early intra-articular corticosteroid injections was defined as having received the first injection within 3 months of diagnosis. Generalized estimating equations were used for data analysis.

Results A total of 310 patients were included, of whom 111 (35.8%) received an early injection. Participants who received an early injection had more severe disease at baseline. Patients exposed to early injections had a similar chance to achieve an active joint count of zero, OR 1.52 (95%CI 0.68-3.37), p=0.306 but were significantly less likely to achieve inactive disease, OR 0.35 (95%CI 0.14-0.88), p=0.026.

Interpretation In this cohort of 310 oligoarticular juvenile idiopathic arthritis patients, early intra-articular corticosteroid injections did not result in an increased risk of achieving an active joint count of zero or inactive disease. Methodological issues encountered when estimating treatment effect using observational data might have biased the estimates obtained. Firm conclusion on the inefficacy of early injections in improving outcomes in this population cannot be drawn from this study. Prospective studies addressing the limitations raised will be needed to clarify if early injections can alter the disease course.

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Abbreviations

ANA	Antinuclear antibody
BeSt	Behandel Strategieën
CAPS	Childhood Arthritis Prospective Study
CHAQ	Childhood Health Assessment Questionnaire
95%CI	95% confidence interval
DMARDs	Disease-modifying antirheumatic drugs
ESR	Erythrocyte sedimentation rate
F	Female
GEE	Generalized estimating equation
IAS	Intra-articular corticosteroid injection
IQR	Interquartile range
JIA	Juvenile idiopathic arthritis
M	Male
MAR	Missing at random
MCAR	Missing completely at random
MNAR	Missing not at random
MP	Methylprednisolone
MTX	Methotrexate
N	Number
n/a	Not available
NDAIDs	Nonsteroidal anti-inflammatory drugs
Oligo-JIA	Oligoarticular juvenile idiopathic arthritis
OR	Odds ratio
Patient Global	Patient global assessment of overall well-being
Pauci	Pauciarticular
PGADA	Physician global assessment of disease activity
RA	Rheumatoid arthritis
ReACCh Out	Research in Arthritis in Canadian Children Emphasizing Outcomes
Oligo-JIA	Oligoarticular juvenile idiopathic arthritis

TA	Triamcinolone acetonide
TH	Triamcinolone hexacetonide
TREAT	Trial of Early Aggressive Therapy in Polyarticular Juvenile Idiopathic Arthritis

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Chapter 1: Introduction

1.1 Juvenile idiopathic arthritis

Juvenile idiopathic arthritis (JIA) is the most frequent rheumatological disease in children (1). It is defined as arthritis of unknown etiology that begins before the 16th birthday and persists for a minimum of 6 weeks (2). In developed countries, the prevalence is estimated at 16-150 cases per 100 000 children (3). The Canadian Pediatric Surveillance Program revealed that from 2007-2009, the annual incidence of JIA in Canada was 4.3 per 100 000 children (4). JIA is an umbrella term encompassing several distinct subtypes of childhood onset arthritis. The current classification, based on clinical features as well as autoantibody profile, consists of 7 different subtypes: systemic-onset JIA, oligoarticular JIA (oligo-JIA), rheumatoid factor negative polyarticular JIA, rheumatoid factor positive polyarticular JIA, psoriatic arthritis, enthesitis related arthritis and undifferentiated arthritis. Oligo-JIA is the subtype most commonly encountered.

The pathogenic steps leading to the development of JIA remain to be characterized. It likely results from an interplay of genetic predisposition, hormonal factors and diverse environmental exposures leading to dysregulation of the immune system. Genome-wide level of significance have been shown for diverse genetic loci, including HLA, PTPN22 and PTPN2 (5, 6). The sex ratio difference seen for most JIA subtype and peak age of onset suggest that the hormonal system is part of the pathogenesis (7, 8). Infectious agents represent the main suspect among environmental factors, although no clear causal link has been established with one specific pathogen (9-12).

1.2 Oligo-JIA

The oligoarticular subtype represents 27-56% of JIA (3). It is characterized by involvement of ≤ 4 joints during the first 6 months of disease. There are 5 exclusion criteria for this subtype 1) psoriasis or a history of psoriasis in the patient or a first-degree relative, 2) HLA B27 in a male whose arthritis started after the 6th birthday, 3) ankylosing spondylitis, enthesitis related

arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome or acute anterior uveitis or a history of one of these conditions in a first-degree relative, 4) positive IgM rheumatoid factor on 2 occasions at least 3 months apart and 5) systemic-onset JIA. The oligo-JIA subtype is further characterized by the number of joints affected after the first 6 months of disease. The persistent course implies that no more than 4 joints are affected during the entire disease course. The extended course applies to those who develop arthritis in >4 joints after the initial 6 months of disease. The risk of progression to an extended course is higher in the first years following diagnosis. Involvement of the hand, wrist, cervical spine, ankle, symmetric disease, having 2-4 active joints, erythrocyte sedimentation rate (ESR) $\geq$ 20 mm/hour and having a positive antinuclear antibody (ANA) in the first 6 months are factors that have been shown to be associated with an extended disease course (13, 14). This sub-classification is not just semantic as long term prognosis seems less favorable in children with an extended course (15).

Girls are more commonly affected than boys, with a 3:1 ratio in Caucasians. The peak age of onset is at 1-2 years old (1). Joints of the lower limbs are more frequently affected than those of the upper limbs or of the axial skeleton. Warmth, swelling, tenderness on palpation or pain with mobilisation are typical physical examination findings. The majority of patients are ANA positive (65-85%) (1). This autoantibody is especially prevalent in younger girls and in patients who have or will develop uveitis. The later is one of the only extra-articular manifestation seen in oligo-JIA.

1.3 Disease course and prognosis of oligo-JIA patients
Although often regarded as the subtype with the best prognosis, oligo-JIA is a chronic disease. A subset of patients will remain with prolonged active disease with ongoing need for systemic medications for years after diagnosis. A recent study comprising 416 Canadian children with oligo-JIA reported that only 7.6% achieved disease remission in the first 2 years following study entry (16). At 5 years, the proportion of patients in remission was 57.6%. The probability to be off medication was 15.5% and 80.7% at 1 and 5 years, respectively. Fantini et al. reported remission rates of 420 oligo-JIA patients attending one Italian center during a

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median (range) observation period of 6.2 (0.5-35.0) years (17). One hundred and forty-two (33.8%) patients were in remission at the last study visit and 55 (13.1%) had been in remission at one point during the study but were not in remission at the last assessment. It is interesting to note that 223 (53.1%) oligo-JIA patients never achieved remission during the study period. In the Nordic Cohort Study, a prospective multicenter JIA cohort, 440 children with JIA were reassessed after a median (range) time of 98 (84-147) months following disease onset (18). The median (interquartile range- IQR) active joint count was 0 (0-0) and 0 (0-1) among the 132 oligo-persistent and 78 oligo-extended JIA patients. Among the 126 oligo-persistent JIA patients for which information was available, 83 (65.9%) were in remission off medications, 4 (3.1%) were in remission on medication and 39 (31.0%) were not in remission. As expected, proportions were different for the oligo-extended subgroup with 16 (21.3%), 12 (16.0%) and 47 (62.7%) children who were in remission off medication, in remission on medication and not in remission, respectively. Another study reported remission data on 167 oligo-persistent and 91 oligo-extended JIA followed for a minimum of 4 years at 3 tertiary care pediatric rheumatology centers (19). Clinical remission on and off medication were found in 60% and 68% of oligo-persistent patients and 81% and 31% of oligo-extended patients, respectively. The median (IQR) length of active disease before patients achieved the first episode of inactive disease was 17 (9-27) months for oligo-persistent and 22 (13-54) months for oligo-extended JIA patients. Once the disease becomes inactive, the risk of disease flare remains, even after years of quiescence. A study of 224 patients with oligo-JIA reported that the median (range) time to flare after the disease was brought under control was 5.2 (2.1-13.4) years (20). These large studies highlight the fact that oligo-JIA must be considered a chronic disease. There is a definite need to optimize therapeutic management of these patients to allow more children to achieve and stay into prolonged remission.

Anatomic damage, functional impairment, quality of life, educational and work status are other aspects that come into play for the prognosis of oligo-JIA patients. Radiologic abnormalities in the form of erosions, joint space narrowing and overgrowth were observed in 25%, 14% and 25%, respectively in a study of 81 oligo-JIA patients who had radiographs done after a median (range) of 8.6 (2.3-24.1) years after disease onset (21). Other studies have reported erosions in 4-35% of patients (14, 22-24). Abnormal Health Assessment

Questionnaire scores were found in 22% and 47% of oligo-persistent and oligo-extended patients, respectively, after a median disease duration of 14.9 years (22). A large multinational cross-sectional study explored the health-related quality of life of 1539 children with oligo-JIA a few years after their diagnosis (25). Not surprisingly, patients of the oligo-persistent subtype faired better than the other JIA subtypes in all of the Child Health Questionnaire domains. The extended-oligo subtype had similar scores on all domains than polyarticular and systemic-onset JIA. A study on 215 JIA patients from Germany of which 85 had oligo-JIA reported educational level and employment status after a median (range) follow up period of 16.5 (10-30) years (26). In the entire cohort, the 20-35 year-old patients achieved a similar or higher educational level than the age-matched controls from the general population. Similarly, in a cohort of American oligo-JIA patients diagnosed in the 1990s and followed for at least 5 years after diagnosis, only 6% had school limitations (27). Although oligo-JIA patients have an overall favorable prognosis compared to their JIA counterparts, they remain at risk to develop anatomic damage, impaired functional status and quality of life. These aspects are not to be neglected and may also benefit from earlier and more aggressive disease control.

Chapter 2: Use of intra-articular corticosteroid injections in oligo-JIA

2.1 Recommendations for intra-articular corticosteroid injections in oligo-JIA

Despite the fact that oligo-JIA is one of the most common rheumatic disease encountered by pediatric rheumatologists, few comparative studies are available to guide therapeutic choices. No prospective randomized control trials comparing the efficacy of different first-line agents have been conducted. In 2011, the American College of Rheumatology published treatment recommendations to help clinicians in therapeutic decision making (28). As general suggestions, intra-articular corticosteroid injections (IAS) were recommended to treat active arthritis regardless of the JIA subtype or intake of systemic medication. Authors also mentioned that when the benefits gained from IAS lasted at least 4 months, subsequent IAS should be considered to treat disease flares. For children with a shorter response to IAS, the addition of systemic medications should be considered. In patients with ≤4 active joints, the use of first-line nonsteroidal anti-inflammatory drugs (NSAIDs) monotherapy was suggested only for those with mildly active disease, without contractures or poor prognostic features. Methotrexate (MTX) was proposed as part of the first-line armentorium in those with highly active disease and poor prognostic features. For patients with a history of arthritis in 5 or more joints, MTX was suggested as part of the first-line therapy in patients with high disease activity or moderate disease activity associated with poor prognostic features. When a patient has only a few active joints, starting systemic therapy may not always be the best option as it implies committing to the intake of daily medication with potential side effects. Also, if a patient is already on a systemic agent, stepping up systemic therapy for 1-2 active joints may not be desirable. The use of IAS becomes an attractive option for these scenarios.

2.2 Mechanisms of action of IAS

Intra-articular corticosteroid injections to treat arthritis was reported for the first time in 1951 (29). Different corticosteroid formulations may be utilized for intra-articular injections but

triamcinolone hexacetonide is most commonly used in pediatrics due to its superior efficacy (30-35). The mechanisms of action of locally injected corticosteroids are diverse (36). Once delivered into the cell, the corticosteroid binds to the cytosolic glucocorticoid receptor. This binding triggers genomic and non-genomic effects. The former results from alteration of gene transcription which will lead to down-regulation of pro-inflammatory mediators and up-regulation of anti-inflammatory mediators expression. Non-genomic effects could potentially account for the rapidity of action of IAS. Diverse mechanisms have been proposed, such as alteration of the physicochemical properties of cellular membranes and binding of glucocorticoid to a membrane-bound receptor instead of a cytosolic one.

2.3 Advantages and potential side effects of IAS

An indisputable advantage of IAS over other anti-inflammatory or immunosuppressive therapies is its rapidity of action. As compared to many weeks to even a few months with NSAIDs and MTX, respectively, response to IAS is usually seen after a few days or weeks. It allows patients to redeem their physical functions more rapidly without the need to take regular systemic medications. As an example, improved gait pattern and increased muscle power were demonstrated in a group of children following lower limb IAS (37). The rapidity of action of IAS could also facilitate physiotherapy, a key component of JIA treatment. Rapid resolution of symptoms could also lower the frequency of local complications such as contractures, muscular atrophy and limb length discrepancy (38, 39). Another benefit of IAS is the possibility to wean off systemic therapies after the procedure. A study conducted mostly among children with JIA showed that 60.6% of patients were able to stop their systemic treatment after IAS (39). The proportion was even higher in children with oligo-JIA (74%).

Intra-articular corticosteroid injections have a favorable adverse effect profile. Side effects resulting from IAS are mainly local. Skin atrophy and depigmentation are one of the most commonly encountered local side effects (40, 41). It is presumed to be secondary to leakage of the corticosteroid within the subcutaneous tissues. Smaller joints are more at risk. The atrophic skin changes will often improve and may even resolve over time. Intra-articular and peri-articular calcifications may also be seen (42). They are often asymptomatic and only identified

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on radiographs. Acute crystal synovitis has been described and should resolve by itself after a few days (39, 43). Septic arthritis is always a potential threat but it remains extremely rare. Cartilage damage does not seem to occur following IAS in children (44, 45). Systemic side effects have also been reported but are felt to be uncommon. Transient suppression of the hypothalamic-pituitary-adrenal axis, altered glucose metabolism and anaphylaxis are among the systemic effects described (46-48).

2.4 Factors influencing IAS efficacy

Specific patient characteristics or elements related to the IAS procedure have been shown to affect the odds of response to the injection. Less favorable response have been described when the joints injected are elbows or ankles (49, 50). Injections done under radiological guidance may offer a benefit as placement of the needle in the intra-articular space can be confirmed (51). Contradictory results were obtained when examining the impact of gender, JIA subtype, disease duration, concomitant intake of systemic medications, ANA status and the presence of an inflammatory profile on the probability and/or duration of a positive response to IAS (30, 32, 34, 49, 51-56). The important heterogenicity in the methodology and patient population included in these studies may explain in part these contradictory results. Identification of biomarkers that could inform on the chance of success of IAS would be helpful in prioritizing therapies. Foell et al. explored the relationship between serum or intra-articular concentration of protein S100A2 and response to IAS in 22 patients with oligo-JIA (57). Non-responders had significantly higher levels of the protein in the serum prior to injection. Moreover, serum levels were increasing in non-responders as opposed to decreasing in responders. Another study suggested that the percentage of neutrophils in synovial fluid was a predictor of duration of response to IAS (34). Longer response time was seen in children with < 20% neutrophils. Other biomarkers such as gamma delta ($\gamma/\delta+$) and B CD5+ lymphocytes in the synovial fluid were not helpful in predicting the response to IAS (55).

2.5 Utilization and efficacy of IAS in oligo-JIA

Various rates of IAS have been reported in JIA patients (32% to >90%) (14, 20, 27). Contemporary data from the Research in Arthritis in Canadian Children Emphasizing Outcomes (ReACCh Out) cohort reported that 43% of oligo-JIA had received at least one IAS in the first 6 months following study entry (58). The wide range seen in the literature may be partly explained by the different follow up time of these studies but also from the absence of evidence-based data on the optimal use of IAS in oligo-JIA. Also, easily accessible joints like knees, ankles and wrists are often injected by the rheumatologist and do not require a specific set-up such as that required for deep seated or less accessible joints (59). For those, patients are often referred to an orthopedic surgeon or an interventional radiologist to allow the injection to be done under radiological guidance.

Studies assessing the efficacy of IAS in oligo-JIA patients are difficult to compare as the study setting and patient population are not homogeneous (Table I). Key elements that allow proper interpretation of these studies such as the JIA classification, number of IAS received, concomitant use of systemic therapy, the definition of response to IAS and of a flare and duration of follow up after the IAS vary or are not always even mentioned. Studies reporting response rates specific to the oligo-JIA subgroup have found favorable responses in 43-100% of children within the first year following IAS (31, 39, 44, 52, 60, 61). The data on the efficacy of re-injections is scant and none targets specifically oligo-JIA patients (30, 52, 53). No clear trend is seen in the re-injection studies as some report similar success rate and others show a lower efficacy. Most importantly, no studies have yet addressed the impact of early IAS on disease activity over time.

Table I. Efficacy of IAS in juvenile idiopathic arthritis patients

	Study design	Oligo-JIA / JIA, N	Girls, %	Corticosteroid formulation used	Concomitant systemic treatment, % [a]	Disease duration, years	Follow up time post IAS, months	Favorable response, %	Duration of response, months
Allen et al. (52)	Prospective, multicentric	29/29	90	TH	100	4.2 ± 4.0	6.0	68	n/a
							12.0	50	
							24.0	17	
Beukelman et al. (62)	Retrospective, unicentric	16/38	87	TA, TH	37 [b]	n/a	≤ 3.3	44	n/a
Bloom et al. (30)	Retrospective, multicentric	37/61	74	TA, TH, MP	97	2.8 (0.1-13.0) [c]	0.3	100	12.5 (0.5-44.0) [c]
							12.0	52	
							24.0	20	
							36.0	7	
Breit et al. (53)	Retrospective, unicentric	83/83 Early onset pauci	72	TH	100	2.7 ± 2.3 (ANA-) 3.0 ± 2.6 (ANA+)	16.0 ± 5.9	n/a	30.3 [d]
		38/38 Late onset pauci	45		100	2.9 ± 2.3 (HLA B27-) 2.4 ± 1.9 (HLA B27+)			11.8 [d]
de Oliveira Sato et al. (63)	Retrospective	64/77	66	TA, TH	100	n/a	51.6 (32.4-73.2) [e]	57	n/a
Eberhard et al. (32)	Retrospective, unicentric	90/124	79	TH	n/a	3.1 ± 3.4	≥15.0	n/a	9.1 ± 3.5
		89/119	81	TA		3.3 ± 3.3			6.8 ± 3.4
Hertzberger-ten Cate et al. (60)	Retrospective, unicentric	21/21	n/a	TA	n/a	n/a	≥6.0	100	15.2 (1.0-40.0) [c]

Table I. Efficacy of IAS in juvenile idiopathic arthritis patients (continued)

	Study design	Oligo-JIA / JIA, N	Girls, %	Corticosteroid formulation used	Concomitant systemic treatment, % [a]	Disease duration, years	Follow up time post IAS, months	Favorable response, %	Duration of response, months
Huppertz et al. (44)	Unicentric	9/9	n/a	TH	100	n/a	1.8	89	n/a
							13.0	86	
Laurell et al. (64)	Prospective, unicentric	19/30	70	TA	87	2.0 (0.5-13.9)	1.0	72	6.0 (4.0-11.0)
Lepore et al. (55)	Unicentric	35/37	81	TH	None were on NSAIDs [f]	n/a	41.8 (26.0-69.0) [c]	33	13.9 (0-54.0) [c]
Marti et al. (54)	Retrospective, unicentric	37/60	70	TA, TH	82	n/a	28.0 (1.0-69.0)	51	23.1 (0-69.0)
Miotto E Silva et al. (51)	Retrospective	48/88	75	n/a	n/a	n/a	84.0 ± 48.0	70	18.1 ± 13.0
Neidel et al. (65)	Prospective, unicentric	18/48	63	TH	100	2.0 (0.1-16.0)	26.4 (24.0-81.6)	76	n/a
Padeh and Passwell (39)	Unicentric	43/43	66	TH	n/a	n/a	6.0	82	n/a
Papadopoulou et al. (66)	Retrospective, unicentric	109/220	80	TH, MP	62	0.6 (0.2-2.5) [e]	12.0	50	n/a
							24.0	32	
							36.0	20	
Ravelli et al. (56)	Prospective, unicentric	81/94	71	TH	82	2.9 ± 3.2 [g] / 4.2 ± 3.9 [h]	6.0	69	n/a
Remedios et al. (67)	Prospective	7/11	64	TH	n/a	5.4 ± 3.0	≤16.0	63	14.0 (12.5-16.0)
Tynjälä et al. (68)	Retrospective, unicentric	15/32	63	Ankles/feet MP Hips TH	69	4.3 (0.5-8.1) Ankles/feet 1.1 (0.5-10.9) Hips	3.0	64	3.5 (0.5-12.0) Ankles/feet 11.5 [d] Hips
							6.0	55	
							12.0	40	

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Table I. Efficacy of IAS in juvenile idiopathic arthritis patients (continued)

	Study design	Oligo-JIA / JIA, N	Girls, %	Corticosteroid formulation used	Concomitant systemic treatment, %	Disease duration, years	Follow up time post IAS, months	Favorable response, %	Duration of response, months
Ünsal et al. (61)	Retrospective, unicentric	17/37	41	TA	n/a	4.7 ± 2.9	6.0	81[i]	n/a
							12.0	69[i]	
Zulian et al. (69)	Prospective, unicentric	85/85	78	TA, TH	n/a	3.6 ± 3.7 (TH) 2.7 ± 2.9 (TA)	6.0	81 (TH) 53 (TA)	n/a
							12.0	67 (TH) 43 (TA)	
							24.0	60 (TH) 33 (TA)	

Data showed as mean ± standard deviation or median (range), unless otherwise specified; [a] NSAIDs and/or disease-modifying antirheumatic drug; [b] Proportion taking NSAIDs not mentioned; [c] Mean (range); [d] Median; [e] Median (IQR); [f] No mention of other systemic therapies; [g] Patients who were in sustained remission at 6 months; [h] Patients who had recurrence of arthritis at 6 months; [i] Proportion of remission in oligo-JIA patients; IAS: intra-articular corticosteroid injection; MP: methylprednisolone; N: number; n/a: not available; NSAIDs: nonsteroidal anti-inflammatory drugs; Pauci: pauciarticular; TA: triamcinolone acetonide; TH: triamcinolone hexacetonide.

2.6 Early disease control and its impact on the disease course

One of the ultimate goals in JIA management would be to alter the course of the disease with early therapy. Not only would patients benefit in the short term from faster disease control but it could translate into longer term benefit by decreasing the occurrence of damage. Early disease control might also impact on the immunological behavior of JIA and alter the long term disease course, a concept called the "window of opportunity". This notion also applies to other conditions related to JIA, namely rheumatoid arthritis (RA) (62). Transformation of an acute self-resolving inflammatory process into a chronic one is a complex, multi-step process. It implies chemokines that will keep effector cells within the joints as well as up-regulation of anti-apoptotic signals preventing death of effector cells. The cytokine profile in synovial fluid of RA patients in the early disease phase has been found to differ from the profile seen in established disease (63). It seems plausible that early therapeutic intervention during this window period could modulate the immune system response and alter the long term disease course. A recent meta-analysis supports this concept in RA (64). Studies considered for this report were those in which at least one disease-modifying antirheumatic drug (DMARD) was started within the first 2 years after onset of symptoms and for which time from onset of symptoms to start of therapy was assessed as a potential predictor. This study showed that duration of symptoms before starting therapy was associated with sustained remission following complete withdrawal of DMARDs. Each additional week of symptoms without DMARDs therapy decreased the risk of a prolonged remission with a hazard ratio of 0.98 (95% confidence interval (95%CI) 0.98-0.99; p< 0.001).

Very few studies have addressed the efficacy and impact of early aggressive therapy in recently diagnosed JIA. Even after expanding to RA studies, the data remains scant when early IAS is the intervention of interest. Early IAS (≤2 months from JIA diagnosis) was shown to lower the frequency of leg length discrepancy in 30 children with oligo-JIA but unfortunately, no data on the effect of early IAS on disease activity was available in that study (38). A recently published sub-analysis of the "Behandel Strategieën" (BeSt) study compared the disease course over 8 years among 508 early RA (diagnosis <2 years) patients who received (N=60) or not (N=448) an IAS within 1 year of study enrollment (65). Rheumatoid arthritis

patients who were injected had higher Disease Activity Score in 44 joints and Health Assessment Questionnaire score during the first year of the study, although the differences were less than the minimal clinically significant difference. No significant differences in the Disease Activity Score in 44 joints and Health Assessment Questionnaire were found afterwards, up to 8 years after enrollment. The systemic treatment steps provided were also similar between both groups. A retrospective study evaluated the efficacy of multiple IAS performed after a median (IQR) of 0.6 (0.2-2.5) years after diagnosis in 220 Italian JIA patients, of whom 109 had oligo-JIA (66). At the time of IAS, 61.8% were taking systemic therapies. Synovitis flare was defined as a flare of arthritis in injected but also in uninjected joints, as the therapeutic steps provided to treat the active uninjected joints could have contributed to the persistence of remission in the injected joints. Survival without synovitis flare was 50.0%, 31.5% and 19.5% at 1, 2 and 3 years after the IAS, respectively. This study had no control group (i.e. systemic therapy without IAS) thus the effect of mutiple IAS per se cannot be isolated. Additionally, although the median disease duration was short, not all patients were injected shortly after JIA diagnosis. Interestingly, the number of joints that flared (n=309) was less than half of the number of injected joints (n=725). This may suggest that following IAS, less aggressive therapy might be needed to treat disease flares, but again, the absence of a control group precludes definitive conclusions.

Studies of JIA patients have focused on early aggressive systemic therapy and not on early IAS as a potential factor influencing disease activity over time. In the Trial of Early Aggressive Therapy in Polyarticular Juvenile Idiopathic Arthritis (TREAT), 85 patients with a recent diagnosis (<12 months) of polyarticular JIA and naive to biologics were randomized to one of 2 treatment group: MTX, etanercept and prednisolone (aggressive treatment arm) or MTX, placebo etanercept and placebo prednisolone (conventional treatment arm) (67). Patients randomized to the aggressive arm were more likely to achieve clinical inactive disease at 6 months (40% vs. 23%; p=0.08) and clinical remission on medication at 12 months (21% vs. 7%; p=0.05), although findings were not statistically significant. Interestingly, the only predictor of clinical inactive disease at 6 months was disease duration at enrollment: for each month gained on therapy after disease onset, the odds of achieving clinical inactive disease were 1.32 greater (p<0.011). The Aggressive Combination Drug Therapy in Very

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Early Polyarticular JIA trial was a randomized, open label multicentric trial enrolling patients within 6 months of JIA diagnosis with at least 5 active joints and who were naive to DMARDs (68). Patients were treated with either MTX alone (N=20), COMBO therapy (MTX, hydroxychloroquine and sulfasalazine; N=20) and MTX and infliximab (N=19). At 54 weeks, inactive disease was achieved by 25%, 40% and 68% of the MTX alone, COMBO and MTX-infliximab groups, respectively (p=0.002). Also, the mean time spent in inactive disease was longest in the MTX-infliximab arm (26 weeks) when compared to the COMBO (13 weeks) and MTX (6 weeks) arms (p=0.001). No similar studies focusing on oligo-JIA are available. Moreover, no long term data is yet available in participants of JIA trials who were provided with early aggressive therapy. The impact of early disease control on the long term risk of achieving sustained complete remission still needs to be determined. Only then will the concept of a window of opportunity in JIA will be better understood.

Although our study was not designed to address the existence of a window of opportunity in oligo-JIA, this concept motivated the search for an effective and acceptable therapeutic option that could be given early following JIA diagnosis and would at least, improve short term outcomes. Long term studies could subsequently address if the therapeutic intervention could modify the disease biology and trajectory over the long term. Due to their efficacy and overall acceptance among both pediatric rheumatologist and patients/parents, IAS are a potential therapeutic candidate for this task.

2.7 Objectives and hypotheses

The primary aim of this study was to examine the association between early IAS and the achievement of an active joint count of zero during the first 2 years after study enrollment. We hypothesized that patients who received an early IAS would be more likely to achieve an active joint count of zero.

The secondary aim was to analyze the effect of early IAS on the achievement of inactive disease during the first 2 years after study enrollment. We hypothesized that inactive disease would be found more frequently in patients who received an early IAS.

Chapter 3: Methodology

3.1 Study population

Patients included in this study were enrolled into the ReACCh Out study, a prospective longitudinal cohort established to study JIA outcomes. A detailed description of the design and methods of the study has been published previously (69). Briefly, ReACCh Out was a prospective multicenter cohort study conducted in 16 pediatric rheumatology centers across Canada (14 academic and 2 community centers). Patients were eligible to take part in that study if they were diagnosed with JIA within the past 12 months, according to the International League Against Rheumatism criteria (2). Participants were followed every 6 months during the first 2 years and then yearly up to 5 years. Demographic, clinical and medication data were collected prospectively on standardized forms at each study visit. Medication changes were recorded at interim visits. This current analysis was undertaken using a subset of patients (oligo-JIA) enrolled in the ReACCh Out cohort study.

3.2 Inclusion and exclusion criteria

Included in this study were all patients with a diagnosis of oligo-JIA, (as defined by the subtype diagnosed at the 6-month visit and confirmed at the 24-month study visit) and those for whom all first 5 visits were completed (baseline, 6-month, 12-month, 18-month and 24-month visit). Patients who received their first IAS before enrollment were excluded.

3.3 Data collection

Eligible participants were identified in the central ReACCh Out database. Data extraction was performed on March 11th 2012. After the completion of the 24-month study visit, a 6 months lag was allowed for data to be entered in the main database. It was expected that patients enrolled before September 11th 2009 would have all data entered by the time of data extraction. Patients missing one or more study visits were excluded. Data included in this report comprise that from enrollment up to the 24-month study visit.

Demographic, clinical and treatment-related information were collected. Data collection in ReACCh Out was performed using standardized forms and questionnaires filled by the physician and the patient or parents (see appendix A). The Childhood Health Assessment Questionnaire (CHAQ), in which 0 indicates the best and 3 the worst function, was used as a measure of physical function (70, 71). The physician global assessment of disease activity (PGADA) and the patient global assessment of overall well-being (Patient Global) were also collected. Both are 10-cm visual analog scales in which 10 cm indicates higher disease activity with respect to the physician and patient's perspective, respectively.

3.4 Definitions of exposure

Exposure to IAS was defined as follows: early IAS, if the first IAS was performed ≤ 3 months after JIA diagnosis and no early IAS, if no IAS was performed during that time period. A minimum consecutive period of medication exposure had to occur for a participant to be labelled as having been exposed to a systemic medication. Each agent had its specific predetermined exposure time: ≥1 month for corticosteroids, ≥2 months for NSAIDs, ≥3 months for MTX, leflunomide, hydroxychloroquine or sulfasalazine and ≥4 months for biologics. These minimal exposure times were used to ensure a patient would not be labelled exposed to a medication when he did not receive it long enough to benefit from it. Early exposure to DMARDs was defined as exposure to MTX, leflunomide, hydroxychloroquine, sulfasalazine and/or biologics in the 6 months following study enrollment.

3.5 Outcomes

The primary outcome was an active joint count of zero, as determined by the treating rheumatologist during physical examination. The active joint count was treated as a categorical variable (active joint count of zero: yes/no). The secondary outcome was inactive disease, derived from the Wallace criteria (72). The Wallace criteria were created in 2003 to help bring homogenicity in the definition of inactive disease used in JIA trials. The state of inactive disease was reached if the following 4 criteria were met for 6 consecutive months (2 consecutive visits), regardless of medication intake: (1) no joints with active arthritis, (2) no

fever, rash, serositis, splenomegaly or generalized lymphadenopathy attributable to JIA, (3) no active uveitis, and (4) PGADA indicates no disease activity. The fifth item, normal ESR or C-reactive protein (CRP) was not included in the definition of inactive disease. Of note, the definition of inactive disease used for this study did not take into account the medication intake; a patient could have inactive disease while on medication.

3.6 Repeated measurements: advantages and statistical considerations

Our current project used data from a prospective longitudinal cohort study which generated repeated measurements over time. Each participant was seen on 5 occasions and at each visit, the same data was collected. These 5 visits took place at predetermined moments and were not dictated by the patient's clinical status. Longitudinal data offers many advantages one of which being the ability to obtain information on the outcome's trajectory over time. Per example, when assessing the effect of treatment A and B on the level of disease activity, the proportion of patients with inactive disease at 24 months may be similar between both groups, but the trajectory of disease activity over time may differ. Patients who received treatment A may have achieved and stayed in remission as soon as the second month of the study as compared to group B who only achieved remission at 18 months. This dynamic information allows to better characterize the effect of one or many independent variables on a dependent variable, taking into consideration the change over time.

Statistical analysis of repeated measurements requires specific considerations. Measurements taken on the same subject over time might be correlated. Overlooking the within-patient correlation might lead to type I or type II errors (73). Assumptions underlying more traditional statistical analysis methods may not be fulfilled and using these methods might lead to biased results. Many statistical methods can assist in the analysis of repeated measurements. We chose the generalized estimating equation method (GEE). The GEE models the population mean of the outcome variable at each time point; this will generate information about the trajectory of the outcome variable at a population level. Visits made at predetermined time points as seen in our study are an ideal scenario for GEE (74). When visits are dictated by the clinical status of participants, using GEE may lead to biased results. GEE can handle missing

data but the missingness mechanism should not be missing at random (MAR) or missing not at random (MNAR) (75). Analyzing a dataset in which missing data are MAR or MNAR may lead to erroneous conclusions.

3.7 Statistical analysis

3.7.1 Descriptive statistics

Patient characteristics at study enrollment were described using frequency (percentages; 95% confidence interval) for categorical variables, mean (standard deviation) for normally distributed continuous data and median (IQR) for non-normally distributed continuous data. Normality of data distribution was determined using the Kolmogorov-Smirnov test. Baseline characteristics were compared between groups based on their exposure status to IAS. Comparisons were made using the chi-square or Fisher's exact test for categorical variables, the independent t test for normally distributed continuous variables and the Mann-Whitney U test for non-normally distributed continuous variables.

3.7.2 GEE analysis

GEE was used for the analysis of our primary and secondary objectives. The logistic binary model was selected since our dependent variables are both binary categorical variables. The use of GEE requires specification of the working correlation matrix, which reflects the correlation present among observations measured on the same subjects on repeated occasions (in our case the outcome). Many types of working correlation matrices exist. For the current study, the working correlation matrix associated with the lowest "quasi-likelihood under the independence model criterion" was selected (76). The following working correlation matrices were assessed: first-order autoregressive, exchangeable, M-dependent and unstructured. The independent working correlation matrix was not tested as it assumed that the repeated measurements were uncorrelated which was not the case for our data. For the primary outcome, the M-dependent, where m=3, was chosen. This correlation matrix assumed that consecutive measurements have a common correlation coefficient, measurements taken 2 time

periods away have a different correlation coefficient, etc. up to m-1 time periods; measurements separated by a time period greater than m-1 are assumed to be non-correlated. A first-order autoregressive working correlation matrix was selected for the secondary outcome. It assumed that the correlation between the measurements decreased with increasing interval of time between measurements. The robust estimator was chosen for the covariance matrix. This allowed to obtain valid estimates even if the working correlation matrix was not correctly specified, assuming that the sample size was large enough, which was the case in our study (N=310) (73).

We first explored the effect of exposure to early IAS and other important patient characteristics on the risk of achieving an active joint count of zero and inactive disease with univariate analyses. Variables with a p value <0.10 were considered for the multivariate model. Early IAS was forced into the model because this was our covariate of interest. Being on NSAIDs at enrollment and early exposure to DMARDs were also included as these variables were considered clinically relevant. In addition, covariate adjustment for statistical models included all empirical confounders for the association between early IAS and the outcome. We used a conservative 8% change-in-estimate rule to identify empirical confounders suitable for inclusion in the model. The following 7 variables were considered to be potential confounders and were tested as described above: oligo-JIA course, active joint count of zero at enrollment, early exposure to DMARDs, on NSAIDs at enrollment, baseline CHAQ, PGADA and Patient Global. In the event that 2 independent variables were strongly correlated (Pearson's or Spearman's coefficient ≥0.6 and p value <0.05), only one was chosen for the multivariate analysis. The choice was based on both the clinical and statistical significance of the covariates. Interaction between exposure to early IAS and time since enrollment was examined. This allowed to assess if early IAS was associated with the change in the outcome *over time*. Our specific research interest was to explore the association between early IAS and the outcomes active joint count of zero and inactive disease rather than to derive an explanatory model for the primary and secondary outcomes. It was extremely important to minimize confounding by including all potential confounding variables. Therefore, we elected to enter the selected independent variables in the GEE multivariate model without performing

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stepwise regression analysis. A p value < 0.05 for the variable early IAS and the interaction term was considered statistically significant.

A first analysis was performed using all available data (complete cases analysis). We also performed multiple imputation (see section 3.8 Handling of missing data for details). Results of both the complete case analysis and the analysis using the imputed dataset are presented. Data analysis was performed using IBM SPSS Statistics Version 21.0. (Armonk, NY: IBM Corp.).

3.8 Handling of missing data

Missing data is not an uncommon issue encountered in prospective multicentric observational studies. Sites from which participants' data was missing were contacted to obtain the missing information, if available. This allowed to decrease significantly the amount of missing data. Unfortunately, certain data were truly missing hence it could not be retrieved. The proportion of missing data for the outcome measures and the independent variables were described. Baseline demographics of participants with and without a complete dataset were compared to assess if these 2 subset of patients differed significantly. Additionally, we explored if having a complete dataset was associated with the primary or secondary outcomes using univariate GEE logistic regression. Lastly, we assessed the missingness mechanism of variables having missing items. This was done by exploring if the outcomes and independent variables in the dataset were associated with the missing status of each variable having missing items. Due to the multiplicity of comparisons (136) performed for this task, Bonferroni correction was applied and only p values < 0.001 were considered statistically significant. If no statistically significant association was found, the missingness mechanism for that variable was presumed to be missing completely at random (MCAR). On the other hand, if a significant association was found with at least one variable, the missingness mechanism was assumed to be at least that of MAR.

We performed multiple imputation for all 8 variables with missing items: the secondary outcome inactive disease, duration of symptoms at diagnosis, oligo-JIA course, ANA status,

early exposure to DMARDs, being on NSAIDs at enrollment, baseline CHAQ and baseline Patient Global. The following variables were used as predictors in the imputation model: gender, age at diagnosis, duration of symptoms at diagnosis, disease duration at enrollment, center, oligo-JIA course, ANA status, exposure to early IAS, early exposure to DMARDs, being on NSAIDs at enrollment, baseline CHAQ, baseline PGADA, baseline Patient Global, active joint count of zero (at each study visit) and inactive disease (at each study visit). The Markov Chain Monte Carlo modelling method was utilized (77). The number of iterations was set at 200 and 10 imputed datasets were created (78). The multiple imputation procedure was done using IBM SPSS Statistics Version 21.0. (Armonk, NY: IBM Corp.).

3.9 Ethics approval

The study was approved by the research ethics board at each institution and carried out in conformity with the declaration of Helsinki.

Chapter 4: Manuscript and results

4.1 Manuscript

Please refer to the manuscript entitled: Do Early Intra-Articular Corticosteroid Injections Improve Outcome in Oligoarticular Juvenile Idiopathic Arthritis: The ReACCh Out Study.

The manuscript is formatted for submission in Arthritis and Rheumatology as a full-length article.

Author contributions :

Julie Barsalou: Actively involved in all phases of this research project: study design, data extraction, data cleaning, data analysis and interpretation, manuscript redaction.

Helen Trottier: Supervision of the research project (thesis co-director), involved in the statistical analysis and revision of the manuscript.

Jaime Guzman: Involved in the design of the study, data collection, data extraction, data cleaning and revision of the manuscript.

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Ray S. M. Yeung: Involved in the design of the study, data collection and revision of the manuscript.

Lori B. Tucker: Involved in the design of the study, data collection and revision of the manuscript.

Ciaran M. Duffy: Supervision of the research project (thesis director), involved in the design of the study, data collection, data interpretation and revision of the manuscript.

Do Early Intra-Articular Corticosteroid Injections Improve Outcome in Oligoarticular Juvenile Idiopathic Arthritis: The ReACCh Out Study.

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Abstract

Objectives One of the goals in oligoarticular juvenile idiopathic arthritis would be to alter the disease course with early therapy. We examined the association between early intra-articular corticosteroid injections and the achievement of an active joint count of zero and inactive disease during the first two years after study enrollment.

Methods Included were oligoarticular juvenile idiopathic arthritis patients enrolled into a prospective longitudinal cohort across Canada. Demographic, clinical and treatment-related information were collected. Early intra-articular corticosteroid injection was defined as having received the first injection within 3 months of diagnosis. Generalized estimating equations were used for data analysis.

Results A total of 310 patients were included, of whom 111 (35.8%) received an early injection. Participants who received an early injection had more severe disease at baseline. Patients exposed to early injections had a similar chance to achieve an active joint count of zero, OR 1.52 (95%CI 0.68-3.37), p=0.306 but were significantly less likely to achieve inactive disease, OR 0.35 (95%CI 0.14-0.88), p=0.026.

Conclusion In this cohort of 310 oligoarticular juvenile idiopathic arthritis patients, early intra-articular corticosteroid injections did not result in an increased risk of achieving an active joint count of zero or inactive disease. Methodological issues encountered when estimating treatment effect using observational data might have biased the estimates obtained. Firm conclusion on the inefficacy of early IAS in improving outcomes in this population cannot be drawn from this study. Prospective studies addressing the limitations raised will be needed to clarify if early injections can alter the disease course.

Introduction

Oligoarticular juvenile idiopathic arthritis (oligo-JIA) is one of the most commonly encountered rheumatological diseases in childhood. Although it is often regarded as the subtype with the best prognosis, studies have reported remission rates off medications varying from 21-68% four to eight years after diagnosis (1, 2). Importantly, the risk of disease flare remains present even after years of quiescence (3). Oligo-JIA must thus be considered a chronic disease.

One of the ultimate goals in JIA management would be to alter the course of the disease with early therapy. Not only would patients benefit in the short term from faster disease control but it could translate into longer term benefit by decreasing the occurrence of damage. Early disease control might also impact on the immunological behavior of JIA and alter the long term disease course, a concept called the "window of opportunity". This notion also applies to other conditions related to JIA, namely rheumatoid arthritis (RA) (4). Interestingly, a shorter duration of symptoms before onset of therapy was associated with sustained RA remission following complete withdrawal of disease-modifying antirheumatic drugs (DMARDs). In the Trial of Early Aggressive Therapy in Polyarticular Juvenile Idiopathic Arthritis (TREAT), the only predictor of inactive disease at 6 months was disease duration at enrollment: for each month gained on therapy after disease onset, the odds of achieving inactive disease were 1.32 greater (p<0.011). No similar studies focusing on the oligo-JIA population are available.

The concept of a potential window of opportunity motivates the search for an effective therapeutic option that could be given early following JIA diagnosis and would improve outcomes. Due to their efficacy and overall acceptance among both pediatric rheumatologists and patients/parents, intra-articular corticosteroid injections (IAS) are a potential therapeutic candidate for this task.

The primary aim of this study was to examine the association between early IAS and the achievement of an active joint count of zero during the first two years after study enrollment. The secondary aim was to analyze the effect of early IAS on the achievement of inactive disease.

Methods

Study population

Patients included in this study were enrolled into the Research in Arthritis in Canadian Children Emphasizing Outcomes (ReACCh Out) study, a prospective longitudinal cohort established to study JIA outcomes. A detailed description of the design and methods of the study has been published previously (5). Briefly, ReACCh Out was a prospective multicenter cohort study conducted in 16 pediatric rheumatology centers across Canada (14 academic and 2 community centers). Patients were eligible to take part in ReACCh Out if they were diagnosed with JIA within the past 12 months, according to the International League Against Rheumatism criteria (6). Participants were followed every 6 months during the first 2 years and then yearly up to 5 years. Demographic, clinical and medication data were collected prospectively on standardized forms at each study visit. Medication changes were also recorded at interim visits. This current analysis was undertaken in a subset of patients (the oligo-JIA subtype) enrolled in the ReACCh Out cohort study.

Inclusion and exclusion criteria

Included in this study were all patients with a diagnosis of oligo-JIA (as defined by the subtype of JIA diagnosed at the 6-month visit and confirmed at the 24-month study visit) and those for whom all first 5 study visits were completed. Patients who received their first IAS before enrollment were excluded.

Data collection

Eligible participants were identified in the central ReACCh Out database. Data extraction was performed on March 11th 2012. Demographic, clinical and treatment-related information were collected. The Childhood Health Assessment Questionnaire (CHAQ), in which 0 indicates the best and 3 the worst function, was used as a measure of physical function (7, 8). The physician global assessment of disease activity (PGADA) and the patient global assessment of overall well-being (Patient Global) were also collected. Both are 10-cm visual analog scales in which 10 cm indicates higher disease activity. Data included in this report comprise that from enrollment up to the 24-month study visit.

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Definitions of exposure

Exposure to IAS was defined as follows: early IAS, if the first IAS was performed ≤3 months of JIA diagnosis and no early IAS, if no IAS was performed during that time period. A minimum consecutive period of medication exposure had to occur for a participant to be labelled as having been exposed to a systemic medication. Each agent had its specific exposure time: ≥1 month for corticosteroids, ≥2 months for nonsteroidal anti-inflammatory drugs (NSAIDs), ≥3 months for MTX, leflunomide, hydroxychloroquine or sulfasalazine and ≥4 months for biologics. These minimal exposure times were used to ensure a patient would not be labelled exposed to a medication when he did not receive it long enough to benefit from it. Early exposure to DMARDs was defined as exposure to MTX, leflunomide, hydroxychloroquine, sulfasalazine and/or biologics in the 6 months following study enrollment.

Outcomes

The primary outcome was an active joint count of zero, as determined by the treating rheumatologist during physical examination. The secondary outcome was inactive disease, derived from the Wallace criteria (9). The state of inactive disease was reached if the following four criteria were met for 6 consecutive months (2 consecutive visits), regardless of medication intake: (1) no joints with active arthritis, (2) no fever, rash, serositis, splenomegaly or generalized lymphadenopathy attributable to JIA, (3) no active uveitis, and (4) PGADA indicates no disease activity. The fifth item, normal ESR or CRP, was not included in the definition of inactive disease due to the high proportion of missing data and the fact that oligo-JIA patients often have normal inflammatory markers.

Statistical analysis

Descriptive statistics were used, as appropriate. Comparisons between patient characteristics, based on their IAS exposure status, were done using the chi-square, Fisher's exact, unpaired t test or Mann-Whitney U test. Because our outcomes consisted of repeated measurements, we used generalized estimating equations (GEE) logistic regression to account for within-patient correlation in the data. Models incorporated an M-dependent (m=3) and first-order autoregressive working correlation matrix for the primary and secondary outcomes,

respectively. We first explored the effect of exposure to early IAS and other important patient characteristics on the risk of achieving an active joint count of zero and inactive disease with univariate analyses. Variables with a p value <0.10 were considered for the multivariate model. Early IAS was forced into the model because this was our covariate of interest. Being on NSAIDs at baseline and early exposure to DMARDs were also included as these variables were considered clinically relevant. In addition, covariate adjustment for statistical models included all empirical confounders for the association between early IAS and the outcome. We used a conservative 8% change-in-estimate rule to identify empirical confounders suitable for inclusion in the model. The following 7 variables were considered to be potential confounders and were tested as described above: oligo-JIA course, active joint count of zero at enrollment, early exposure to DMARDs, on NSAIDs at enrollment, baseline CHAQ, PGADA and Patient Global. Interaction between exposure to early IAS and time since enrollment was examined. A p value < 0.05 for the variable early IAS and the interaction term was considered statistically significant in the multivariate model. Multiple imputation was performed for 8 variables with missing data: inactive disease (0.2% of missing data), duration of symptoms at diagnosis (2%), oligo-JIA course (1%), ANA status (4%), early exposure to DMARDs (8%), on NSAIDs at enrollment (7%), baseline CHAQ (19%) and baseline Patient Global (19%). The following variables were used as predictors in the imputation model: gender, age at diagnosis, duration of symptoms at diagnosis, disease duration at enrollment, higher volume center, oligo-JIA course, ANA status, exposure to early IAS, early exposure to DMARDs, on NSAIDs at enrollment, baseline CHAQ, baseline PGADA, baseline Patient Global, active joint count of zero and inactive disease. The Markov Chain Monte Carlo modelling method was utilized (10). The number of iterations was set at 200 and 10 imputed datasets were created. Data imputation and analysis was performed using IBM SPSS Statistics Version 21.0. (Armonk, NY: IBM Corp.).

Results

Patient characteristics

Up to September 11th 2009, 524 oligo-JIA patients had been enrolled into ReACCh Out and had their baseline visit entered into the central database. A total of 214 patients were excluded from the current study for the following reasons: one or more of the first five study visits were

missing (N=181), the first IAS was done before study enrollment (N=22) or no information on whether or not IAS was performed was available (N=11). Baseline demographics of these 214 patients were compared to those of the 310 children included in the study (Table II). Excluded patients were older and had milder disease as suggested by a higher proportion of patients without active joints and a lower PGADA score at study enrollment.

The study population consisted of 310 children with oligo-JIA, of whom 230 (74.2%) were girls. Two hundred forty-nine (81.4%) patients had a persistent oligo-JIA course (course unknown in 4 patients). The median (IQR) age at JIA diagnosis was 4.9 (2.3-9.4) years and the median (IQR) disease duration at enrollment was 0.7 (0-2.2) months. Three (academic centers) of the 16 enrolling centers did not contribute any participants for this study as data from these centers had not been entered in the central database at time of data extraction. During the study period, 111 (35.8%) patients received an early IAS. Characteristics of patients at study entry are shown in Table III. At baseline, important differences between IAS exposure groups were a shorter disease duration and a higher active joint count, CHAQ, PGADA and Patient Global in the early IAS group. The proportion of patients taking NSAIDs at enrollment was higher in the group of patients who did not receive an early IAS.

Treatment received during the study period

Among the 310 patients, 184 (59.4%) received at least one IAS during follow-up in both groups (early IAS or no early IAS) combined (Table III). The majority of participants were taking NSAIDs at one point during the study but the proportion was higher in the group who did not receive an early IAS. Patients in the early IAS group were less likely to have received early DMARD therapy. Less than a third of patients received MTX and the proportion was similar between groups. Leflunomide, hydroxychloroquine and sulfasalazine were not frequently utilized. Only 4 patients received therapy with a biologic.

Primary outcome: Active joint count of zero

From the 6-month study visit onward, an active joint count of zero was found in >60% of participants at all study time points (Figure 1. a)). At the 24-month visit, 79 (71.2%; 95%CI

61.7-79.2%) and 150 (75.4%; 95%CI 68.7-81.1%) of participants had no active joint in the early and no early IAS group, respectively.

On univariate analysis, exposure to early IAS had no significant effect on the outcome active joint count of zero (Table IV). Three of the seven tested potential confounding variables were found to have a confounding effect: active joint count of zero at baseline (10.6% change in estimate), baseline CHAQ (8.5%) and baseline PGADA (16.0%). Time since enrollment, oligo-JIA course, ANA status, early IAS exposure, the active joint count of zero at enrollment, early exposure to DMARDs, on NSAIDs at enrollment, baseline CHAQ and PGADA were included in the multivariate model. The final model is shown in Table V. Exposure to early IAS, OR 1.52 (95%CI 0.68-3.37; p=0.306), was not statistically significantly associated with the outcome active joint count of zero. The direction of the effect was positive i.e. associated with an increased risk of reaching an active joint count of zero, which contrasted to what was found in univariate analysis. There were no significant interactions between early IAS and time since enrollment, OR 0.92 (95%CI 0.85-1.01; p=0.455).

Secondary outcome: Inactive disease

The number of patients with inactive disease increased at each study visit. Figure 1. b) shows the proportion of patients with inactive disease at each time point, depending on their exposure status to IAS. The group of patients who did not receive an early IAS was found to have inactive disease more frequently during the entire study period. At 24 months, 41 (36.9%; 95%CI 28.1-46.7%) and 92 (46.2%; 95%CI 39.2-53.4%) participants in the early and no early IAS group, respectively, had achieved inactive disease.

Univariate analysis revealed that patients who received an early IAS were significantly less likely to achieve inactive disease as compared to those who did not receive an early IAS (Table VI). The following two variables were identified as confounders for the association between early IAS and inactive disease: active joint count of zero at enrollment (25.4% change in estimate) and baseline PGADA (32.2%). Disease duration, time since enrollment, oligo-JIA course, ANA status, IAS exposure, on NSAIDs at enrollment, early exposure to DMARDs, the active joint count of zero at enrollment, baseline PGADA and baseline CHAQ

were included in the multivariate model. The variable Patient Global was not retained for the multivariate model because it was highly correlated with baseline CHAQ (Spearman's coefficient 0.6; p<0.001). The multivariate model is shown in Table VII. Patients who received an early IAS were significantly less likely to achieve inactive disease, OR 0.35 (95%CI 0.14-0.88; p=0.026). Here again, there were no significant interactions between early IAS and time since enrollment, OR 1.21 (95%CI 0.96-1.53; p=0.107).

Discussion

In this large cohort of Canadian children with oligo-JIA, no significant association was shown between early IAS and the achievement of an active joint count of zero in the first two years following study enrollment. The OR of early IAS was suggestive of a protective effect on the outcome active joint count of zero in multivariate analysis, although the finding was not statistically significant. In contrast, patients who received an early IAS were significantly less likely to achieve inactive disease. The discrepancy in the direction of effect of early IAS on the primary vs. secondary outcomes was surprising. Inactive disease requires the absence of active uveitis thus it is possible that early IAS offers benefit only for the arthritis but not the uveitis component of JIA.

No previous studies have addressed the effect of early IAS on disease activity over time in oligo-JIA patients. A recently published sub-analysis of the "Behandel Strategieën" (BeSt) study compared the disease course over 8 years among 508 early RA (diagnosis <2 years) patients who received (N=60) or not (N=448) an IAS within 1 year of study enrollment (11). RA patients who were injected had higher Disease Activity Score in 44 joints and Health Assessment Questionnaire score during the first year of the study, although the differences were less than the minimal clinically significant difference. No significant differences in the Disease Activity Score in 44 joints and in the Health Assessment Questionnaire scores were found afterwards, up to 8 years after enrollment. Although this study differs in many points from our study, it is interesting to note that results were similar to what was found for our primary aim i.e. IAS given early on did not seem to impact significantly on the later disease course. A retrospective study evaluated the efficacy of multiple IAS performed after a median (IQR) of 0.6 (0.2-2.5) years after diagnosis in 220 Italian JIA patients, of whom 109 had oligo-

JIA (12). Synovitis flare was defined as a flare of arthritis in injected but also in uninjected joints. Survival without synovitis flare was 50.0%, 31.5% and 19.5% at 1, 2 and 3 years after IAS, respectively. This study had no control group (i.e. systemic therapy without IAS) thus the effect of mutiple IAS per se cannot be isolated. Interestingly, the number of joints that flared (n=309) was less than half of the number of injected joints (n=725). This may suggest that following IAS, less aggressive therapy may be needed to manage disease flares, although the absence of a control group precludes definitive conclusions.

The concept of a "window of opportunity" during which one can alter the course of JIA remains to be proven. If this window truly exists, it may be that localized, intra-articular therapy is not sufficient to alter the disease course. Stronger systemic medications like DMARDs or even biologics might be required to achieve this goal. Very few studies have addressed the efficacy and impact of more aggressive therapy in recently diagnosed JIA. The Aggressive Combination Drug Therapy in Very Early Polyarticular JIA trial was a randomized, open label multicentric trial enrolling patients within 6 months of JIA diagnosis who were naive to DMARDs (13). Patients were treated with either MTX alone (N=20), COMBO therapy (MTX, hydroxychloroquine and sulfasalazine; N=20) and MTX and infliximab (N=19). At 54 weeks, inactive disease was achieved by 25%, 40% and 68% of the MTX alone, COMBO and MTX-infliximab groups, respectively (p=0.002). Also, the mean time spent in inactive disease was longest in the MTX-infliximab arm (26 weeks) when compared to the COMBO (13 weeks) and MTX (6 weeks) arms (p=0.001). The TREAT trial is another study that relates to the concept of early aggressive therapy in JIA (14). Briefly, 85 patients with a diagnosis of polyarticular JIA within the last 12 months naive to biologics were randomly assigned to either aggressive (MTX, etanercept and prednisolone) or conventional (MTX, placebo etanercept and placebo prednisolone) therapy. Patients randomized to the aggressive arm were more likely to achieve clinical inactive disease at 6 months (40% vs. 23%; p=0.08) and clinical remission on medication at 12 months (21% vs. 7%; p=0.05), although findings were not statistically significant. No long term data is yet available on the outcome of participants of JIA trials who were provided with early aggressive therapy. Only then will the concept of a window of opportunity in JIA will be better understood.

An encouraging finding was that the proportions of patients that met the primary and secondary outcomes were increasing throughout the study duration. On the other hand, at 24 months, the proportion of patients who still had active joints and who did not achieve inactive disease were 26.1% (95%CI 21.4-31.5%) and 57.1% (95%CI 51.4-62.7%) respectively. These numbers suggest that there is definitely room for improvement in the oligo-JIA treatment scheme. Faster disease control will likely lead to improved physical function and quality of life and will possibly prevent the occurrence of damage in these children.

The ReACCh Out cohort contains valuable information on choices of therapeutic agents used to treat oligo-JIA. Out of 310 included patients, 184 (59.4%) received at least one IAS during the study period. Various rates of IAS have been reported in JIA patients. Oen et al. studied a group of Canadian children diagnosed with JIA between 1974 and 1994, of whom 224 were of the oligo-JIA subtype (3). Thirty-two percent had received at least one IAS. Another retrospective study of 376 American patients with oligo-JIA diagnosed between 1992-1997 reported a similar frequency (33%) of IAS use (15). Other authors have reported higher rates ranging from 65.8% to as high as >90% (16-18). This wide range might be partly explained by the different time periods, locations and duration of follow up of these studies but it also reflects the absence of evidence based, formal recommendations on the place of IAS in the treatment of JIA.

Strengths and limitations

This study is the first to address the impact of early IAS on oligo-JIA disease activity over time. Because early IAS could have been effective only during the initial stage of the study, obtaining multiple data points for the outcome was mandatory to truly appreciate the effect of early IAS on disease activity. Missing data is not an uncommon issue in prospective multicentric observational studies. Although very few missing data were found for the outcome measures, two of the covariates (baseline CHAQ and Patient Global) had both 19% of missing data, which led to the exclusion of up to 25% of data if complete case analysis was performed. This could have placed a threat on the validity of the study findings. The use of multiple imputation is a definite strength as it enabled the use of every included patient and minimized the risk of obtaining biased estimates.

The absence of a favorable effect of early IAS on the disease course may be due to confounding by indication. Early IAS allocation in this study was not randomized but was left to the discretion of the treating physician, as this was an observational study. Treatment decisions were based on the patients' clinical status and on the physicians' prescribing habits. The disease of participants in the early IAS group was more active at study entry, as reflected by a higher active joint count, CHAQ and PGADA scores. Hence, it is possible that the patient characteristics per se rather than the exposure status to IAS were associated with a worse outcome. Confounding by indication is one of the main limitations when estimating treatment effect using observational data. We used a conservative 8% change-in-estimate rule to identify empirical confounders. It is possible that certain confounders were not adjusted for because they were not measured. Multivariate analysis might minimize but may not completely eliminate confounding effects. Also, children exposed to an early IAS were less frequently prescribed early DMARD therapy and NSAIDs throughout the study. Lack of systemic therapy and not necessarily early IAS might explain the apparent worse outcome of these children.

Despite the fact that a substantial proportion of enrolled ReACCh Out patients with oligo-JIA were excluded from the present analysis, included patients were still representative of the typical patients with oligo-JIA, that is young girls with ANA positive persistent oligo-JIA. Patients were excluded from this study mainly because they had missed one or more study visits. Our inclusion criteria specified that all first five study visits had to be completed. This criteria was chosen to ensure we had an adequate number of data points to explore the trajectory of outcomes over time. Unfortunately, it might have affected the generalizability of the study. We do acknowledge that our findings may not be representative of the overall oligo-JIA population as we likely selected a subgroup of patients with more active disease at baseline. Caution should then be used before generalizing our results to a population of patients with milder disease.

Conclusion

In this study of 310 children with oligo-JIA, no significant association was found between early IAS and the achievement of an active joint count of zero during the first two years after

study enrollment. Early IAS was associated with a lower risk of achieving inactive disease. Methodological issues encountered when estimating treatment effect using observational data might have biased the estimates obtained. Firm conclusion on the inefficacy of early IAS in improving outcomes of oligo-JIA patients cannot be drawn. Prospective studies addressing the limitations raised in this manuscript will be needed to clarify if early IAS can alter the disease course over time.

Table II. Baseline demographics of included and excluded patients

	Included in study (N=310)	Excluded from study (N=214)	p value
Female / male, N [a]	230 / 80	134 / 70	**0.038**
Age at diagnosis, years	4.9 (2.4-9.4)	7.3 (3.5-12.3)	**<0.001**
Duration of symptoms at diagnosis, months	3.6 (2.1-6.1)	4.2 (2.1-9.4)	0.139
Disease duration, months	0.7 (0-2.2)	1.2 (0-2.9)	0.076
Higher volume center, N (%) [b]	180 (58.1)	113 (52.8)	0.233
Active joint count	1 (1-2)	1 (0-2)	**0.015**
Active joint count of zero, N (%)	40 (12.9)	52 (25.0)	**<0.001**
Baseline PGADA	2.1 (1.0-3.5)	1.3 (0.3-2.9)	**0.002**

Data presented as median (interquartile range) unless otherwise specified; [a] N=204 for excluded patients; [b] Center which enrolled ≥ 45 patients; F: female; M: male; PGADA: physician global assessment of disease activity.

Table III. Patient characteristics

	Early IAS (N=111)	No early IAS (N=199)	p value
At enrollment			
Female / male, N	86 / 25	144 / 55	0.312
Age at diagnosis, years	4.5 (2.3-8.4)	5.3 (2.4-9.9)	0.188
Duration of symptoms at diagnosis, months [a]	3.6 (2.2-6.0)	3.4 (2.1-6.1)	0.739
Disease duration, months	0 (0-0.7)	1.2 (0-3.5)	**<0.001**
Higher volume center, N (%) [b]	64 (57.7)	116 (58.3)	0.914
Oligo-JIA course, N (%) [c]			0.206
Persistent	92 (85.2)	157 (79.3)	
Extended	16 (14.8)	41 (20.7)	
Active joint count	2 (1-3)	1 (1-2)	**<0.001**
Active joint count of zero, N (%)	0	40 (20.1)	**<0.001**
ANA positive, N (%) [d]	78 (73.6)	104 (54.5)	**0.001**
Systemic treatment, N (%)			
NSAIDs [e]	34 (32.1)	92 (50.8)	**0.002**
Methotrexate [f]	2 (2.0)	3 (1.7)	0.999
Leflunomide [g]	0	0	-
Corticosteroids [g]	0	1 (0.6)	0.999
Hydroxychloroquine [g]	0	0	-
Sulfasalazine [g]	0	0	-
Biologics [g]	0	0	-
Baseline CHAQ [h]	0.37 (0.12-0.75)	0.12 (0-0.62)	**0.003**
Baseline PGADA	2.6 (1.7-4.3)	1.5 (0.5-3.2)	**<0.001**
Baseline Patient Global [i]	1.2 (0.4-3.4)	0.8 (0-2.6)	**0.031**
During the study			
Number of IAS received, N (%)			**<0.001**
None	0	126 (63.3)	
1	49 (44.1)	38 (19.1)	
2	26 (23.4)	19 (9.6)	
≥3	36 (32.5)	16 (8.0)	
Disease duration at first IAS, months	1.0 (0.4-1.9)	9.0 (4.5-16.5)	**<0.001**
Systemic treatment received, N (%)			
NSAIDs [J]	94 (89.5)	176 (95.7)	**0.043**
Corticosteroids [k]	0	5 (2.8)	0.164
Methotrexate [l]	25 (24.8)	54 (29.8)	0.362
Leflunomide [k]	0	1 (0.6)	1.000
Hydroxychloroquine [k]	2 (2.0)	1 (0.6)	0.291
Sulfasalazine [k]	1 (1.0)	2 (1.1)	1.000
Biologics [k]	1 (1.0)	3 (1.7)	1.000
Early DMARDs [m]	5 (4.7)	26 (14.4)	**0.011**

Data presented as median (IQR) unless otherwise specified; [a] N=304, [b] Center which enrolled ≥ 45 patients; [c] N=306; [d] N=297; [e] N=287; [f] N=279; [g] N=277; [h] N=251; [i] N=250; [j] N=289; [k] N=280; [l] N=282; [m] N=286; ANA: antinuclear antibody; CHAQ: Childhood Health Assessment Questionnaire; DMARDs: disease-modifying antirheumatic drugs; F: female; IAS: intra-articular corticosteroid injection; M: male; NSAIDs: nonsteroidal anti-inflammatory drugs; Oligo-JIA: oligoarticular juvenile idiopathic arthritis; Patient Global: patient global assessment of overall well-being; PGADA: physician global assessment of disease activity.

Figure 1.

a) Proportion of patients with an active joint count of zero
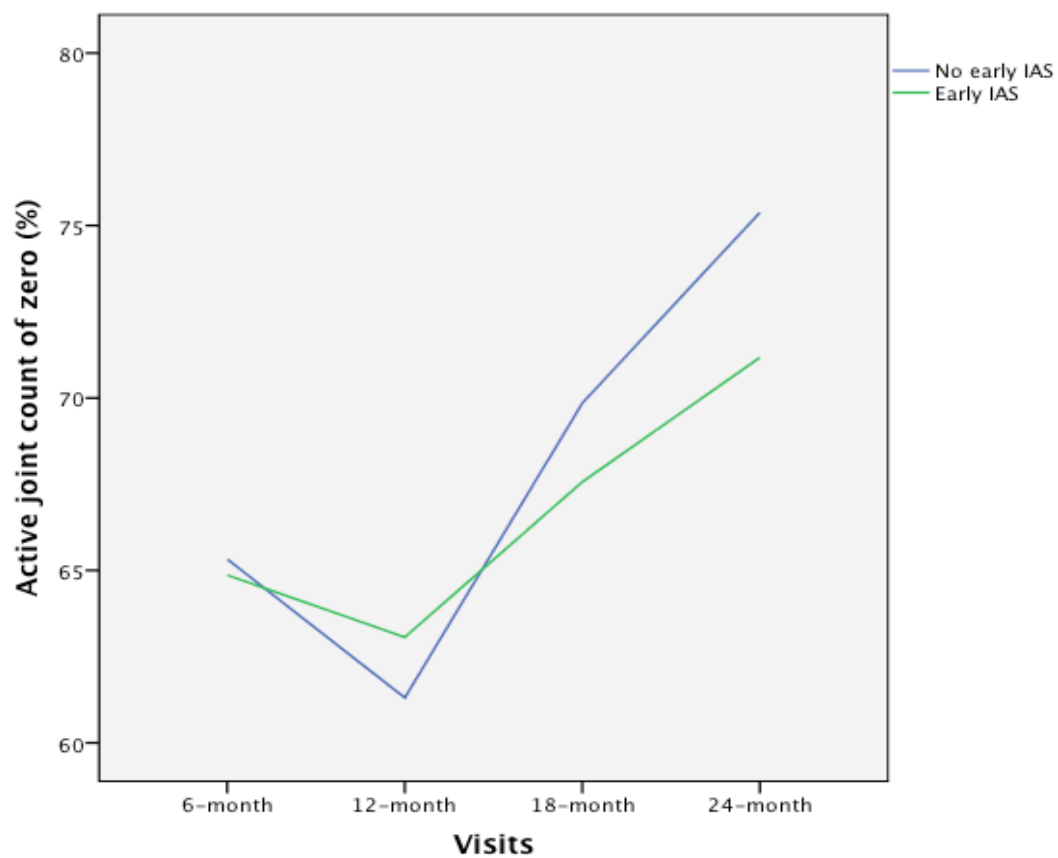
b) Proportion of patients with inactive disease
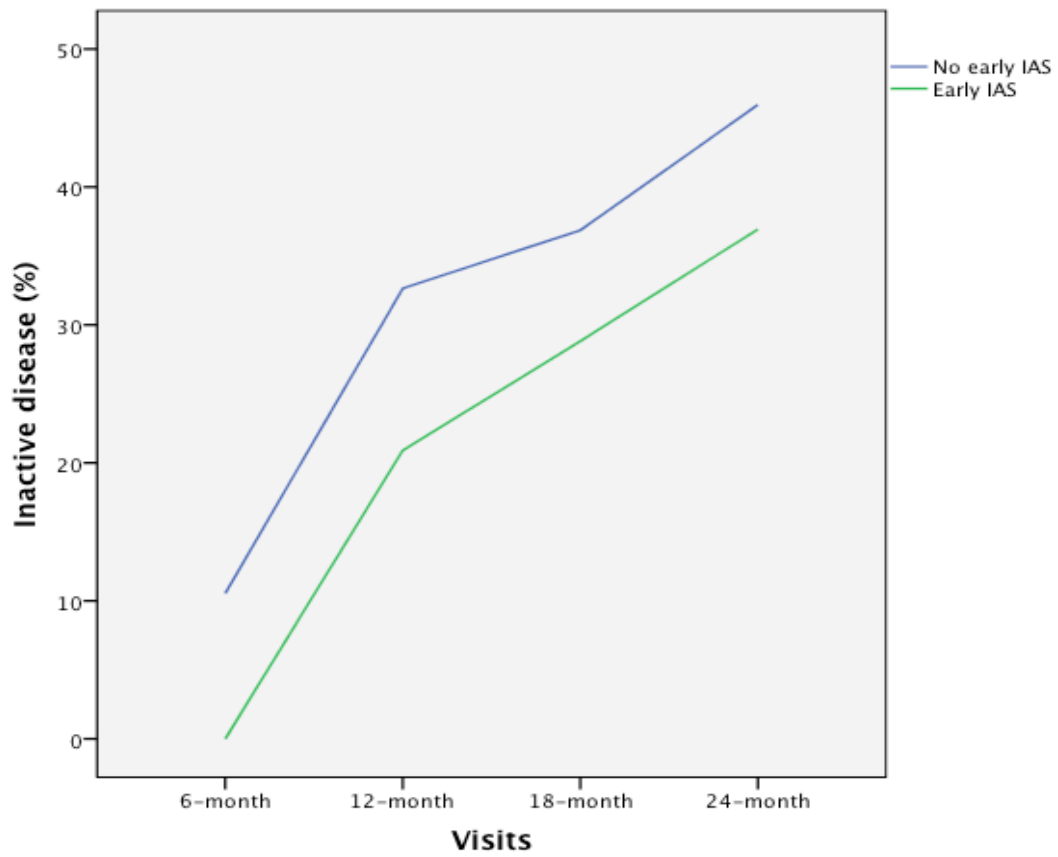
Table IV. Univariate GEE analysis for variables associated with an active joint count of zero

	OR (95%CI)	p value
Gender		
Male	1.07 (0.73-1.58)	0.713
Female	1	
Age at diagnosis, years	1.00 (0.97-1.04)	0.891
Time from onset of symptoms to diagnosis, months	0.98 (0.96-1.01)	0.167
Disease duration, months	1.01 (0.94-1.07)	0.878
Time since enrollment [a]	1.16 (1.05-1.27)	**0.002**
Higher volume center		
≥45 patients recruited	1.08 (0.78-1.49)	0.656
<45 patients recruited	1	
Oligo-JIA course		
Extended	0.31 (0.22-0.45)	**<0.001**
Persistent	1	
ANA status		
Positive	0.69 (0.49-0.96)	**0.027**
Negative	1	
IAS exposure		
Early IAS	0.94 (0.68-1.31)	0.718
No early IAS	1	
NSAIDs at enrollment		
Yes	1.01 (0.72-1.40)	0.973
No	1	
Early DMARDs		
Yes	0.75 (0.45-1.26)	0.281
No	1	
Active joint count of zero at enrollment		
Yes	1.71 (1.02-2.87)	**0.042**
No	1	
Baseline CHAQ	0.68 (0.49-0.96)	**0.026**
Baseline PGADA	0.87 (0.81-0.94)	**0.001**
Baseline Patient Global	0.95 (0.88-1.02)	0.164

[a] 6-monthly visits; ANA: antinuclear antibody; CHAQ: Childhood Health Assessment Questionnaire; DMARDs: disease-modifying antirheumatic drugs; IAS: intra-articular corticosteroid injection; NSAIDs: nonsteroidal anti-inflammatory drugs; Oligo-JIA: oligoarticular juvenile idiopathic arthritis; OR (95%CI): odds ratio (95% confidence interval); Patient Global: patient global assessment of overall well-being; PGADA: physician global assessment of disease activity.

Table V. Multivariate GEE analysis for the association between early IAS and an active joint
count of zero

	OR (95%CI)	p value
Independent variables		
Time since enrollment [a]	1.20 (1.06-1.37)	0.004
Oligo-JIA course		
Extended	0.31 (0.21-0.45)	<0.001
Persistent	1	
ANA status		
Positive	0.78 (0.56-1.10)	0.162
Negative	1	
IAS exposure		
Early IAS	1.52 (0.68-3.37)	0.306
No early IAS	1	
NSAIDs at enrollment		
Yes	0.97 (0.69-1.37)	0.879
No	1	
Early DMARDs		
Yes	1.25 (0.67-2.33)	0.483
No	1	
Active joint count of zero at enrollment		
Yes	1.40 (0.80-2.44)	0.237
No	1	
Baseline CHAQ	0.79 (0.55-1.12)	0.182
Baseline PGADA	0.89 (0.81-0.98)	0.016
Interaction term		
Early IAS * time since enrollment	0.92 (0.85-1.01)	0.455

[a] 6-monthly visits; ANA: antinuclear antibody; CHAQ: Childhood Health Assessment Questionnaire; DMARDs: disease-modifying antirheumatic drugs; IAS: intra-articular corticosteroid injection; NSAIDs: nonsteroidal anti-inflammatory drugs; Oligo-JIA: oligoarticular juvenile idiopathic arthritis; OR (95%CI): odds ratio (95% confidence interval); PGADA: physician global assessment of disease activity.

Table VI. Univariate GEE analysis for variables associated with inactive disease

	OR (95%CI)	p value
Gender		
Male	1.17 (0.79-1.72)	0.428
Female	1	
Age at diagnosis, years	1.03 (0.99-1.07)	0.161
Time from onset of symptoms to diagnosis, months	0.98 (0.94-1.01)	0.141
Disease duration, months	1.07 (1.01-1.14)	**0.027**
Time since enrollment [a]	1.84 (1.66-2.04)	**<0.001**
Higher volume center		
≥45 patients recruited	1.09 (0.78-1.53)	0.605
<45 patients recruited	1	
Oligo-JIA course		
Extended	0.33 (0.19-0.58)	**<0.001**
Persistent	1	
ANA status		
Positive	0.74 (0.53-1.03)	0.078
Negative	1	
IAS exposure		
Early IAS	0.59 (0.42-0.83)	**0.003**
No early IAS	1	
NSAIDs at enrollment		
Yes	0.92 (0.45-1.40)	0.662
No	1	
Early DMARDs		
Yes	0.80 (0.40-1.22)	0.429
No	1	
Active joint count of zero at enrollment		
Yes	3.15 (1.96-5.07)	**<0.001**
No	1	
Baseline CHAQ	0.68 (0.48-0.98)	**0.037**
Baseline PGADA	0.73 (0.66-0.81)	**<0.001**
Baseline Patient Global	0.91 (0.84-1.00)	**0.049**

[a] 6-monthly visits; ANA: antinuclear antibody; CHAQ: Childhood Health Assessment Questionnaire; DMARDs: disease-modifying antirheumatic drugs; IAS: intra-articular corticosteroid injection; NSAIDs: nonsteroidal anti-inflammatory drugs; Oligo-JIA: oligoarticular juvenile idiopathic arthritis; OR (95%CI): odds ratio (95% confidence interval); Patient Global: patient global assessment of overall well-being; PGADA: physician global assessment of disease activity.

Table VII. Multivariate GEE analysis for the association between early IAS and inactive disease

	OR (95%CI)	p value
Independent variables		
Disease duration, months	0.93 (0.85-1.02)	0.138
Time since enrollment [a]	1.87 (1.62-2.17)	<0.001
Oligo-JIA course		
Extended	0.25 (0.13-0.47)	<0.001
Persistent	1	
ANA status		
Positive	0.88 (0.58-1.33)	0.537
Negative	1	
IAS exposure		
Early IAS	0.35 (0.14-0.88)	**0.026**
No early IAS	1	
NSAIDs at enrollment		
Yes	0.76 (0.51-1.13)	0.180
No	1	
Early DMARDs		
Yes	1.52 (0.79-2.94)	0.211
No	1	
Active joint count of zero at enrollment		
Yes	2.16 (1.12-4.20)	0.022
No	1	
Baseline CHAQ	0.93 (0.62-1.40)	0.735
Baseline PGADA	0.73 (0.63-0.83)	<0.001
Interaction term		
Early IAS * time since enrollment	1.21 (0.96-1.53)	0.107

[a] 6-monthly visits; ANA: antinuclear antibody; CHAQ: Childhood Health Assessment Questionnaire; DMARDs: disease-modifying antirheumatic drugs; IAS: intra-articular corticosteroid injection; NSAIDs: nonsteroidal anti-inflammatory drugs; Oligo-JIA: oligoarticular juvenile idiopathic arthritis; OR (95%CI): odds ratio (95% confidence interval); PGADA: physician global assessment of disease activity.

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4.2 Missing data

Due to the potential bias induced by certain types of missing data, this topic deserved further exploration. Table VIII shows the proportion of missing data for the dependent and independent variables. The primary outcome had no missing data. The variable inactive disease used for the secondary outcome only had 3 missing items. The proportions of missing data for the independent variables were overall low, except for the variables baseline CHAQ and baseline Patient Global, which both had 19% of missing data.

Table VIII. Frequency of missing data

	Missing data N (%)
Dependent variables [a]	
Active joint count of zero	0
Inactive disease	3 (0.2)
Independent variables [b]	
Gender	0
Age at diagnosis	0
Duration of symptoms at diagnosis	6 (1.9)
Disease duration	0
Higher volume center [c]	0
Oligo-JIA course	3 (1.0)
ANA status	13 (4.2)
Early IAS	0
Early DMARDs	24 (7.7)
NSAIDs at enrollment	23 (7.4)
Active joint count of zero at enrollment	0
Baseline CHAQ	59 (19.0)
Baseline PGADA	0
Baseline Patient Global	60 (19.4)

[a] N= 1240 (310 patients, 4 visits per patients); [b] N=310 patients; [c] Center which enrolled ≥45 patients; ANA: antinuclear antibody; CHAQ: Childhood Health Assessment Questionnaire; DMARDs: disease-modifying antirheumatic drugs; IAS: intra-articular corticosteroid injection; NSAIDs: nonsteroidal anti-inflammatory drugs; Oligo-JIA: oligoarticular juvenile idiopathic arthritis; Patient Global: patient global assessment of overall well-being; PGADA: physician global assessment of disease activity.

To explore the missingness mechanism(s), participant characteristics were compared between those with and without a complete dataset (Table IX). Gender, the active joint count of zero at enrollment and baseline PGADA were significantly different between the 2 groups. These findings suggest that participants with a complete dataset had slightly more active disease at enrollment than those who had missing variables.

Table IX. Patient characteristics as per the completeness of their data

	Complete data N=217	Missing data N=93	p value
Female / male, N	168 / 49	62 / 31	**0.047**
Age at diagnosis, years	5.1 (2.6-9.4)	4.0 (2.0-9.8)	0.252
Duration of symptoms at diagnosis, months	4.0 (2.2-6.5)	3.2 (2.0-5.4)	0.112
Disease duration, months	0.5 (0-2.0)	1.0 (0-3.3)	0.133
Higher volume center, N (%) [a]	121 (55.8)	59 (63.4)	0.209
Oligo-JIA course, N (%)			0.232
Persistent	173 (79.7)	77 (85.6)	
Extended	44 (20.3)	13 (14.4)	
Active joint count of zero at enrollment, N (%)	15 (6.9)	25 (26.9)	**<0.001**
ANA positive, N (%) [b]	129 (59.4)	53 (63.3)	0.286
Early IAS, N (%)	73 (33.6)	38 (40.9)	0.224
NSAIDs at enrollment, N (%) [c]	93 (42.9)	33 (47.1)	0.530
Early DMARDs, N (%) [d]	26 (12.0)	5 (7.2)	0.270
Baseline CHAQ [e]	0.25 (0-0.62)	0.25 (0-0.56)	0.872
Baseline PGADA	2.1 (1.1-3.6)	1.7 (0.3-3.3)	**0.043**
Baseline Patient Global [f]	1.0 (0.2-2.7)	0.7 (0.1-3.4)	0.861

Data presented as median (IQR) unless otherwise specified; [a] Centers which enrolled $\geq$ 45 patients ; [b] N=297; [c] N=287; [d] N=286; [e] N=251; [f] N=250; ANA: antinuclear antibody; CHAQ: Childhood Health Assessment Questionnaire; DMARDs: disease-modifying antirheumatic drugs; F: female; IAS: intra-articular corticosteroid injection; M: male; NSAIDs: nonsteroidal anti-inflammatory drugs; Oligo-JIA: oligoarticular juvenile idiopathic arthritis; Patient Global: patient global assessment of overall well-being; PGADA: physician global assessment of disease activity.

The presence of differences in baseline demographics between participants with and without missing data suggested that the missingness mechanism was not MCAR. All 8 variables

(inactive disease, duration of symptoms at diagnosis, oligo-JIA course, ANA status, early DMARDs, on NSAIDs at enrollment, baseline CHAQ and baseline Patient Global) with missing items were assessed for their missingness mechanism. Results are presented in Table X. Four of these 8 variables showed a statistically significant association with at least one independent variable. This suggested that the missingness pattern for these variables was at least that of MAR.

Table X. Associations between the missing status of independent variables and variables in the dataset

	ANA status missing		Early DMARDs missing		NSAIDs at enrollment missing	
	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value
Female gender	0.77 (0.23-2.59)	0.677	0.83 (0.33-2.09)	0.696	0.78 (0.31-1.97)	0.599
Age at diagnosis, years	1.02 (0.90-1.17)	0.735	1.00 (0.91-1.11)	0.933	1.02 (0.92-1.12)	0.761
Duration of symptoms at diagnosis, months	0.99 (0.93-1.05)	0.713	0.91 (0.80-1.04)	0.161	0.92 (0.81-1.04)	0.194
Disease duration, months	1.07 (0.90-1.28)	0.452	1.37 (1.22-1.54)	**<0.001**	1.38 (1.23-1.56)	**<0.001**
Higher volume center [a]	0.84 (0.27-2.55)	0.753	0.49 (0.21-1.14)	0.096	0.53 (0.23-1.25)	0.146
Extended oligo-JIA course	0	0.997	0.38 (0.09-1.65)	0.195	0.40 (0.09-1.74)	0.221
Active joint count	0.91 (0.59-1.41)	0.663	0.24 (0.13-0.46)	**<0.001**	0.16 (0.07-0.33)	**<0.001**
Active joint count of zero at enrollment	1.24 (0.26-5.81)	0.785	14.0 (5.66-34.65)	**<0.001**	15.62 (6.17-39.55)	**<0.001**
ANA positive	-	-	0.83 (0.34-2.04)	0.687	0.76 (0.30-1.89)	0.552
Early IAS	1.13 (0.36-3.53)	0.838	0.45 (0.16-1.23)	0.119	0.47 (0.17-1.32)	0.152
Early DMARDs	0	0.998	-	-	-	-
NSAIDs at enrollment	0.85 (0.23-3.07)	0.800	0	0.996	-	-
Baseline CHAQ	1.03 (0.30-3.52)	0.960	1.06 (0.44-2.54)	0.897	1.10 (0.45-2.67)	0.831
Baseline PGADA	1.10 (0.85-1.43)	0.459	0.57 (0.41-0.81)	0.002	0.52 (0.35-0.76)	0.001
Baseline Patient Global	1.17 (0.91-1.51)	0.218	0.85 (0.65-1.12)	0.256	0.84 (0.63-1.12)	0.244
Active joint count of zero	0.82 (0.10-6.65)	0.853	1.64 (0.21-12.78)	0.639	1.56 (0.20-12.21)	0.672
Inactive disease	1.64 (0.48-5.57)	0.426	3.32 (1.21-9.14)	0.020	3.13 (1.13-8.65)	0.028

Table X. Associations between the missing status of independent variables and variables in the dataset (continued)

	Baseline CHAQ missing		Baseline Patient Global missing		Oligo-JIA course missing	
	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value
Female gender	0.56 (0.30-1.02)	0.058	0.70 (0.38-1.29)	0.250	$e^{16.88}$	0.997
Age at diagnosis, years	0.96 (0.89-1.03)	0.226	0.96 (0.89-1.03)	0.226	1.07 (0.83-1.38)	0.610
Duration of symptoms at diagnosis	0.96 (0.92-1.01)	0.154	0.98 (0.94-1.02)	0.268	0.83 (0.50-1.40)	0.492
Disease duration, months	0.98 (0.88-1.10)	0.777	1.00 (0.90-1.11)	0.959	0.25 (0.01-4.99)	0.361
Higher volume center [a]	3.48 (1.76-6.86)	**<0.001**	4.05 (2.01-8.14)	**<0.001**	0.36 (0.03-3.99)	0.403
Extended oligo-JIA course	1.06 (0.51-2.20)	0.875	1.18 (0.58-2.41)	0.645	-	-
Active joint count	0.97 (0.80-1.17)	0.739	0.93 (0.76-1.14)	0.503	1.09 (0.64-1.85)	0.759
Active joint count of zero at enrollment	2.03 (0.97-4.29)	0.062	1.98 (0.94-4.17)	0.072	0	0.998
ANA positive	1.52 (0.81-2.85)	0.190	1.42 (0.77-2.64)	0.263	1.27 (0.11-14.13)	0.848
Early IAS	2.17 (1.22-3.86)	0.008	2.27 (1.28-4.02)	0.005	$e^{17.62}$	0.995
Early DMARDs	0.83 (0.30-2.27)	0.716	0.81 (0.30-2.21)	0.679	0	0.998
NSAIDs at enrollment	1.18 (0.65-2.14)	0.596	1.35 (0.75-2.45)	0.317	0	0.996
Baseline CHAQ	-	-	2.28 (0.77-6.77)	0.137	0.12 (0-503.64)	0.615
Baseline PGADA	0.95 (0.82-1.10)	0.479	0.95 (0.82-1.10)	0.476	1.00 (0.57-1.76)	0.990
Baseline Patient Global	1.11 (0.78-1.57)	0.563	-	-	0.84 (0.26-2.74)	0.767
Active joint count of zero	0.94 (0.30-2.91)	0.090	0.96 (0.31-2.98)	0.940	$e^{16.64}$	0.999
Inactive disease	0.91 (0.51-1.61)	0.743	0.80 (0.45-1.41)	0.437	0.40 (0.04-4.45)	0.456

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Table X. Associations between the missing status of independent variables and variables in the dataset (continued)

	Duration of symptoms at diagnosis missing		Inactive disease missing	
	OR (95%CI)	p value	OR (95%CI)	p value
Female gender	0.35 (0.02-5.58)	0.454	0.17 (0.02-1.90)	0.151
Age at diagnosis, years	1.08 (0.79-1.48)	0.620	1.02 (0.79-1.34)	0.862
Duration of symptoms at diagnosis	-	-	1.08 (1.00-1.16)	0.049
Disease duration, months	1.12 (0.75-1.68)	0.585	0	0.945
Higher volume center [a]	0	0.995	0.36 (0.03-3.99)	0.403
Extended oligo-JIA course	4.45 (0.27-72.17)	0.294	0	0.997
Active joint count	0.210 (0.02-1.98)	0.173	0.54 (0.14-1.99)	0.352
Active joint count of zero at enrollment	6.90 (0.42-112.53)	0.175	0	0.998
ANA positive	$e^{16.70}$	0.996	0.63 (0.04-10.17)	0.745
Early IAS	0	0.997	0.90 (0.08-9.99)	0.928
Early DMARDs	8.47 (0.52-138.89)	0.134	0	0.998
NSAIDs at enrollment	$e^{17.08}$	0.996	0	0.996
Baseline CHAQ	0	0.988	0.09 (0-54.64)	0.456
Baseline PGADA	1.54 (0.86-2.77)	0.147	0.80 (0.40-1.62)	0.541
Baseline Patient Global	1.01 (0.42-2.43)	0.988	0.45 (0.06-3.24)	0.429
Active joint count of zero	$e^{16.23}$	0.999	$e^{16.64}$	0.999
Inactive disease	0	0.996	-	-

Variables for which the OR is 0 or e^x have no 95%CI because the computation of the 95%CI was not possible; [a] Centers which enrolled ≥ 45 patients; ANA: antinuclear antibody; CHAQ: Childhood Health Assessment Questionnaire; DMARDs: disease-modifying antirheumatic drugs; F: female; IAS: intra-articular corticosteroid injection; M: male; NSAIDs: nonsteroidal anti-inflammatory drugs; Oligo-JIA: oligoarticular juvenile idiopathic arthritis; OR (95%CI): odds ratio (95% confidence interval); Patient Global: patient global assessment of overall well-being; PGADA: physician global assessment of disease activity.

To explore the association between the completeness of the dataset and the primary or secondary outcomes, a univariate GEE model was created using the independent variable "incomplete dataset" (at least one independent and/or outcome variable missing vs. complete dataset). No statistically significant association was found between the variable "incomplete dataset" for the primary outcome, active joint count of zero (incomplete dataset OR 1.15 (0.81-1.63); p=0.428) and the secondary outcome, inactive disease (incomplete dataset OR 1.25 (0.88-1.78); p=0.218). This suggested that the primary and secondary outcomes of patients with and without a complete dataset was not significantly different. This may suggest that the missingness mechanism is less likely to be MNAR but this cannot be confirm or infirm as it relies on unobserved/unmeasured data.

4.3 Exploration to identify potential confounders

The search for potential confounding variables for the association between early IAS and the primary and secondary outcomes was done by comparing the change in the crude OR from the adjusted OR in the presence of the potential confounding variable using multivariate GEE. The adjusted OR and OR differences are shown in Tables XI and XII. An OR difference of at least 8% was considered significant for a confounding effect. As shown in Table XI, 3 of the 7 tested variables satisfied the 8% change-in-estimate rule for the primary outcome. Two potential confounders were found for the outcome inactive disease (Table XII).

Table XI. Potential confounders for the association between early IAS and active joint count of
zero

	Adjusted OR (95%CI) of early IAS	OR difference [a] (%)
Analysis adjusting for the following variables		
Oligo-JIA course	0.87 (0.62-1.21)	7.4
Active joint count of zero at enrollment	1.04 (0.74-1.46)	**10.6**
On NSAIDs at enrollment	0.94 (0.67-1.31)	0
Early DMARDs	0.91 (0.65-1.27)	3.2
Baseline CHAQ	1.02 (0.73-1.44)	**8.5**
Baseline PGADA	1.09 (0.78-1.52)	**16.0**
Baseline Patient Global	0.96 (0.69-1.34)	2.1

[a] OR difference ((crude OR-adjusted OR) / crude OR) x 100; crude OR: 0.94; CHAQ: Childhood Health Assessment
Questionnaire; 95%CI: 95% confidence interval; DMARDs: disease-modifying antirheumatic drugs; IAS: intra-
articular corticosteroid injection; NSAIDs: nonsteroidal anti-inflammatory drugs; Oligo-JIA: oligoarticular juvenile
idiopathic arthritis; OR: odds ratio; Patient Global: patient global assessment of overall well-being; PGADA: physician
global assessment of disease activity.

Table XII. Potential confounders for the association between early IAS and inactive disease

	Adjusted OR (95%CI) of early IAS	OR difference [a] (%)
Analysis adjusting for the following variables		
Oligo-JIA course	0.55 (0.39-0.78)	6.8
Active joint count of zero at enrollment	0.74 (0.52-1.06)	**25.4**
On NSAIDs at enrollment	0.57 (0.40-0.81)	3.4
Early DMARDs	0.57 (0.40-0.81)	3.4
Baseline CHAQ	0.62 (0.44-0.89)	5.1
Baseline PGADA	0.78 (0.55-1.11)	**32.2**
Baseline Patient Global	0.61 (0.43-0.86)	3.4

[a] OR difference ((crude OR-adjusted OR) / crude OR) x 100; crude OR: 0.59; CHAQ: Childhood Health Assessment
Questionnaire; 95%CI: 95% confidence interval; DMARDs: disease-modifying antirheumatic drugs; IAS: intra-
articular corticosteroid injection; NSAIDs: nonsteroidal anti-inflammatory drugs; Oligo-JIA: oligoarticular juvenile
idiopathic arthritis; OR: odds ratio; Patient Global: patient global assessment of overall well-being; PGADA: physician
global assessment of disease activity.

4.4 Complete case analysis

When analysis was performed as complete case analysis, similar results were obtained than those presented for the imputed dataset for the relationship between early IAS and the primary outcome (Tables XIII and XIV). For the secondary outcome inactive disease, the covariate early IAS was not statistically significant when included in the multivariate model but the direction of effect remained non-protective (Tables XV and XVI).

Table XIII. Complete case univariate GEE analysis for variables associated with an active joint count of zero

	OR (95%CI)	p value
Gender		
Male	1.07 (0.73-1.58)	0.713
Female	1	
Age at diagnosis, years	1.00 (0.97-1.04)	0.891
Time from onset of symptoms to diagnosis, months	0.98 (0.96-1.01)	0.176
Disease duration, months	1.01 (0.94-1.07)	0.878
Time since enrollment [a]	1.16 (1.05-1.27)	**0.002**
Higher volume center		
≥45 patients recruited	1.08 (0.78-1.49)	0.656
<45 patients recruited	1	
Oligo-JIA course		
Extended	0.31 (0.22-0.45)	**<0.001**
Persistent	1	
Active joint count of zero at enrollment		
Yes	1.71 (1.02-2.87)	**0.042**
No	1	
ANA status		
Positive	0.69 (0.49-0.97)	**0.032**
Negative	1	
IAS exposure		
Early IAS	0.94 (0.68-1.31)	0.718
No early IAS	1	
NSAIDs at enrollment		
Yes	0.95 (0.68-1.31)	0.739
No	1	
Early DMARDs		
Yes	0.67 (0.41-1.10)	0.115
No	1	
Baseline CHAQ	0.68 (0.49-0.95)	**0.022**
Baseline PGADA	0.87 (0.81-0.94)	**0.001**
Baseline Patient Global	0.96 (0.89-1.03)	0.292

[a] 6-monthly visits; ANA: antinuclear antibody; CHAQ: Childhood Health Assessment Questionnaire; DMARDs: disease-modifying antirheumatic drugs; IAS: intra-articular corticosteroid injection; NSAIDs: nonsteroidal anti-inflammatory drugs; Oligo-JIA: oligoarticular juvenile idiopathic arthritis; OR (95%CI): odds ratio (95% confidence interval); Patient Global: patient global assessment of overall well-being; PGADA: physician global assessment of disease activity.

Table XIV. Complete case multivariate GEE analysis for the association between early IAS and an active joint count of zero

	OR (95%CI)	p value
Independent variables		
Time since enrollment [a]	1.28 (1.05-1.48)	0.001
Oligo-JIA course		
Extended	0.33 (0.22-0.50)	<0.001
Persistent	1	
ANA status		
Positive	0.65 (0.44-0.96)	0.029
Negative	1	
IAS exposure		
Early IAS	2.00 (0.77-5.20)	0.157
No early IAS	1	
NSAIDs at enrollment		
Yes	0.96 (0.65-1.41)	0.821
No	1	
Early DMARDs		
Yes	1.25 (0.63-2.50)	0.521
No	1	
Active joint count of zero at enrollment		
Yes	1.56 (0.63-3.84)	0.337
No	1	
Baseline CHAQ	0.75 (0.52-1.07)	0.115
Baseline PGADA	0.88 (0.79-0.99)	0.034
Interaction term		
Early IAS * time since enrollment	0.91 (0.71-1.16)	0.457

[a] 6-monthly visits; ANA: antinuclear antibody; CHAQ: Childhood Health Assessment Questionnaire; DMARDs: disease-modifying antirheumatic drugs; IAS: intra-articular corticosteroid injection; NSAIDs: nonsteroidal anti-inflammatory drugs; Oligo-JIA: oligoarticular juvenile idiopathic arthritis; OR (95%CI): odds ratio (95% confidence interval); PGADA: physician global assessment of disease activity.

Table XV. Complete case univariate GEE analysis for variables associated with inactive disease

	OR (95%CI)	p value
Gender		
Male	1.17 (0.79-1.72)	0.437
Female	1	
Age at diagnosis, years	1.03 (0.99-1.07)	0.147
Time from onset of symptoms to diagnosis, months	0.98 (0.95-1.01)	0.151
Disease duration, months	1.06 (0.99-1.13)	0.066
Time since enrollment [a]	1.84 (1.66-2.05)	**<0.001**
Higher volume center		
≥45 patients recruited	1.10 (0.79-1.53)	0.590
<45 patients recruited	1	
Oligo-JIA course		
Extended	0.33 (0.19-0.58)	**<0.001**
Persistent	1	
Active joint count of zero at enrollment		
Yes	2.75 (1.68-4.50)	**<0.001**
No	1	
ANA status		
Positive	0.74 (0.53-1.04)	0.087
Negative	1	
IAS exposure		
Early IAS	0.59 (0.42-0.83)	**0.003**
No early IAS	1	
NSAIDs at enrollment		
Yes	0.92 (0.65-1.31)	0.662
No	1	
Early DMARDs		
Yes	0.70 (0.40-1.22)	0.207
No	1	
Baseline CHAQ	0.66 (0.45-0.96)	**0.031**
Baseline PGADA	0.73 (0.66-0.81)	**<0.001**
Baseline Patient Global	0.91 (0.83-0.99)	**0.033**

[a] 6-monthly visits; ANA: antinuclear antibody; CHAQ: Childhood Health Assessment Questionnaire; DMARDs: disease-modifying antirheumatic drugs; IAS: intra-articular corticosteroid injection; NSAIDs: nonsteroidal anti-inflammatory drugs; Oligo-JIA: oligoarticular juvenile idiopathic arthritis; OR (95%CI): odds ratio (95% confidence interval); Patient Global: patient global assessment of overall well-being; PGADA: physician global assessment of disease activity.

Table XVI. Complete case multivariate GEE analysis for the association between early IAS and
inactive disease

	OR (95%CI)	p value
Independent variables		
Disease duration, months	0.88 (0.77-1.00)	0.054
Time since enrollment [a]	2.16 (1.86-2.51)	<0.001
Oligo-JIA course		
Extended	0.26 (0.13-0.53)	<0.001
Persistent	1	
ANA status		
Positive	0.63 (0.39-1.03)	0.066
Negative	1	
IAS exposure		
Early IAS	0.58 (0.19-1.78)	0.343
No early IAS	1	
NSAIDs at enrollment		
Yes	0.75 (0.45-1.23)	0.257
No	1	
Early DMARDs		
Yes	1.61 (0.74-3.51)	0.234
No	1	
Active joint count of zero at enrollment		
Yes	3.42 (1.27-9.25)	0.015
No	1	
Baseline CHAQ	0.87 (0.53-1.42)	0.572
Baseline PGADA	0.70 (0.60-0.81)	<0.001
Interaction term		
Early IAS * time since enrollment	1.15 (0.87-1.52)	0.321

[a] 6-monthly visits; ANA: antinuclear antibody; CHAQ: Childhood Health Assessment Questionnaire; DMARDs: disease-modifying antirheumatic drugs; IAS: intra-articular corticosteroid injection; NSAIDs: nonsteroidal anti-inflammatory drugs; Oligo-JIA: oligoarticular juvenile idiopathic arthritis; OR (95%CI): odds ratio (95% confidence interval); PGADA: physician global assessment of disease activity.

Chapter 5: Discussion

In this large cohort of Canadian children with oligo-JIA, no significant association was found between early IAS and the achievement of an active joint count of zero in the first 2 years following study enrollment. The OR of early IAS was suggestive of a protective effect on the outcome active joint count of zero in multivariate analysis, although the finding was not statistically significant. In contrast, early IAS remained associated with a decreased risk of achieving inactive disease, even after adjusting for potential confounders. The discrepancy in the direction of effect of early IAS on the primary vs. secondary outcomes was surprising. Inactive disease requires the absence of active uveitis thus it is possible that early IAS offers benefit only for the arthritis but not the uveitis component of JIA. Overall, our results suggest that performing IAS early after oligo-JIA diagnosis offers no clear benefit in terms of improving the initial disease course. Early localized injections of corticosteroid may not be enough to put the disease in check. If a window of opportunity truly exists in oligo-JIA, systemic medications, like DMARDs or biologics, may be needed to favorably alter the disease course.

No similar studies completed in a JIA population has addressed the efficacy of early IAS on the disease course over time. It is interesting to note that results of the BeSt study were similar to our findings for the primary aim i.e. IAS given to RA patients within 2 years after diagnosis did not seem to impact significantly on the later disease course (65). We believe that the shorter interval (3 months) between disease diagnosis and IAS used in our study was preferable. Until the concept of a window of opportunity is better defined, studies aiming to explore this theory should err on the side of caution and use narrower time intervals. This could lower the risk of making erroneous conclusion resulting from the administration of the intervention outside the critical window period. On the other hand, longer follow up time than what was done in our study is needed to ascertain if earlier disease control will offer sustained benefit.

An encouraging finding was that chances to meet the primary and secondary outcomes were increasing throughout the study duration. At least 60% of participants had an active joint count of zero throughout the study. At 24 months, the proportion of patients with an active joint count of zero and inactive disease were 73.9% (95%CI 68.5-78.6%) and 42.9% (95%CI 37.4-48.6%), respectively. Although the concept of improvement over time is encouraging, these numbers suggest that there is definitely room for improvement in the oligo-JIA treatment management scheme. Faster disease control will likely lead to improved physical function and quality of life and will possibly prevent the occurrence of damage in these children. Comparisons with other JIA cohorts are difficult to make as follow up time and definition used for inactive disease vary. Most of the other studies distinguished between remission on and off medications but our study did not. We used the absence of active joints and inactive disease for a minimum of 6 consecutive months regardless of medication intake, as the focus was set on having inactive disease. A recently published retrospective study with a median (IQR) follow up of 4.3 (2.7-6.1) years reported the rates of inactive disease and remission following at least one IAS in 77 children with JIA of whom 64 (83.1%) had oligoarticular disease (79). At the last recorded visit, 15 (19.5%) had inactive disease, 3 (3.9%) were in remission on medication and 20 (26.0%) were in remission off medication. Taken together, 49.4% of participants had no active joints at the last study visit, which is lower than what was reported in our study. This could be explained by the longer follow up time, allowing time for patients to flare, and the higher proportion of patients with oligo-extended JIA and other non-oligo subtypes included in that study. The Childhood Arthritis Prospective Study (CAPS) reported the outcome of 385 oligo-JIA patients followed at 5 tertiary centers in the United Kingdom (80). One year after presentation, the median (IQR) active joint count was 0 (0-1) in both oligo-persistent and extended JIA patients. The same results were obtain in our oligo-persistent JIA patients but our oligo-extended group had a higher median (IQR) active joint count at the 12-month visit (2 (0-3)). The difference seen in oligo-extended children may be partly explained by the higher proportion of patients that received systemic medications or IAS in the CAPS cohort. In the Nordic Cohort Study, 87 (69.0%) of 126 oligo-persistent JIA were either in remission on or off medications after a median (range) time of 98 (84-147) months following disease onset. As expected, the proportion was lower for the oligo-extended subgroup with 28 (37.3%) patients in remission on or off medication. These longer term

studies reinforce the fact that oligo-JIA must be considered a chronic disease as a significant proportion of patients may have active disease many years after onset. The scientific community should aggressively pursue the search for better treatment combination that would enable more children to become, and most importantly, stay in remission over the long term.

The ReACCh Out cohort allowed to obtain valuable contemporary information on the use of IAS in oligo-JIA. Among the 310 participants included in our study, 184 (59.4%) received at least one IAS during the first 2 years following study enrollment. Studies have reported a wide range of IAS utilization in JIA. Oen et al. retrospectively studied a cohort of Canadian JIA patients diagnosed between 1974 et 1994 of whom 224 had an oligoarticular disease course (20). After a median (range) follow up duration of 13.5 (5.6-25.8) years, 32% had received at least one IAS. Another retrospective study done on 376 American children diagnosed with oligo-JIA between 1992-1997 who were followed for at least one year, reported a very similar rate of IAS use (33%) (27). Other studies have reported a much higher frequency of IAS. More recent data coming from the Childhood Arthritis Rheumatology Research Alliance registry informed us on the use of IAS among 2748 JIA patients after a median (IQR) disease course of 3.9 (1.8-7.2) years (81). Among the 948 oligo-JIA patients, 65.8% had been given at least one IAS. In the CAPS cohort, 75.1% of 385 oligo-JIA patients received an IAS within the first year after presentation (80). Guillaume et al. found even a higher proportion in their retrospective study of 207 French oligo-JIA patients seen between 1988-1998 (14). Despite a relatively short mean follow up time (4.2 ± 2.5 years), >90% of patients had received an IAS. This wide range of IAS utilization might be partly explained by the different time periods, locations and duration of follow up of these studies. It also reflects the absence of evidence-based, formal recommendations on the place of IAS in the treatment of JIA. It will be interesting to see if, following the American College of Rheumatology recommendations for the treatment of JIA published in 2011, in which IAS is part of first-line agent choices, a change in the prescription pattern of IAS for children with JIA will be detected.

The use of IAS as a first-line agent is often dictated by its perceived efficacy, the ease with which it can be performed, the number of joints involved, the age of the patient and the presence of comorbidities (i.e. uveitis). A survey conducted among pediatric rheumatologist

across Canada and the United States showed that the majority of physicians thought that IAS were more effective than NSAIDs as first-line therapy in children with knee monoarthritis (82). Despite their belief in the efficacy of IAS, 63% proposed initial treatment with NSAIDs in a fictional scenario involving a 2 year old girl. They proposed IAS as the next therapeutic step if the patient was not improving. When the scenario involved an older patient, only an additional 11% of physicians changed their initial recommendations and suggested IAS as first-line therapy. On the other hand, the presence of local complications such as joint contracture or limb length discrepancy led a majority of physicians (64%) to suggest IAS as the initial therapeutic step. A survey performed among 127 Canadian and American pediatric rheumatologists explored barriers to IAS use in children with JIA (59). The most frequent limiting step was the lack of easy access to patient sedation (33%) followed by lack of physician's time (22%) and insufficient medical support staff (21%).

The vast majority of participants received NSAIDs at one point during the study. This class of medication is the one most commonly used for the systemic treatment of oligo-JIA patients. Nearly a third of patients received MTX and a small proportion of participants received leflunomide (1/280) and biologics (4/280). Considering that throughout the study, the highest proportion of patients found with inactive disease was only 42.9% (95%CI 37.4-48.6%), one may question the low frequency with which DMARDs were prescribed. The definition used to consider a patient exposed to a specific medication required a minimum period of intake hence it is possible that the proportions were underestimated. Certain physicians may be reluctant to start a DMARD or a biologic agent when the child only has 1 or 2 active joints. The use of IAS alone or as complementary therapy to NSAIDs is an attractive option for these scenarios. The early use of DMARDs in our cohort of oligo-JIA patients resembles that reported in the Nordic Cohort Study (18). In the later cohort, 9.3% of oligo-JIA patients were started on DMARDs within 7 months of disease onset. Among the 385 oligo-JIA enrolled in the CAPS cohort, 329 (85.5%), 89 (23.1%) and 6 (1.6%) had received treatment with NSAIDS, MTX and biologics, respectively, one year after presentation (80). The frequencies of DMARDs and biologics use were similar to that reported in our study despite the fact that our follow up time extended to 2 years. The Childhood Arthritis Rheumatology Research Alliance registry reported the use of DMARDs in 587 (61.9%) and of biologics in 247 (26.1%) of 948 enrolled

oligo-JIA patients (81). These higher numbers likely reflect the longer disease duration of these patients at time of data analysis. It also highlights the fact that oligo-JIA is not a benign condition and will not uncommonly need immunosuppressive therapy for adequate disease control.

5.1 Strengths

The ReACCh Out cohort provides valuable contemporary information on JIA patients and their outcomes. This study is the first to address the impact of early IAS on oligo-JIA disease activity. Studies aiming to identify therapeutic agents that will lead to early disease control are extremely valuable as early disease control is most likely a key element in improving patients outcome over the long run. The repeated measure design allowed to obtain information on the outcome over time and not just at a fixed time point. The visualization of the trajectory of the outcome is a definite strength of this study as one can better understand the behavior of oligo-JIA over time. Also, because early IAS could have been effective only during the initial stage of the study, obtaining multiple data points for the outcome was mandatory to truly appreciate the effect of early IAS on disease activity. Not surprisingly in this longitudinal study, approximately 25% of observations would have been lost if analysis would have been performed as complete case analysis. This could have placed a threat on the validity of study findings. The missingness mechanism of variables with missing items was thoroughly investigated. It was found to be MCAR but also MAR which prompted the use of multiple imputation. This is a definite strength in the study as it enabled the use of every included patient and minimized the risk of obtaining biased estimates.

5.2 Important methodological considerations and limitations

5.2.1 Confounding

The absence of a favorable effect of early IAS on the disease course may be due to confounding by indication. Early IAS allocation in this study was not randomized but was left to the discretion of the treating physician, as this was an observational study. Treatment

decisions were based on patients' clinical status and on physicians' prescribing habits. Participants in the early IAS group had more active disease at study entry, as reflected by a higher active joint count, CHAQ and PGADA scores. Hence, it is possible that the patient characteristics per se rather than the exposure status to IAS were associated with a worse outcome (figure).

Figure 2. Schematization of confounding
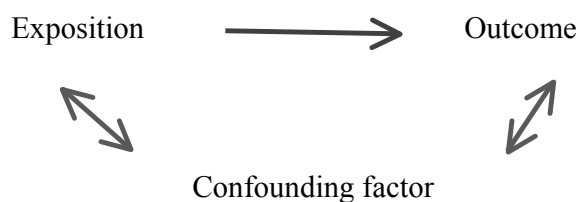
Exposition   ⟶   Outcome

Confounding factor

Confounding by indication is one of the main limitations when estimating treatment effect using observational data. Different methods may be utilized to minimize confounding (83). Certain methods need to be implemented in the design of the study such as randomization, restriction and matching. Others can be used during the analysis stage such as stratification and multivariable analysis. The use of propensity score is another method that can be applied (84). For the current study, we used multivariable analysis to adjust for confounding. We chose a conservative 8% change-in-estimate rule to identify empirical confounders; this threshold was selected to ensure all potential confounding variables would be identified. It is possible that certain confounders were not adjusted for because they were not measured. Also, multivariable analysis might minimize but may not completely eliminate the confounding effect(s). The presence of multiple potential confounders would have made stratification a complex process to undertake. Propensity score matching could have been an option but this method usually requires a certain degree of planning during the design of the trial to allow for an adequate degree of overlap in the baseline covariates.

Another potential issue was that children exposed to an early IAS were less likely to be taking NSAIDs and were less frequently prescribed early DMARD therapy. Lack of systemic therapy and not necessarily early IAS might explain the apparent worse outcome of these children. Only a small proportion of patients in both groups were exposed to early DMARDs, it is therefore difficult to properly assess the effect of this variable on the outcomes and on the relationship between early IAS and the outcomes. Both variables were included in the multivariate model as adjustment for these 2 variables was felt to be clinically relevant, despite the fact that they did not appear to have a confounding effect.

5.2.2 Difference in disease duration at enrollment

The ReACCh Out cohort is an inception cohort recruiting participants within one year of their JIA diagnosis. Although this may seem to be a relatively narrow time frame, patients may not be at the same disease stage when they were enrolled in the study. To illustrate this concept better, the following example will be used. Two patients (A and B) take the same number of months (i.e. 15 months) to achieve an active joint count of zero. These 2 patients are followed for 2 years. Patient A is enrolled at the time of his JIA diagnosis but patient B is enrolled 10 months after his diagnosis. At the last study visit, patient A has not yet reached an active joint count of zero but patient B has. We could falsely conclude that patient A's outcome is less favorable than patient B. Both are following the same disease trajectory but are being observed at different moments in their disease course.

Figure 3. Effect of disease duration at time of study enrollment

Patient A

Disease active

Study enrollment   Assessment of outcome: Active joint count of zero: no

Patient B

Disease active

Study enrollment   Assessment of outcome: Active joint count of zero: yes
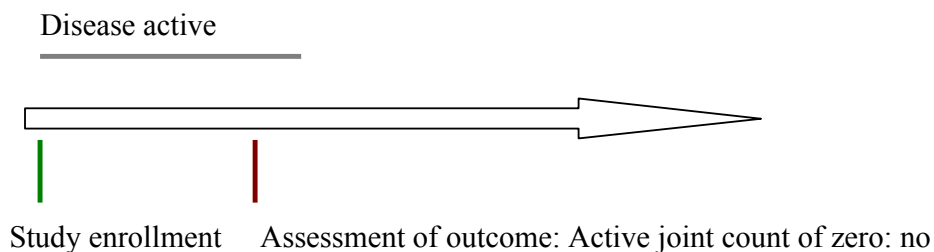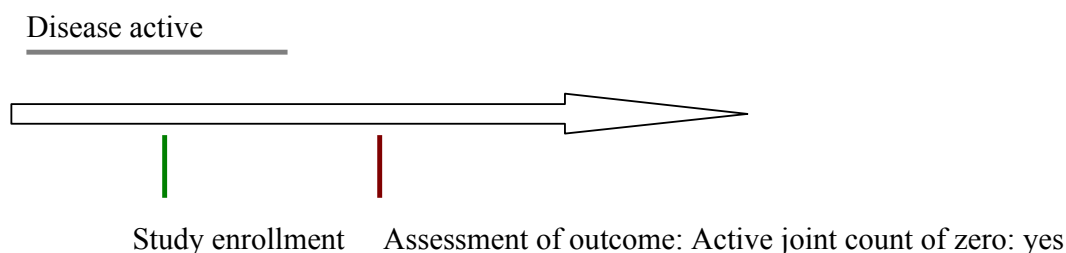
In our study, disease duration of the early IAS group was shorter, with a median (IQR) of 0 (0-0.7) months as compared to the group no early IAS, who had a median (IQR) of 1.2 (0-3.5) months (p<0.001). The early IAS group was in an earlier stage of disease but the absolute difference was small. It seems unlikely that the apparent better evolution in those who did not receive an early IAS would be explained by this phenomenon. The variable disease duration at study entry was included in the multivariate model of the secondary aim but not of the primary aim, as it was not statistically significant in univariate analysis and 3 other independent variables had already been forced into the model. To ensure that this potential bias did not impact on results obtained for the primary aim, the multivariate model for the primary outcome was re-run adding disease duration at study enrollment as an independent variable. The result obtained for early IAS remained similar (OR 1.44 (95%CI 0.64-3.21), p=0.377 for the model with disease duration at enrollment vs. OR 1.52 (95%CI 0.68-3.37); p=0.306 for the model without disease duration at enrollment).

5.2.3 Considerations related to the IAS procedure

Information on the type and dose of corticosteroid injected were not considered as potential explanatory variables. Triamcinolone hexacetonid is recognized as being superior to other corticosteroid formulation and doses used are quite standard. It seemed unlikely that these 2 elements would have had a significant impact on the outcomes. Also, the use of radiological guidance was not taken into account as this information was not available in the central database. It is possible that the response to corticosteroid injected under radiological guidance differs as intra-articular deposition of the medication can be confirmed whereas it can only be presumed when injection is performed without guidance. Therefore we are unable to comment on the effect of this variable on the outcomes or on the interaction it could have had with early IAS.

5.2.4 Missing data

Missing data is not an uncommon issue in prospective multicentric observational studies. No data was missing for the primary outcome and only a small proportion of data was missing for the secondary outcome. The proportions of missing data for some of the independent variables were significant, leading to the exclusion of up to 25% of the data when complete case multivariate analyses were performed. This could have led to loss of power and precision and to biased estimates.

Missing data are often categorized as per their missingness mechanism. This classification is not just semantic. Specific analysis performed with a dataset containing certain types of missing data may lead to biased estimates. The choice of statistical modeling needs to take into account the missingness mechanisms. Three main mechanisms are recognized (85). First, MCAR. This mechanism applies when data is missing due to reasons unrelated to observed and unobserved data. In other words, the probability that the data is missing is not associated with any variable in the dataset (outcomes and independent variables). An hypothetical example of this type of missing data in our study would be that for a given patient, the baseline CHAQ questionnaire was lost hence no result was available. This type of missing data is infrequent. When data are MCAR, most simple techniques that deal with missing data

should give valid inferences (86). The second type of missing data is referred to as MAR. This applies when data is missing for reasons related to the subject's observed data. With MAR data, the simple techniques to handle missing data will often lead to biased estimates (85). Also, ignoring the missing data mechanism and performing certain statistical procedures, such as GEE analysis, may also lead to biased estimates (75). Multiple imputation is a technique that can be used in that scenario (87). The last missingness category is MNAR. This entails that the data is missing for reasons related to the subject's unobserved data i.e. it depends on a variable that has not been measured because it is missing. One of the issue with the later category is that we can never be certain that the missingness mechanism is or isn't MNAR as it depends on unobserved data. Analysis of MNAR data requires more complex statistical procedures (88). When there is a reasonable possibility that the missing data is MNAR, sensitivity analysis should be performed to examine the effect of different assumptions (i.e. MAR vs. MNAR data) on the conclusions drawn. When there is a minimal amount of missing data, the identification of the missingness mechanism and resulting choice of statistical procedure may not impact on results significantly. On the other hand, when a large amout of data is missing, even the most advanced statistical computations may not be enough to compensate for the missing data and may result in invalid estimates.

As shown in the result section, the missingness mechanism for 4 of the 8 variables with missing items was likely not MCAR as the probabilities of having missing data were significantly associated with at least one observed data. This suggested that the missingness pattern for those 4 variables was at least that of MAR. This prompted the use of multiple imputation to maximize the use of all available data in the dataset and to reduce the risk of obtaining bias estimates (73). This method was likely more efficient in minimizing the chances of obtaining misleading results as compared to more simple ways of dealing with missing data like the missing indicator method or single imputation using the mean/median value. Results obtained for the analysis of the primary aim from the imputed vs. the complete case dataset were similar i.e. the association between early IAS and the active joint count of zero was protective but not statistically significant. The relationship between early IAS and inactive disease was statistically significant with the imputed dataset but not when a complete case analysis was performed. The imputed dataset allowed to use information from every

participants included in this study which could have led to increased power to detect a significant difference. Another possibility was that the use of multiple imputation in our study setting led to biased results. Simulation studies have shown that when missingness was associated with covariates but independent of the outcome, as seen in our study, using multiple imputation may biased results away from the null hypothesis as compared to complete case analysis which introduces negligible bias (89).

5.3 Internal validity

Although we tried to minimize confounding by indication, we were most likely unable to eliminate this risk completely, as discussed in section 5.2.1. Therefore, we believe that the absence of a significant association between early IAS and improved outcomes in our study does not preclude that early IAS could potentially alter the oligo-JIA disease course. Future work designed specifically to answer that question and thereby addressing the limitations of this study will be needed to draw conclusions on this important topic.

Another bias to consider in our study is a selection bias. If the distribution of exposure to IAS and outcome in the included study population did not reflect what was observed in the source population, a selection bias might have occurred. We found that the group of excluded participants had what seemed to be a milder disease at enrollment. Unfortunately, the IAS exposure status and outcome of the excluded participants were not available for analysis. Formal comparisons of the exposure and outcome status between enrolled and excluded children were not feasible. Therefore, we cannot ascertain if this type if bias is present in our study.

Another potential threat to internal validity of a study is an information bias. This bias occurs when part of the information gathered on the study participants are incorrect. In our study, the collection of data on the primary outcome was not blinded to IAS status. Concern for a differential information bias may arise. We believe that the later bias is unlikely to have occurred. First, physicians who were assessing the primary and secondary outcomes were not aware of our specific study objectives when the original data collection took place. Secondly,

a request for chart review was sent for every patient with an initially "missing" outcome, regardless of the patient exposure status. The chart review was performed in a blinded fashion i.e. by a person who was not aware of the participant's exposure status to IAS.

5.4 Generalizability

Despite the fact that a substantial proportion of enrolled ReACCh Out patients with oligo-JIA were excluded from the present analysis, included patients were still representative of the typical patients with oligo-JIA, that is young girls with ANA positive persistent oligo-JIA. Patients were excluded from this study mainly because they had missed one or more study visits. Our inclusion criteria specified that all first 5 study visits had to be completed. This criteria was chosen to ensure we had an adequate number of data points to explore the trajectory of outcomes over time. Unfortunately, it might have altered the external validity of our study. The group of excluded children seemed to represent a subset of oligo-JIA patients with milder disease at enrollment. We do acknowledge that our findings may not be representative of the overall oligo-JIA population as we likely selected a subgroup of patients with more active disease at baseline. Caution should then be used before generalizing our results to a population of patients with milder disease.

 The majority of participants were followed at academic centers and all were under the care of rheumatologists. Only 2 out of 13 centers were considered community-based centers. This could raise concerns about generalizability of findings as one may infer that patients followed at academic centers might be sicker than those followed in the community. The participant characteristics did not support this statement; median PGADA and CHAQ at baseline were not indicative of highly active disease or major functional impairment (90). Few pediatric rheumatologists in Canada are practicing at centers that were not recruiting patients in ReACCh Out. The predominance of academic centers reflected Canada's pediatric rheumatology reality and is unlikely to have skewed participant's selection toward an unrepresentative subgroup of oligo-JIA patients.

Finally, it is important to realize that GEE models the population means at each point in time and from that a trajectory of averages is derived (91). Results obtained from GEE modeling will not necessarily apply to one individual i.e. may not allow to predict one individual's trajectory but it will inform on the population's trajectory given specific predictors.

Chapter 6: Conclusion

Oligoarticular JIA is one of the most frequent rheumatologic disease encountered in children. Despite the prevalence of this autoimmune condition, no evidence-based recommendations are available on the optimal use of IAS in oligo-JIA and on the impact of early IAS on disease control and future disease trajectory. In this study of 310 children with oligo-JIA, no significant association was found between early IAS and the achievement of an active joint count of zero over the first 2 years after study enrollment. Participants who received an early IAS were less likely to achieve inactive disease. Methodological issues encountered when estimating treatment effect using observational data might have biased the estimates obtained. Hence, firm conclusion on the inefficacy of early IAS in improving outcomes of oligo-JIA patients cannot be drawn. Prospective studies addressing the limitations raised in this manuscript will be needed to clarify if early IAS can alter the disease course over time.

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Annex 1: ReACCh Out enrollment form

Study Identification Number: ☐☐☐☐☐

ENROLLMENT VISIT DATE: Y Y Y Y M M D D

Site Identification Number: ☐☐☐ - ☐

Date of Birth: Y Y Y Y M M D D

☐ Male ☐ Female

First 3 Characters of Postal Code: ☐☐☐

History of Presenting Illness

	Yes	No	Details
Joint Pain	☐	☐	
Joint Swelling	☐	☐	
Limp	☐	☐	
Heel Pain or Other Enthesitis	☐	☐	Location:
Low Back Pain	☐	☐	
Morning Stiffness	☐	☐	☐ ≥ 30 min ☐ < 30 min
Fever	☐	☐	☐ Quotidian Pattern ☐ Other Pattern
Systemic JIA Rash	☐	☐	
Psoriasis	☐	☐	
Other Rash	☐	☐	
Uveitis - Anytime	☐	☐	
Active Uveitis - Now	☐	☐	☐ Asymptomatic ☐ Symptomatic
Complications of Uveitis	☐	☐	
JIA Onset Symptom Date	☐	☐	Y Y Y Y M M
Inflammatory Bowel Disease	☐	☐	☐ Active Now ☐ Inactive Now ☐ Crohn's ☐ Ulcerative Colitis Date of Diagnosis (YEAR) _____

Social History

Grade at school : ☐ N/A ☐ Preschool ☐ JK ☐ SK GRADE: ☐☐

	Education					Employment/Occupation			
	Elementary	Secondary	Some Post Secondary	University Degree	Post Graduate	Full-Time	Part-Time	Not in the workforce	Describe
Father – years of education	☐	☐	☐	☐	☐	☐	☐	☐	
Mother – years of education	☐	☐	☐	☐	☐	☐	☐	☐	

Ethnic Origin of Parent:
(Please enter ethnic origin number code(s) in the corresponding boxes.)

☐☐ ☐☐ ☐☐ ☐☐ ☐☐ ☐☐

Family History

	Yes	No	Don't Know	Who						Degree of Relation		
										1st	2nd	Others
JRA or JIA	☐	☐	☐	☐ Oligo ☐ RF (−) ☐ RF (+) ☐ Poly ☐ Systemic Who: _____						☐	☐	☐
Lupus	☐	☐	☐							☐	☐	☐

Study Identification Number: | ENROLLMENT VISIT DATE: | Site Identification Number:

Y Y Y Y M M D D

Family History continued:

	Yes	No	Dont Know	Who	Degree of Relative		
					1st	2nd	Others
Psoriasis	☐	☐	☐		☐	☐	☐
Psoriatic Arthritis	☐	☐	☐		☐	☐	☐
Ankylosing Spondylitis	☐	☐	☐		☐	☐	☐
Uveitis	☐	☐	☐	☐ Asymptomatic ☐ Symptomatic	☐	☐	☐
Inflammatory Bowel Disease	☐	☐	☐		☐	☐	☐
Rheumatoid Arthritis	☐	☐	☐		☐	☐	☐

Current Medications

Name (Generic)	Dose	Frequency	Route	Start Date	Side Effects (If Any)
	___ mg other	☐ ☐ ☐ ___ od bid tid other	☐ ☐ ___ po sc other	Y Y M M	
	___ mg other	☐ ☐ ☐ ___ od bid tid other	☐ ☐ ___ po sc other	Y Y M M	
	___ mg other	☐ ☐ ☐ ___ od bid tid other	☐ ☐ ___ po sc other	Y Y M M	
	___ mg other	☐ ☐ ☐ ___ od bid tid other	☐ ☐ ___ po sc other	Y Y M M	
	___ mg other	☐ ☐ ☐ ___ od bid tid other	☐ ☐ ___ po sc other	Y Y M M	

	Yes	No	Details
Complementary Therapy	☐	☐	
Splints and Assistive Device	☐	☐	

Ophthalmology Exam: Y Y Y Y M M D D ☐ Normal ☐ Abnormal ☐ Not Done

Physical Examination

Height [ ] cm   Weight [ ] kg   Systolic B.P. / Diastolic B.P. [ ] / [ ]

	Yes	No	Details
Systemic Rash	☐	☐	
Psoriasis	☐	☐	
Onycholysis	☐	☐	

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Study Identification Number: ENROLLMENT VISIT DATE: Site Identification Number:

[ ][ ][ ][ ][ ][ ]   Y Y Y Y M M D D   [ ][ ][ ][ ] ■

Physical Examination Continued:

	Yes	No	Describe/ How Diagnosed
Nail Pits	☐	☐	
Rheumatoid Nodules	☐	☐	
Pericarditis	☐	☐	
Pleuritis	☐	☐	
Other Cardiovascular Abnormality	☐	☐	
Generalized Lymphadenopathy	☐	☐	
Hepatomegaly	☐	☐	
Splenomegaly	☐	☐	

Rheumatology Examination

	Yes	No	N/A	Details
Dactylitis	☐	☐	☐	Number of digits affected: [ ][ ]
Enthesitis	☐	☐	☐	
Tenosynovitis	☐	☐	☐	Number of sites affected: [ ][ ] Site(s):
Leg Length Discrepancy $\geq$ 1 cm	☐	☐	☐	
Localized Growth Abnormalities	☐	☐	☐	Site(s):
Micrognathia	☐	☐	☐	
Muscle Atrophy	☐	☐	☐	☐ Generalized ☐ Localized

Physician's Global Assessment of Disease Activity

0 ├─────────────────────────┤ 10

[ ][ ].[ ] cm PGA

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Joint Figure

Active Joint: Swelling/effusion
or 2 of the following: limited ROM
or tenderness/ painful ROM. All
effusions should be marked with ●
and active joints (not effused) with X.
Please CIRCLE all joints with limited
ROM.

R   L

TMJ

Mid Foot   Mid Foot

Subtalar

| ☐☐ | No. Effused (●) ONLY | ☐☐ | No. Active: includes swollen/ effused joints (Sum of ● and X) | ☐☐ | No. Joints with limited ROM |

v

Y Y Y Y M M D D

Enthesitis Figure (Please mark site(s) with Enthesitis with a X)

☐ Form Not Applicable   R   L   Number of Enthesitis sites
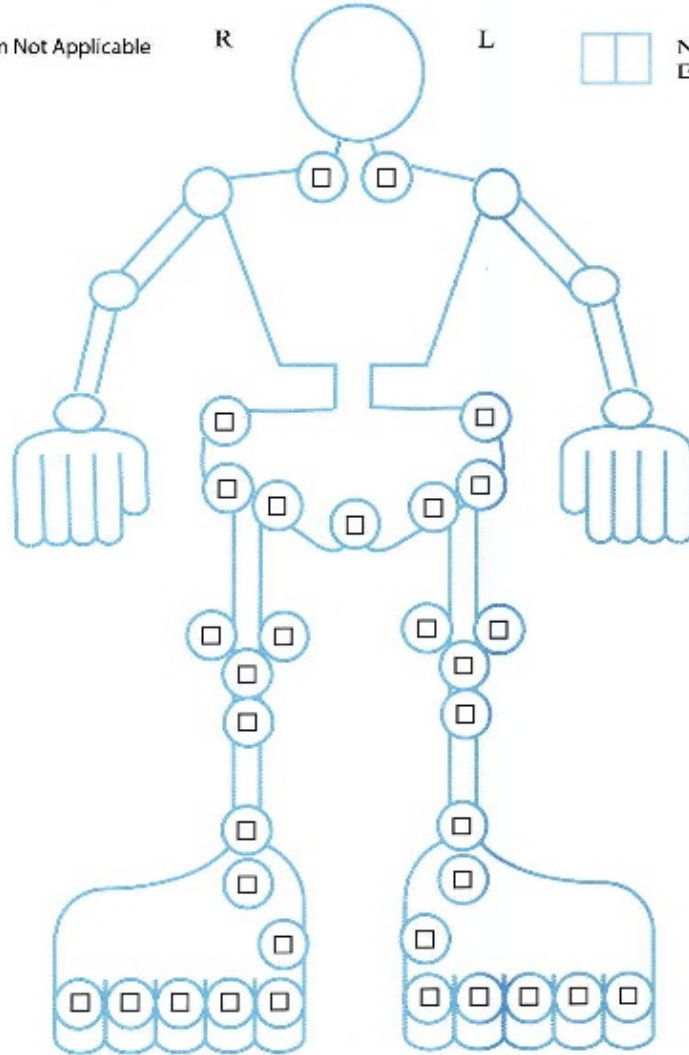
	YES	NO	DETAILS
Abnormal Modified Schober	☐	☐	
Abnormal Chest Expansion	☐	☐	

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Study Identification Number: □□□□□

ENROLLMENT VISIT DATE: `Y Y Y Y M M D D`

Site Identification Number: □□□□□

Diagnosis: □ Systemic □ Oligo □ Poly RF(-) □ Poly RF(-) □ Psoriatic □ Enthesitis Related □ Undifferentiated _____

□ Persistent Oligo   □ Arthritis with IBD
□ Extended Oligo

□ Does NOT meet criteria for any category
□ Meets criteria for >1 category

Date of Diagnosis □ Today or `Y Y Y Y M M D D`

Medication Changes (If medication stopped, indicate reason)

Name (Generic)	D/C	New	Dose Change	Dose		Frequency	Route	Comments
	□	□	□	□□□□□ . mg / other	□ □ □ ___ od bid tid other	□ □ ___ po sc other	
	□	□	□	□□□□ mg / other	□ □ □ ___ od bid tid other	□ □ ___ po sc other	
	□	□	□	□□□□ mg / other	□ □ □ ___ od bid tid other	□ □ ___ po sc other	
	□	□	□	□□□□ mg / other	□ □ □ ___ od bid tid other	□ □ ___ po sc other	
	□	□	□	□□□□□ mg / other	□ □ □ ___ od bid tid other	□ □ ___ po sc other	
	□	□	□	□□□□ mg / other	□ □ □ ___ od tid tid other	□ □ ___ po sc other	

Lab Tests

Test Date:
Labs `Y Y Y Y M M D D`

Test Date:
Serology `Y Y Y Y M M D D`

		Serology	Pos	Neg	N/A	Titre/Pattern/Comment
Haemoglobin	___					
Total Neutro	___	ANA	□	□	□	___
Total Lymph	___					
Platelet count	___	RF	□	□	□	___
WBC	___					
ESR	___	B27	□	□	□	___
CRP	___					

■ Other blood sample taken: □ YES   □ NO

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Study Identification Number:

[ ][ ][ ][ ][ ]

ENROLLMENT VISIT DATE:

[Y][Y][Y][Y][M][M][D][D]

Site Identification Number:

[ ][ ][-][ ][ ]

Additional Medication- [Current or Changes + Comment(s)

Name (Generic)	Dose	Unit	Frequency	Route	Side Effects (If Any)/ Other Comment(s)

Other Supplemental Info:

Date of First Clinic Visit: [Y][Y][Y][Y][M][M][D][D]

Previous Medication(s)	Start Date	Stop Date	Comments
1.	[Y][Y][M][M]	[Y][Y][M][M]	
2.	[Y][Y][M][M]	[Y][Y][M][M]	
3.	[Y][Y][M][M]	[Y][Y][M][M]	
4.	[Y][Y][M][M]	[Y][Y][M][M]	
5.	[Y][Y][M][M]	[Y][Y][M][M]	

Additional Info:

Study Identification Number:

Site Identification Number:

Ethnic Origin Number Codes

Certain conditions in Rheumatology are more common in certain ethnic origins than others. Your child's origin/descent is (check as many as apply):   (These categories are from Statistics Canada and the Ministry of Citizenship)

CODE   ETHNIC ORIGIN

Africa & Carribean Islands

☐ 01   Arab (Egyptian, Iraqi, Lebanese, Maghrebian, Moroccan, Palestinian, Syrian, and other Arab)

☐ 02   Black (African Black, Barbadian, Cuban, Ethiopian, Ghanaian, Haitian, Jamaican, other Caribbean, other West Indian, Puerto Rican and Somalian)

America

☐ 11   Aboriginal Inuit

☐ 12   Aboriginal North American Indian   Band _____   Language _____

☐ 13   Latin American (Argentinean, Brazilian, Chilean, Colombian, Ecuadorian, Guatemalan, Hispanic, Mexican, Nicaraguan, Peruvian, Salvadoran, and other Latin, Central and South American)

Asia

☐ 21   Chinese (Chinese, Mongolian, Tibetan)

☐ 22   Filipino

☐ 23   Korean

☐ 24   Japanese

☐ 25   Pacific Islander (Fijian, Polynesia, and other Pacific Islanders)

☐ 26   South Asian (Bengali, Gujarati, Punjabi, Tamil, East Indian, Bangladeshi, Pakistani, Sigalese and Sri-Lankan)

☐ 27   Southeast Asian (Vietnamese, Burmese, Cambodian, Laotian, Thai, Malay, and Indonesian)

☐ 28   West Asian (Afghan, Armenian, Iranian, Israeli, Kurdish, Turk and West Asian)

Europe

☐ 31   British Origin (English, Irish, Scottish, Welsh and Other British)

☐ 32   Eastern European (Baltic origins, Byelorussian, Czech, Slovak, Hungarian [Magyar], Polish, Romanian, Russian and Ukrainian)

☐ 33   French Origin (Acadian, Franco-Manitoban, Franco-Ontarian, French, French Canadian and Quebecois)

☐ 34   Northern European (Finnish and Scandinavian origins)

☐ 35   Southern European (Balkan origins, Cypriot, Greek, Italian, Maltese, Portuguese and Spanish)

☐ 36   Western European (Austrian, Belgian, Dutch (Netherlands), Flemish, German, Luxembourg and Swiss)

☐ **40 Other. Please specify:** _____

These information sheets were completed by (check all that apply):

mother ☐   father ☐

child/patient ☐   guardian ☐

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Annex 2: ReACCh Out follow up form

Study ID#:

Visit Date:

| D | D | M | M | Y | Y | Y | Y |

Site ID#:

REACCH-OUT – FOLLOW-UP FORM

Subject's last ReACCh-OUT visit: _____

Type of visit:

☐ 6 month   ☐ 1 year   ☐ 18 month   ☐ 2 year   ☐ 3 year   ☐ 4 year   ☐ 5 year

Diagnosis

Previous diagnosis:
(from last study visit, to be completed by RA)

- ☐ Systemic
- ☐ Arthritis + IBD
- ☐ Polyarthritis RF +ve
- ☐ Polyarthritis RF –ve
- ☐ Oligoarthritis – Persistent
- ☐ Oligoarthritis – Extended
- ☐ Psoriatic arthritis
- ☐ Enthesitis related arthritis
- ☐ Undifferentiated

Today's diagnosis:

- ☐ Systemic
- ☐ Arthritis + IBD
- ☐ Polyarthritis RF +ve
- ☐ Polyarthritis RF –ve
- ☐ Oligoarthritis – Persistent
- ☐ Oligoarthritis – Extended
- ☐ Psoriatic arthritis
- ☐ Enthesitis related arthritis
- ☐ Undifferentiated

Interim History

Joint Pain	☐ Yes	☐ No		
Joint Swelling	☐ Yes	☐ No		
Limp	☐ Yes	☐ No		
Symptomatic Enthesitis	☐ Yes	☐ No		
Inflammatory Low Back Pain	☐ Yes	☐ No		
Morning Stiffness	☐ Yes	☐ No	If YES:	☐ >= 30 mins ☐ < 30 mins
Fever	☐ Yes	☐ No	If YES:	☐ Quotidian pattern ☐ Other pattern
Systemic JIA Rash	☐ Yes	☐ No		
Psoriasis	☐ Yes	☐ No		
Any Ophthalmology Exam during the last 12 months	☐ Yes	☐ No		
If yes, was uveitis present at any of these exams?	☐ Yes	☐ No	If YES:	☐ Asymptomatic uveitis ☐ Symptomatic uveitis
Complications of uveitis at any time (cataract/ glaucoma/ synechia/ band keratopathy, phisis)	☐ Yes	☐ No		
New Onset Inflammatory Bowel Disease since last visit	☐ Yes	☐ No	If YES:	☐ Undifferentiated ☐ Crohn's ☐ Ulcerative Colitis

X

Study ID#:	Visit Date:		Site ID#:	
☐☐☐☐	D D M M Y Y Y Y		☐☐ - ☐☐☐	

| **School:** (tick box) | ☐ N/A ☐ Pre-school ☐ JK ☐ SK ☐ Elementary | ☐ High School ☐ Other Post-Secondary ☐ University ☐ Other: _____ | **Grade:** (tick box) | ☐ 1 ☐ 5 ☐ 9 ☐ 2 ☐ 6 ☐ 10 ☐ 3 ☐ 7 ☐ 11 ☐ 4 ☐ 8 ☐ 12 |

Medications (since last study visit or today)

NSAID

Medications include, but are not limited to: Acetylsalicylic acid (Aspirin), Arthrotec, Celecoxib, Diclofenac, Flurbiprofen, Ibuprofen, Indocid, Indomethacin, Ketorolac, Lumiracoxib, Meloxicam, Nabumetone, Naproxen, Piroxicam

Other non-listed NSAID: _____

☐ Yes ➔ ☐ No	**Was it D/C since the last study visit or today?** ☐ Yes ☐ No	**Did the subject experience side effects that required a dose change or discontinuation of medication today or since the last study visit?** ☐ Yes ☐ No If yes, details: _____

DMARD

Medications include, but are not limited to: Azathioprine, Colchicine, Cyclosporin, Hydroxychloroquine, Intravenous gammaglobulin (IVIG), Leflunomide, Mercaptopurine (Purinethol, 6-Mercaptopurine, 6-MP), Mesalamine (5-ASA), Methotrexate oral, Methorexate SQ, Minocycline, Mycophenolate Mofetil, Sulfasalazine (SSZ), Thalidomide

Other non-listed DMARD: _____

	Name of drug	**Start date** *(if started since last study visit or today)*	**Stop date** *(if stopped since last study visit or today)*	**Any side effects that required a dose change or D/C of medication today or since the last study visit?**
☐ Yes ➔ ☐ No	1. _____ 2. _____ 3. _____ 4. _____	dd / mmm / yyyy_ dd / mmm / yyyy_ dd / mmm / yyyy_ dd / mmm / yyyy_	dd / mmm / yyyy_ dd / mmm / yyyy_ dd / mmm / yyyy_ dd / mmm / yyyy_	☐ Yes ☐ No If yes, details: _____ _____

Biologics

Medications include, but are not limited to: Abatacept, Adalimumab (HUMIRA), Anakinra(KINARET), Canakinumab (ILARIS), Etanercept, Golimumab, Infliximab (REMICADE), Rituximab, Tociluzimab

Other non-listed Biologic: _____

☐ Yes ➔ ☐ No	1. _____	**Dose:** _____ mg **Dose Interval:** ☐ daily ☐ qwk ☐ q2wk ☐ q4wk ☐ q6wk ☐ q8wks ☐ q10wks ☐ q12wks ☐ variable	**Any side effects that required a dose change or D/C of medication today or since the last study visit?** ☐ Yes ☐ No If yes, details: _____ _____ _____
		Start date *(If started today, or since last the study visit)*	**Stop date** *(If stopped today, or since last the study visit)*	
		dd / mmm / yyyy_	dd / mmm / yyyy_	

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Biologics (continued)	2. _____	Dose: _____ mg Dose Interval: ☐ daily ☐ qwk ☐ q2wk ☐ q4wk ☐ q6wk ☐ q8wks ☐ q10wks ☐ q12wks ☐ variable		Any side effects that required a dose change or D/C of medication today or since the last study visit? ☐ Yes ☐ No If yes, details: _____ _____ _____
		Start date *(If started today, or since last the study visit)* dd / mmm / yyyy_	**Stop date** *(If stopped today, or since last the study visit)* dd / mmm / yyyy_	

Steroids	**Medications include, but are not limited to:** Dexamethasone, Methylprednisolone (MP pulse), Prednisone, Solumedrol			
☐ Yes ➔ ☐ No	**Name of drug** 1. _____ 2. _____ 3. _____ 4. _____	**Start date** *(if started since last study visit or today)* dd / mmm / yyyy_ dd / mmm / yyyy_ dd / mmm / yyyy_ dd / mmm / yyyy_	**Stop date** *(if stopped since last study visit or today)* dd / mmm / yyyy_ dd / mmm / yyyy_ dd / mmm / yyyy_ dd / mmm / yyyy_	**Any side effects that required a dose change or D/C of medication today or since the last study visit?** ☐ Yes ☐ No If yes, details: _____ _____ _____

Topical Eye Medication (at this visit)	**Corticosteroids and mydriatics only. Medications include, but are not limited to:** Atropine, Brimonidine, Combigan, Cyclopentolate, Dorzolamide, Fluorometholone, Homatropine, Lotemax, Maxidex, Mydriacyl, Prednisone eye drops, Rimexolone , Steroid eye ointment, Timoptic ☐ Yes ☐ No

Other Drugs (at this visit)	Analgesics (non-NSAID)	☐ Yes ☐ No	**Includes:** Acetaminophen, Codeine, Gabapentin, Robaxacet
	Antinauseants/ antiemetics	☐ Yes ☐ No	**Includes:** Dimenhydrinate (GRAVOL), Ondansetron
	Gastric Protectants	☐ Yes ☐ No	**Includes:** Esomeprazole, Famotidine, Omeprazole, Pantoprazole, Ranitidine, Sucralfate
	Biphosphonates	☐ Yes ☐ No	**Includes:** Alendronate, Pamidronate, Zoledronic Acid, Risedronate
	Oral Contraceptives	☐ Yes ☐ No	
	Calcium	☐ Yes ☐ No	
	Vitamin D	☐ Yes ☐ No	
	Folic or folinic acid or leukovorin	☐ Yes ☐ No	

VERSION DATE: 15 July 2011

Study ID#: ☐☐☐☐

Visit Date: D D M M Y Y Y Y

Site ID#: ☐☐☐ - ☐☐☐

Physical Exam

Height: __ __ __ . __ __ cm   Weight: __ __ __ . __ __ kg

Systemic Rash	☐ Yes	☐ No	Pleuritis	☐ Yes	☐ No
Psoriasis	☐ Yes	☐ No	Peritonitis	☐ Yes	☐ No
Onycholysis	☐ Yes	☐ No	Generalized Lymphadenopathy	☐ Yes	☐ No
Nail Pits	☐ Yes	☐ No	Hepatomegaly	☐ Yes	☐ No
Rheumatoid Nodules	☐ Yes	☐ No	Splenomegaly	☐ Yes	☐ No
Pericarditis	☐ Yes	☐ No			

Rheumatology Exam

Dactylitis	☐ Yes	☐ No	IF YES: Number of digits affected: _____
Leg length Discrepancy >=1cm	☐ Yes	☐ No	
Micrognathia or asymmetry of the jaw	☐ Yes	☐ No	
Abnormal Modified Schober	☐ Yes	☐ No	☐ N/A
Abnormal Chest Expansion	☐ Yes	☐ No	☐ N/A

Physician's Global Assessment of Disease Activity

0   10

|··|

Not active   Active

☐☐ . ☐ cm PGA

Active and Limited Range of Movement Joints

Any active joints?   ☐ Yes   ☐ No

Active joint: swelling/effusion or 2 of the following: limited ROM or tenderness or painful ROM.

Any joints with limited ROM?   ☐ Yes   ☐ No

Active Joints — Right side / Left side

Range of Movement — Right side / Left side

subtalar / midfoot

VERS

Study ID#:

Visit Date:

D D M M Y Y Y Y
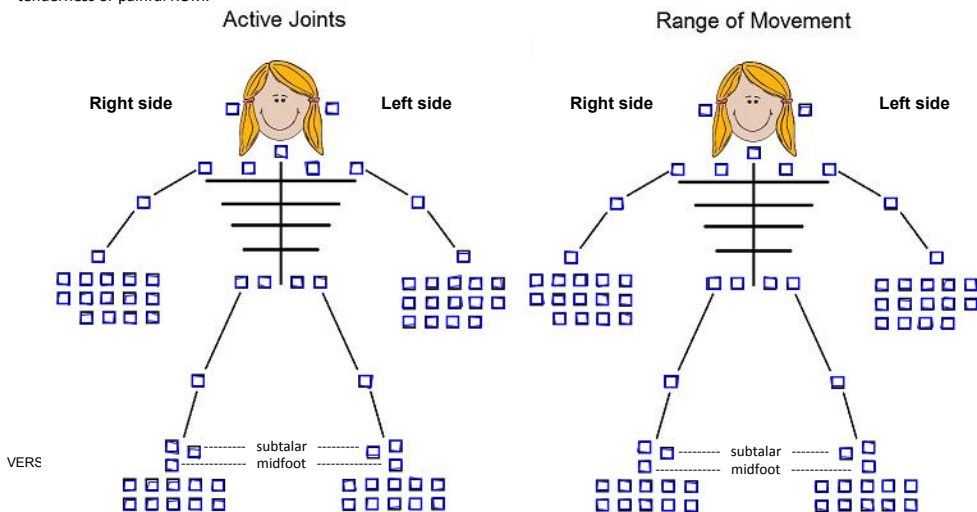
Site ID#:

Enthesitis

Any sites with enthesitis?   ☐ Yes   ☐ No
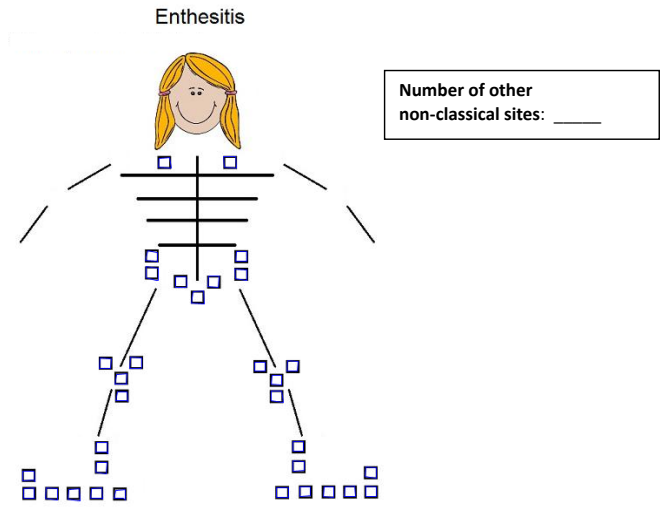
Enthesitis

| Number of other non-classical sites: _____ |

Labs (today or most recent one since last study visit)

To identify lab results from today that are pending, check here ☐

Test	Test Performed	Result	Unit	Date
Haemoglobin	☐ Done ☐ Not Done	_____	☐ g/L Other: ____	dd / mmm / yyyy
Platelet Count	☐ Done ☐ Not Done	_____	☐ 10^9/L Other: ____	
WBC	☐ Done ☐ Not Done	_____	☐ 10^9/L Other: ____	
ESR	☐ Done ☐ Not Done	_____	☐ mm/hr Other: ____	_dd / mmm / yyyy_
CRP	☐ Done ☐ Not Done	_____	☐ mg/L Other: ____	_dd / mmm / yyyy_

Serology (since last study visit)

Were any of the following serology tests done? ☐ Yes ☐ No			
ANA	☐ Positive ☐ Negative	**Date:**	_dd / mmm / yyyy_
RF	☐ Positive ☐ Negative	**Date:**	_dd / mmm / yyyy_
B27	☐ Positive ☐ Negative	**Date:**	_dd / mmm / yyyy_

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Intraarticular Injections (since last study visit or today)

☐ Yes ☐ No   *If yes, fill in details below.*

Joint (s)		Date	Medication	Dosage	Unit
_____	☐ Left ☐ Right	dd / mmm / yyyy	☐ Triamcinolone hexacetonide ☐ Triamcinolone acetonide ☐ Methylprednisolone acetate ☐ Other: _____		mg
_____	☐ Left ☐ Right	dd / mmm / yyyy	☐ Triamcinolone hexacetonide ☐ Triamcinolone acetonide ☐ Methylprednisolone acetate ☐ Other: _____		mg
_____	☐ Left ☐ Right	dd / mmm / yyyy	☐ Triamcinolone hexacetonide ☐ Triamcinolone acetonide ☐ Methylprednisolone acetate ☐ Other: _____		mg
_____	☐ Left ☐ Right	dd / mmm / yyyy	☐ Triamcinolone hexacetonide ☐ Triamcinolone acetonide ☐ Methylprednisolone acetate ☐ Other: _____		mg
_____	☐ Left ☐ Right	dd / mmm / yyyy	☐ Triamcinolone hexacetonide ☐ Triamcinolone acetonide ☐ Methylprednisolone acetate ☐ Other: _____		mg

Surgical Procedures (since last study visit or today)

Joint Arthroplasty: ☐ Yes ☐ No	Date: dd / mmm / yyyy	**Joint:** ☐ Knee ☐ Hip ☐ Other	**Side:** ☐ Left ☐ Right ☐ Bilateral	**Describe other joint:** _____ _____ _____

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Annex 3: ReACCh Out interim visit form

Study ID#:

Visit Date:

| D | D | M | M | Y | Y | Y | Y |

Site ID#:

REACCH-OUT – INTERIM VISIT FORM

Subject's last ReACCh-OUT visit: _____

Active and Limited Range of Movement Joints

Any active joints?   ☐ Yes   ☐ No

Active joint: swelling/effusion or 2 of the following: limited ROM or tenderness or painful ROM.

Any joints with limited ROM?   ☐ Yes   ☐ No

Active Joints

Right side   Left side

Range of Movement

Right side   Left side

subtalar
midfoot
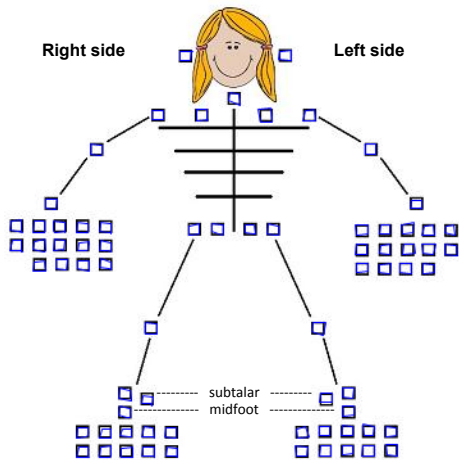
subtalar
midfoot

Enthesitis

Any sites with enthesitis?   ☐ Yes   ☐ No

Enthesitis

Number of other non-classical sites: _____

VERSION DATE: 15 JULY 2011

Physician's Global Assessment of Disease Activity

0   10

|..|
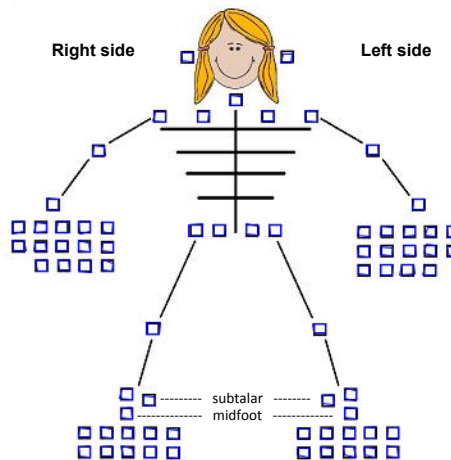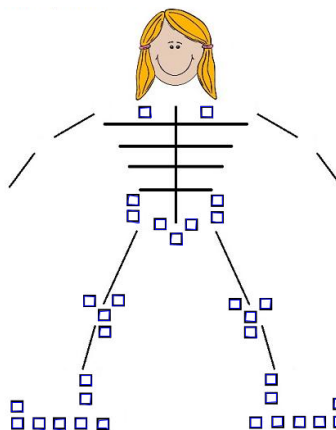
Not active   Active

[ ] [ ] . [ ]   cm PGA

Labs (today or most recent one since last study visit)

To identify lab results from today that are pending, check here □

Test	Test Performed	Result	Unit	Date
ESR	□ Done □ Not Done	_____	□ mm/hr Other: ____	_dd_ / _mmm_ / _yyyy_
CRP	□ Done □ Not Done	_____	□ mg/L Other: ____	_dd_ / _mmm_ / _yyyy_

Medications (since last study visit or today's visit)

NSAID	**Medications include, but are not limited to:** Acetylsalicylic acid (Aspirin), Arthrotec, Celecoxib, Diclofenac, Flurbiprofen, Ibuprofen, Indocid, Indomethacin, Ketorolac, Lumiracoxib, Meloxicam, Nabumetone, Naproxen, Piroxicam **Other non-listed NSAID**: _____

□ Yes ➔ □ No	**Was it D/C since the last study visit or today?** □ Yes □ No	**Did the subject experience side effects that required a dose change or discontinuation of medication today or since the last study visit?** □ Yes □ No If yes, details: _____

DMARD	**Medications include, but are not limited to:** Azathioprine, Colchicine, Cyclosporin, Hydroxychloroquine, Intravenous gammaglobulin (IVIG), Leflunomide, Mercaptopurine (Purinethol, 6-Mercaptopurine, 6-MP), Mesalamine (5-ASA), Methotrexate oral, Methorexate SQ, Minocycline, Mycophenolate Mofetil, Sulfasalazine (SSZ), Thalidomide **Other non-listed DMARD**: _____

	Name of drug	**Start date** *(if started since last study visit or today)*	**Stop date** *(if stopped since last study visit or today)*	**Any side effects that required a dose change or D/C of medication today or since the last study visit?**
□ Yes ➔ □ No	1. _____ 2. _____ 3. _____ 4. _____	dd / mmm / yyyy_ dd / mmm / yyyy_ dd / mmm / yyyy_ dd / mmm / yyyy_	dd / mmm / yyyy_ dd / mmm / yyyy_ dd / mmm / yyyy_ dd / mmm / yyyy_	 □ Yes □ No If yes, details: _____ _____ _____

Medications (continued)

Biologics

Medications include, but are not limited to: Abatacept, Adalimumab (HUMIRA), Anakinra (KINARET), Canakinumab (ILARIS), Etanercept, Golimumab, Infliximab (REMICADE), Rituximab, Tociluzimab

Other non-listed Biologic: _____

☐ Yes ➔
☐ No

1. _____

Dose: _____ mg

Dose Interval: ☐ daily ☐ qwk ☐ q2wk
☐ q4wk ☐ q6wk ☐ q8wks
☐ q10wks ☐ q12wks
☐ variable

Start date *(If started today, or since last the study visit)*	Stop date *(If stopped today, or since last the study visit)*
dd / mmm / yyyy	dd / mmm / yyyy

Any side effects that required a dose change or D/C of medication today or since the last study visit?

☐ Yes ☐ No

If yes, details: _____
_____
_____

2. _____

Dose: _____ mg

Dose Interval: ☐ daily ☐ qwk ☐ q2wk
☐ q4wk ☐ q6wk ☐ q8wks
☐ q10wks ☐ q12wks
☐ variable

Start date *(If started today, or since last the study visit)*	Stop date *(If stopped today, or since last the study visit)*
dd / mmm / yyyy	dd / mmm / yyyy

Any side effects that required a dose change or D/C of medication today or since the last study visit?

☐ Yes ☐ No

If yes, details: _____
_____
_____

Steroids

Medications include, but are not limited to: Dexamethasone, Methylprednisolone (MP pulse), Prednisone, Solumedrol

☐ Yes ➔
☐ No

Name of drug	Start date *(if started since last study visit or today)*	Stop date *(if stopped since last study visit or today)*	Any side effects that required a dose change or D/C of medication today or since the last study visit?
1. _____	dd / mmm / yyyy	dd / mmm / yyyy	☐ Yes ☐ No
2. _____	dd / mmm / yyyy	dd / mmm / yyyy	
3. _____	dd / mmm / yyyy	dd / mmm / yyyy	If yes, details: _____
4. _____	dd / mmm / yyyy	dd / mmm / yyyy	_____ _____

Topical Eye Medication (at this visit)

Corticosteroids and mydriatics only. Medications include, but are not limited to: Atropine, Brimonidine, Combigan, Cyclopentolate, Dorzolamide, Fluoromethalone, Homatropine, Lotemax, Maxidex, Mydriacyl, Prednisone eye drops, Rimexolone , Steroid eye ointment, Timoptic

☐ Yes ☐ No

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Other Drugs (at this visit)	Analgesics (non-NSAID)	☐ Yes ☐ No	**Includes:** Acetaminophen, Codeine, Gabapentin, Robaxacet
	Antinauseants/ antiemetics	☐ Yes ☐ No	**Includes:** Dimenhydrinate (GRAVOL), Ondansetron
	Gastric Protectants	☐ Yes ☐ No	**Includes:** Esomeprazole, Famotidine, Omeprazole, Pantoprazole, Ranitidine, Sucralfate
	Biphosphonates	☐ Yes ☐ No	**Includes:** Alendronate, Pamidronate, Zoledronic Acid, Risedronate
	Oral Contraceptives	☐ Yes ☐ No	
	Calcium	☐ Yes ☐ No	
	Vitamin D	☐ Yes ☐ No	
	Folic or folinic acid or leukovorin	☐ Yes ☐ No	

Intraarticular Injections (since last study visit or today)

☐ Yes   ☐ No   *If yes, fill in details below.*

Joint (s)		Date	Medication	Dosage	Unit
_____	☐ Left ☐ Right	dd / mmm / yyyy	☐ Triamcinolone hexacetonide ☐ Triamcinolone acetonide ☐ Methylprednisolone acetate ☐ Other: _____		mg
_____	☐ Left ☐ Right	dd / mmm / yyyy	☐ Triamcinolone hexacetonide ☐ Triamcinolone acetonide ☐ Methylprednisolone acetate ☐ Other: _____		mg
_____	☐ Left ☐ Right	dd / mmm / yyyy	☐ Triamcinolone hexacetonide ☐ Triamcinolone acetonide ☐ Methylprednisolone acetate ☐ Other: _____		mg
_____	☐ Left ☐ Right	dd / mmm / yyyy	☐ Triamcinolone hexacetonide ☐ Triamcinolone acetonide ☐ Methylprednisolone acetate ☐ Other: _____		mg
_____	☐ Left ☐ Right	dd / mmm / yyyy	☐ Triamcinolone hexacetonide ☐ Triamcinolone acetonide ☐ Methylprednisolone acetate ☐ Other: _____		mg

Surgical Procedures (since last study visit or today)

Joint Arthroplasty: ☐ Yes ☐ No	**Date:** dd / mmm / yyyy	**Joint:** ☐ Knee ☐ Hip ☐ Other	**Side:** ☐ Left ☐ Right ☐ Bilateral	**Describe other joint:** _____ _____ _____

Annex 4: CHAQ form

Study Identification Number: ☐☐☐☐☐☐   Site Identification Number: ☐☐☐☐☐   Date: Y Y Y Y - M M - D D

BBOP Visit Month: ☐ 0 ☐ 6 ☐ 12 ☐ 18 ☐ 24

BBOP: ☐

Child Health Assessment Questionnaire

In this section, we are interested in learning how your child's illness affects his/her ability to function in daily life. Please feel free to add any comments on the extra page provided at the end of this questionnaire package. In the following questions, please mark an X in the box corresponding to the one response which best describes your child's usual activities (averaged over an entire day) **OVER THE PAST WEEK**. **ONLY NOTE THOSE DIFFICULTIES OR LIMITATIONS WHICH ARE DUE TO ILLNESS.** If most children at your child's age are not expected to do a certain activity, please mark as "Not Applicable". For example, if your child has difficulty in doing a certain activity or is unable to do it because he/she is too young but NOT because he/she is RESTRICTED BY ILLNESS, please mark as "Not Applicable".

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To DO	Not Applicable
DRESSING and GROOMING					
Is your child able to: - Dress, including tying shoelaces and doing buttons?	☐	☐	☐	☐	☐
- Shampoo his/her hair?	☐	☐	☐	☐	☐
- Remove socks?	☐	☐	☐	☐	☐
- Cut fingernails?	☐	☐	☐	☐	☐
ARISING					
Is your child able to: - Stand up from a low chair or floor?	☐	☐	☐	☐	☐
- Get in and out of bed or stand up in a crib?	☐	☐	☐	☐	☐
EATING					
Is your child able to: - Cut his/her own meat?	☐	☐	☐	☐	☐
- Lift a cup or glass to mouth?	☐	☐	☐	☐	☐
- Open a new cereal box?	☐	☐	☐	☐	☐
WALKING					
Is your child able to: - Walk outdoors on flat ground?	☐	☐	☐	☐	☐
- Climb up five steps?	☐	☐	☐	☐	☐

Please mark any AIDS or DEVICES that your child usually uses for any of the above activities:

☐ Cane   ☐ Walker   ☐ Crutches   ☐ Wheelchair   ☐ Devices used for dressing (button hooks, zipper pull, long handled shoehorn, etc.)

☐ Built up or special utensils   ☐ Special or built up chair   ☐ Other (specify below)
_____

Please mark any categories for which your child usually needs help from another person **BECAUSE OF ILLNESS**:

☐ Dressing and Grooming   ☐ Arising   ☐ Eating   ☐ Walking

■ VERSION DATE: 2007/09/13

Child Health Assessment Questionnaire - continued

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To DO	Not Applicable
HYGIENE					
Is your child able to: - Wash and dry entire body?	☐	☐	☐	☐	☐
- Take a tub bath (get in and out of tub)?	☐	☐	☐	☐	☐
- Get on and off toilet or potty chair?	☐	☐	☐	☐	☐
- Brush teeth?	☐	☐	☐	☐	☐
- Comb/brush hair?	☐	☐	☐	☐	☐
REACH					
Is your child able to: - Reach and get down a heavy object such as a large game or book from just above his/her head?	☐	☐	☐	☐	☐
- Bend down to pick up clothing or a piece of paper from the floor	☐	☐	☐	☐	☐
- Pull on a sweater over his/her head?	☐	☐	☐	☐	☐
- Turn neck to look back over shoulder?	☐	☐	☐	☐	☐
GRIP					
Is your child able to: - Write or scribble with pen or pencil?	☐	☐	☐	☐	☐
- Open car doors?	☐	☐	☐	☐	☐
- Open jars which have been previously opened?	☐	☐	☐	☐	☐
- Turn faucets on and off?	☐	☐	☐	☐	☐
- Push open a door when he/she has to turn a door knob?	☐	☐	☐	☐	☐
ACTIVITIES					
Is your child able to: - Run errands and shop?	☐	☐	☐	☐	☐
- Get in and out of car or toy car or school bus?	☐	☐	☐	☐	☐
- Ride bicycle or tricycle?	☐	☐	☐	☐	☐
- Do household chores (for example, wash dishes, take out trash, vacuuming, yardwork, make bed, clean room)?	☐	☐	☐	☐	☐
- Run and play?	☐	☐	☐	☐	☐

■ VERSION DATE: 2007/09/13

☐ ☐ ☐ ☐ ☐ ☐　　☐ ☐ ☐ ☐ ☐　　Y Y Y Y M M D D

Child Health Assessment Questionnaire - continued

Please mark any AIDS or DEVICES that your child usually uses for any of the above activities (page 3):

☐ Raised toilet seat　　☐ Bathtub seat　　☐ Jar opener (for jars previously opened)　　☐ Bathtub bar

☐ Longhandled appliance for reach　　☐ Longhandled appliance for bathroom

Please mark any categories for which your child usually needs help from another person **BECAUSE OF ILLNESS**:

☐ Hygiene　　☐ Reach　　☐ Gripping and opening things　　☐ Errands and chores

We are also interested in learning whether or not your child has been affected by pain because of his or her illness.

How much pain do you think your child has had because of his or her illness IN THE PAST WEEK?

Place a mark on the line below to indicate the severity of the pain.

No pain　　　　　　　　　　　　　　　　　　　Very severe pain

├─────────────────────────────────────┤

0　　　　　　　　　　　　　　　　　　　　　　10　　　　☐ ☐ . ☐ **cm**
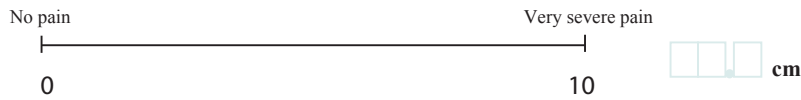
HEALTH STATUS

1. Considering all the ways that arthritis affects your child, rate how your child is doing on the following scale by placing a mark on the line.

Very well　　　　　　　　　　　　　　　　　　Very poor

├─────────────────────────────────────┤

0　　　　　　　　　　　　　　　　　　　　　　10　　　　☐ ☐ . ☐ **cm**
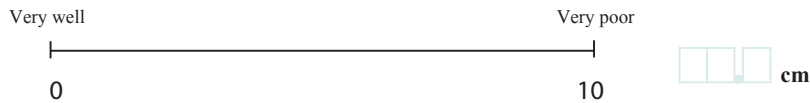
2. Is your child stiff in the morning?　　☐ Yes　　☐ No

If YES, about how long does the stiffness usually last (in the past week)?　　☐ ☐　　☐ Hours　　☐ Minutes

Date:　Y Y Y Y M M D D　　　　Completed by:　☐ Parent/Guardian

☐ Patient