Intraarticular infliximab therapy in patients with juvenile idiopathic arthritis: the role of musculoskeletal ultrasound and disease activity scores in monitoring therapy response

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Abstract

Objective

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in children, with heterogeneous clinical features. Although therapeutic options are wide and in the majority of children symptoms improve with the combination of non-steroidal anti-inflammatory and disease-modifying drugs, there are a number of patients who do not respond to conventional therapy and who do not meet the criteria for systemic biologics, namely anti TNF-alpha. Those patients are potential candidates for intraarticular therapy with biologics and in this report we present the results of intra-articular infliximab treatment in a series of patients diagnosed with oligoarticular subtype of JIA.

Methods

Twenty patients (30 joints) were treated with intraarticular infliximab and monitored by power Doppler musculoskeletal ultrasound according to the OMERACT and Juvenile Arthritis Disease Activity Score (JADAS 10) before intraarticular application and during the follow-up period of 18 months (0, 1, 12, 18 months).

Results

The results showed statistically significant improvement in power Doppler musculoskeletal ultrasonography (PD-MSUS) measures and JADAS in both B mode and power Doppler mode scores ($p<0.001$, $p<0.001$, respectively) in patients treated with i.a. infliximab with persistent response in fifteen patients. The JADAS score, as well as the ultrasound scores, were significantly reduced during the follow-up period.

Conclusion

This study showed promising results, good safety and potential for the clinical benefit of intraarticular infliximab treatment in a selected group of patients with oligoarticular subtype of JIA.

Key words

juvenile idiopathic arthritis, intraarticular infliximab, activitiy score, musculosceletal ultrasound

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Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in children. This umbrella term represents a heterogeneous group of inflammatory arthritides that affect children and young adults before the age of 16 and persists for at least six weeks (1). The pathogenesis is still unclear, but it is known to include genetic and environmental factors (2, 3). Chronic inflammation of the synovia causes joint effusion, synovial membrane hypertrophy, and periarticular soft tissue oedema, finally leading to the degeneration of the osseocartilaginous structures and joint destruction, resulting in disability, and interrupted growth both locally and systemically (3). Musculoskeletal ultrasonography with power-Doppler (PD-MSUS), magnetic resonance (MR), conventional x-ray, computerised tomography (CT), synovial fluid evaluation, synovial biopsy, synovial cytokines evaluation and SPECT (Single-Photon Emission Computed Tomography) are all used as instruments to diagnose and follow the patient (4). MSUS is emerging as a simple, painless and inexpensive "point-of-care" tool for detecting synovitis, defining the subtypes of JIA and assessing the efficacy of various therapeutic approaches in everyday practice. It is easily accessible, non-ionising and has been proven more sensitive to clinical examination in detecting synovial disease (5). Although MSUS has high sensitivity and specificity in detecting synovial effusions, thickening and tenosynovitis, the differentiation between normal and pathological findings can be challenging, particularly in early disease (5, 6). In addition to MSUS, power Doppler (PD) modality detects increased vascularisation in active inflammation which helps distinguish more benign forms (*e.g.* reactive arthritis) from chronic disease and may be useful in detecting subclinical synovitis of joints in JIA patients with clinically defined inactive joints (7, 8). Several studies have shown a good correlation of PD-MSUS with MRI in the comparison of cartilage thickness in both healthy and diseased children as well as synovial proliferation in JIA patients, suggesting that PD-MSUS can be used for both initial and follow-up evaluation (9,10). In addition, MSUS can also be of assistance in different interventional procedures such as aspiration of the joints, intra-articular administration of medication or steroid injections of the tendon sheets. The downsides of MSUS are operator-dependence, lack of standardised procedure protocols and the small number of well-trained paediatric rheumatologists capable of using MUSUS (11). To minimise those downsides, the Outcome Measures in Rheumatology (OMERACT) group, an informal international network of working groups interested in outcome measurement, published a semi-quantitative scale for assessing synovitis in both B mode and power Doppler and, more recently, definitions for the sonographic features of joints in healthy children (5, 12-14). Nevertheless, in order to standardise the procedure, more studies with both healthy children and children with JIA are needed (9).

Along with MSUS, the Juvenile Arthritis Disease Activity score (JADAS) was proven to be valid for clinical assessment. JADAS is a composite disease activity score specificly designed for JIA patients. It is simply calculated using the four variables measured in the clinical settings: active joint count (AJC), physician and parent global assessment measured on a 10-cm visual analogue scale (VAS) and erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) (8, 14-16). There are three different JADAS scores depending on number of examined joints – JADAS 27, JADAS 71 and JADAS 10.

There are many therapeutic options available for JIA patients, with overall good response, especially for patients with fewer joints involved. Nevertheless, some patients with oligarticular subtype of JIA according to ILAR classification have continued active joint inflammation observed by MSUS and normal to slightly elevated inflammation markers (CRP, ESR), despite the standard treatment with non-steroidal anti-inflammatory drugs (NSAIDs), i.a. steroid injections and disease-modifying anti-rheumatic drugs (DMARDs). According to the ACR features of prognosis and treatment recommendations,

they do not meet the criteria for systemic biologics (1, 17).

In the past, synovectomy was one of the treatment options for those patients but recurrence in cases of oligoarthritis after arthroscopic knee synovectomy reached up to 67% (18). In adult RA patients, intra-articular anti TNF-α therapy has emerged as a rational therapeutic option, while the effectivnes of this treatment modality in selected patients with recalcitrant oligo JIA has not been reported (19).

Herein, we present a case series of 20 patients with persistent or extended oligoarticular form of JIA injected with intra-articular infliximab into 30 joints, including the results of their 18-month follow-up. Musculosceletal ultrasound was used to assess joint inflammation and effect of *i.a.* infliximab therapy, together with JADAS 10 as a disease acitivtiy score.

Methods

This was a prospective pilot study conducted at a single centre that included 20 patients with 30 active joints in total. All of the patients were diagnosed according to the ILAR criteria with persistent or extended type of oligoarthritis (20, 21).

Prior to intraarticular infliximab injection, all of the patients were treated with NSAIDs. Nineteen pateints received *i.a.* glucocorticoids in the joint later treated with *i.a.* infliximab; twelve on one occasion and seven on two or more occasions. The time between the last *i.a.* glucocorticoid injection and *i.a* infliximab injection was 1 to 9 months (median 4, 10 months). Finnaly, 19 patients were treated with DMARDs (17 with methotrexate and 2 with leflunomide) for at least three months prior to I.A. infliximab injection. Only one patient was not treated with DMARD due to parents rejection.

Patient demographics and treatment modalities are shown in Table I.

Written consent from each parent/guardian or child older than 12 years of age was obtained. Since the use of *i.a.* infliximab is off-label, the study was approved by hospital Ethics Committee and was conducted in concordance with the Helsinki declaration.

Table I. Decriptive parameters of the sample.

Number (m/f)		20 (4/16)
Disease onset (mean years – range)		4.6 (1.9–11.2)
Oligoarticular persistent JIA patients		14
Oligoarticular extended JIA patients		6
ANA + patients		3
RF + patients		0
PRIOR TREATMENT		
NSAID		20
MTX		17
Leflunomide		2
Glucocorticoids systemic		12
Glucocorticoids intaarticular	1x	12
	2-3x	7
JOINTS TREATED		
Knee		27
Ankle		2
Wrist		1

Table II. OMERACT grades for MSUS.

Grade	B mode	Power Doppler
0	Normal joint (no synovial hyperthrophy, no joint effusion)	No vessel in the synovium
1	Minimal synovitis (minimal synovial hyperthrophy, with or without minimal joint effusion)	Up to 3 single spots signals or 1 confluent spot + up to 2 single spots
2	Moderate synovitis (moderate synovial hyperthrophy with or without minimal or moderate joint effusion)	Vessel signals in less than half of the area of the synovium (< 50%)
3	Severe synovitis (severe synovial hypertrophy, with or without severe joint effusion)	Vessel signals in more than half of the area of the synovium (> 50%)

Intra-articular infliximab (Remicade®) injection was made in 30 joints. All of those joints had signs of synovial inflammation detected by MSUS and PDUS. One patient was injected with 25 mg into each knee, one received 25 mg into radiocarpal joint and one 100 mg into the talocrural joint. The remaining seventeen patients received 50 mg of infliximab intraarticulary in one talocrural and 25 knee joints. The dose was calculated according to literature data from previous studies and case reports, minding the type of joint and the volume of medication instilled.

The patients were followed for up to 18 months with the last visit between 12 and 18 months.

Clinical, laboratory, demographic and radiographic data were obtained. JADAS 10 score was calculated for each patient prior to injection and at follow-up visits (1, 12, 18 months). PD-MSUS was performed at each visit using a 6-13 MHz variable linear probe (Medison Samsung Accuvix V10) by an experienced paediatric rheumatologist. Ultrasonographic features were assessed using OMERACT semiquantitative grades (0–3 grades) in both B-mode and power Doppler (PD) (21), Table II.

Comparisons of pre- and post- intraarticular infliximab JADAS and PD-MSUS scores data were performed using Friedman ANOVA (Statistica 13.0 -DELL Software, USA) and ad hoc analysis between pairs of subsequent measures (follow-up visits).

Clinical remission on medications was defined as inactive disease for at least six consecutive months while the patient is taking medication (22-24). Off-medication clinical remission was defined as inactive disease for at least twelve consecutive months without patient taking any anti-arthritis or anti-uveitis medications (22, 23). Criteria for inactive disease were as follows: no joints with active arthritis; absence of

fever, rash, serositis, splenomegaly or generalised lymphadenopathy attributable to JIA; no active uveitis; normal ESR or CRP (if both are tested, both must be normal); physician's global assessment of disease activity indicates no disease activity (22). Disease flare was defined as 40% worsening in two out of six core set items without improvement in more than one core set variable by 30% or more (22). In our study the state of remission/relapse was defined on second visit and third visit (12 and 18 months, respectivley).

Comparisons of pre- and post- intraarticular infliximab JADAS 10 and PD-MSUS scores data were performed using Friedman ANOVA (Statistica 13.0 -DELL Software, USA) and ad hoc analysis between pairs of subsequent measures (follow-up visits). Non-parametric Mann Whitney test was used to test for differences between the only sterod group and steroid plus infliximab group. The contingency tables were used to search for differences in the number of affected joints that relapsed after the steroid therapy in comparison with the number of relapsed joints after infliximab. Kaplan-Meier curves were used to estimate the relapse rate after *i.a.* infliximab therapy.

The survival analysis was performed comparing cumulative "survival" times, meaning times to relapse in the same patients while treated with *i.a.* steroids and later *i.a.* infliximab.

Fig. 1. The values of B mode score initially and during the follow-up period.

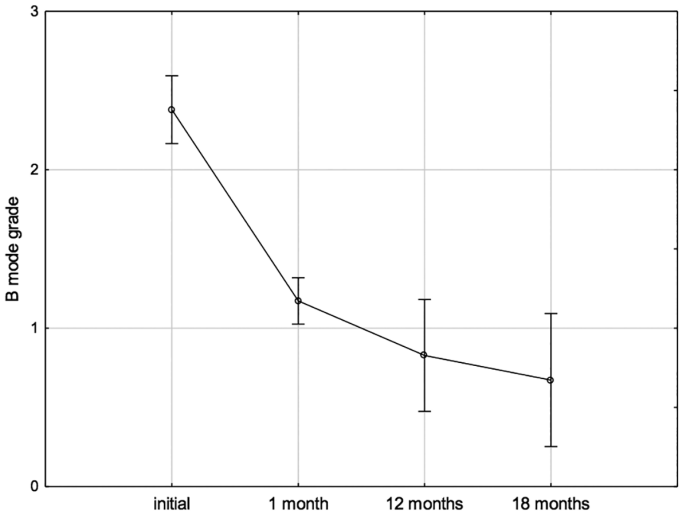


Fig. 2. The values of PD grade initially and during the follow-up period.

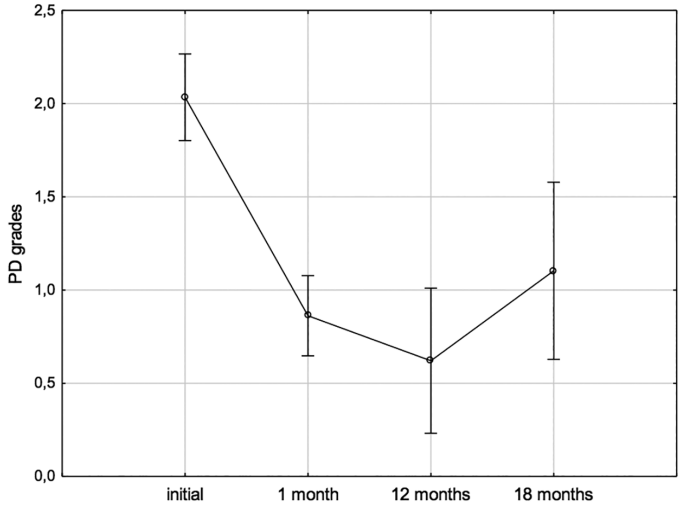
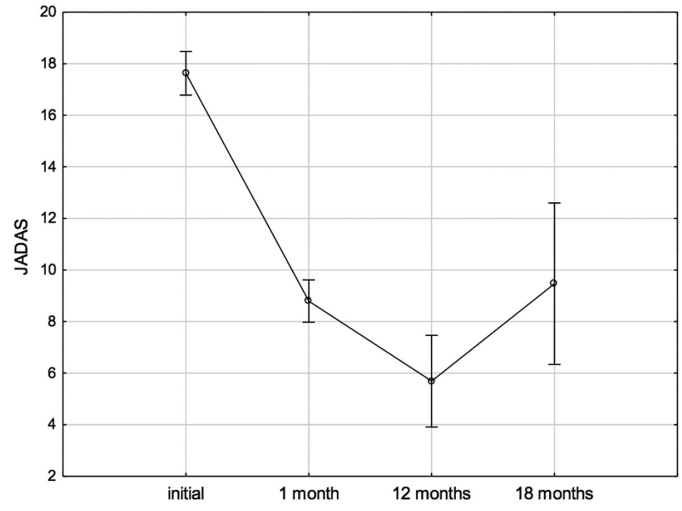


Fig. 3. The values of JADAS score initially and during the follow-up period.



Results

B mode scores analysed by ANOVA were significantly lower after *i.a.* application of infliximab ($p<0.001$) compared to initial findings. In the post hoc analysis of the pairs of subsequent measurements a statistically significant change was observed between the initial and one month follow-up B mode scores ($p<0.001$). Comparison of B mode scores between second and third as well as between third and fourth follow-up visit were not significant ($p=0.214$ and $p=0.815$, respectively) (Fig. 1).

PD MSUS ANOVA analysis showed similar statistical significance between the initial and one month follow-up measurements ($p<0.001$). Also, between second and third and third and fourth follow-up visit changes in B mode score were not statistically significant ($p=0.791$ and $p=0.957$, respectively) (Fig. 2).

The ANOVA model for JADAS also showed significance ($p<0.001$). Statistically significant change in the post hoc tests was observed between the initial and one month follow-up score

(p<0.001) and up to the one year follow-up (p<0.05). Changes in scores at 12 and 18 months visits compared to initial were also significant (p<0.05), although the patient's JADAS score slightly increased with time (Fig. 3).

By the end of the study, at their last follow-up, 8 patients fullfiled the criteria for remission off medication and 7 patients for remission on medications. Only five patients with in total ten active joints flared.

The Spearman rank correlation coefficient calculated in order to investigate possible correlations between the previous use of intraarticular glucocorticoid therapy and the state of remission/relapse 12 months after I.A. injection of infliximab showed no significant correlation (Spearman R=0.25).

The relationship between the dosage and the decrease in both PD and JADAS was also tested by Spearman correlation, which confirmed the significantly greater improvement in indices with higher infliximab dosage.

Kaplan-Meier analysis was performed for 82.35% of patients who showed up for their last follow-up. Out of 5 relapsed patients, 3 patients finished the study and relapsed at the end of the observational period and two relapsed before the end of the observational period. Figure 4 shows that 80% of patients did not relapse. For those 5 patients who relapsed critical time was first 240 days (10 months) (Fig. 4).

The contingency tables were used to search for differences in the number of affected joints that relapsed after the steroid therapy in comparison with the number of relapsed joints after infliximab, as in steroid group 28 joints relapsed, and in infliximab group only ten. The Chi square test proved to be significant (p<0.00001).

The median value of time to relapse after infliximab was 720 days while on steroids the median value was 105 days. Mann Whitney U-test was used to test for differences between the groups in time to relapse and it proved the difference to be significant (U=61: Z= -5.744; p<0.001) (Fig. 5).

Out of five relapsed patients, two received 25 mg and one 50 mg of infliximab in both knees because of the availability of the medication. One patient recieved 25 mg into the radiocarpal joint because the smaller volume of the medication needed for this joint andrelapsed during the follow-up period.

No local or systemic side effects of either local and systemic therapy was observed during the treatment and follow-up period.

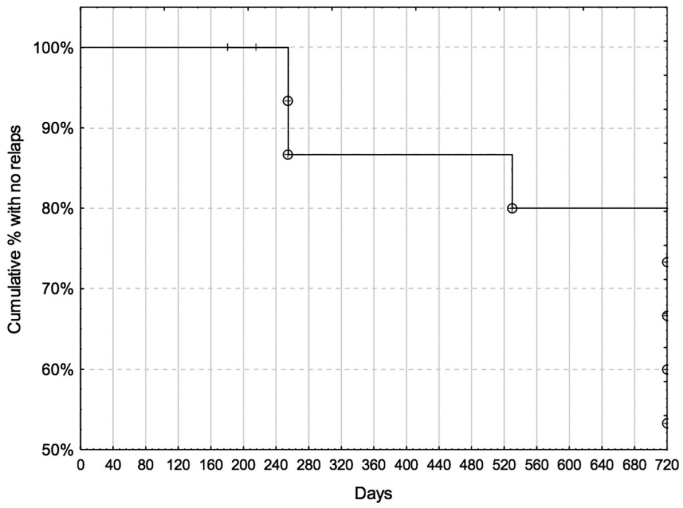


Fig. 4. Cumulative percantage of patiens with no relapse over 240 days with projection to 2 years.

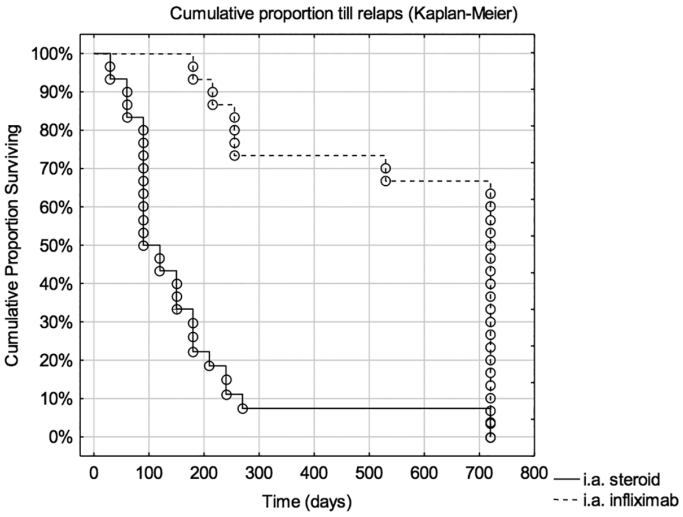


Fig. 5. Kaplan-Meier curves show shorter time to relapse in higher percentage of joints after only steroid therapy.

Discussion

Patients with oligoarthritis who have some activity of the disease, inadequate response to conventional NSAID or DMARDs and do not fulfill criteria for systemic biologicsare not rare (1, 25). Infliximab is a chimeric antibody that blocks TNF-α and is usually administered intravenously (26, 27). Prior studies have shown the reduction in cellular infiltrate (macrophages and T cells respectively), decreased levels of TNF-α and IL1β in synovial membrane and adhesion molecules expression after i.a. infliximab (28), which provided a rationale for the described treatment approach. However, there are limited number of studies with intra-articular anti TNF-α injections in adults as well as children, most of them with variable clinical and US improvement and short follow-up period (up to 6 months) (28). Several questions were raised considering the safety and efficacy of i.a. biologisc, patient selection, type of biological therapy and dosage and last but not least, preferred joint (28). There is also a question of repeated i.a. anti-TNF-α injections since some data showed improvement after second and even multiple injections (29). In our case there was only one application due to the limitations of the study and technical reasons (avalibility of the medication,

parental/patient consent) and appearance of biosimilars.

In the series of twenty-four children with refractory tempromandibular joint arthritis who underwent bilateral *i.a.* infliximab injection (10 mg/ml infliximab per joint) the procedure was found to be safe and there was a reversal of arthritis progression in nine patients (30). To the best of our knowdlege, this was the only paediatric study with *i.a.* infliximab published to date.

Furthermore, in adult patients with spondyloarthritis, *i.a.* infliximab proved to be effective, especially in large joints and even sacroiliac joints (31-37). RA and psoriatic arthritis patients also benefited from this therapeutic approach (29, 38-40), while ostearthritis patients experienced only short-term positive symptomatic effect (31, 32, 41). Etanercept did not show superiority over *i.a.* glucocorticoids, but both approaches had positive clinical and radiological effect (42, 43). Other studies with RA patients and villonodular synovitis, temporomandibural joint and even in sacroiliacal joint in spondyloarthropathy patients had positive outcome, but the number of cases is still too small and more studies are required (44-47). Adalimumab also showed some success in adults and there are no reports on use of other intraarticular biologics so far either in adults or children (48, 49).

Recently our group published the results of the follow-up of patients who were treated either with *i.a.* infliximab or triamcinolone hexacetonide with 3D/4D PD sonography. The data showed a significant difference in vascularisation index for patients treated with i.a. infliximab and a decrease in JADAS in both treatment groups (50).

In this study, *i.a.* injection of infliximab in 30 active joints of 20 children diagnosed with JIA was well tolerated and without any local or systemic adverse reactions.

On their last follow-up visit, eight out of twenty patients (40%) were in complete remission off medications, and seven patients (35%) in remission on medications. Just five patients (25%) relapsed. Those patients developed extended oligo JIA and after fulfilling criteria were put on systemic biologics. The previous therapy with *i.a.* glucocorticoids did not affect remission/relapse ratio.

The reason for poor outcome in these patients could be the smaller dose administered and subsequently lower concentration of the medication in the joint. Also, all five patients who relapsed had higher initial PD-MSUS and disease activity scores suggesting more severe disease requiring different treatment approach.

This study showed statistically significant improvement in PD-MSUS measures in both B mode and power Doppler mode scores in patients with moderate but persistent arthritis. JADAS composite disease activity score also improved. On the last follow-up visit MSUS measures were still improved over baseline in most patients.

In summary, although progression of the disease was slowed down, only 10 out of 27 knee joints showed almost complete resolution of arthritis (B mode 0/3, PD 0/3). This could be explained by the low dose and the single administration of the drug. In some reports there was a significant reduction in synovitis in adult patients after repeated *i.a.* infliximab administration (35). The dose and injected joint also varied in different reports although most studies used 100 mg infliximab for injection into the knee and 25–50 mg for small joints (wrist, sacroilial joint and ankle) (28). Most reports showed that i.a. anti TNF-α therapy was effective in patients with large joint arthritis (most commonly the knee) who did not receive biologic DMARDs and that MSUS was the best method of evaluation (28).

This is one of the very few studies with a longer follow-up period and only the second of its kind in the paediatric population. Limitations of the study are lack of blindness to therapy with PD-MSUS and disease activity assessment, no intra- and interobserver variability analysis, and the relatively small number of patients/joints injected.

Furthermore, *i.a.* infliximab use is off-label and more data are missing on long-term effects on cartilage and bone growth after injection. Our study showed a longer period of remission on *i.a.* infliximab that on *i.a.* steroids.

More multicentric or double-blinded placebo controlled studies are clearly needed before any final conclusions about i.a. infliximab efficacy in the large joints of JIA patients can be drawn.

From that perspective, the promising results of the present study, including good safety and potential for high clinical benefit, may encourage other centres to use *i.a.* infliximab in patients with the mono- or oligo-articular form of JIA.

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