Improving targeted treatment in early rheumatoid and undifferentiated arthritis

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Chapter 5

SIGNS OF INFLAMMATION ON MAGNETIC RESONANCE IMAGING BEFORE AND AFTER INTRA-ARTICULAR INFLIXIMAB OR CORTICOSTEROIDS IN RECURRENT GONARTHRITIS

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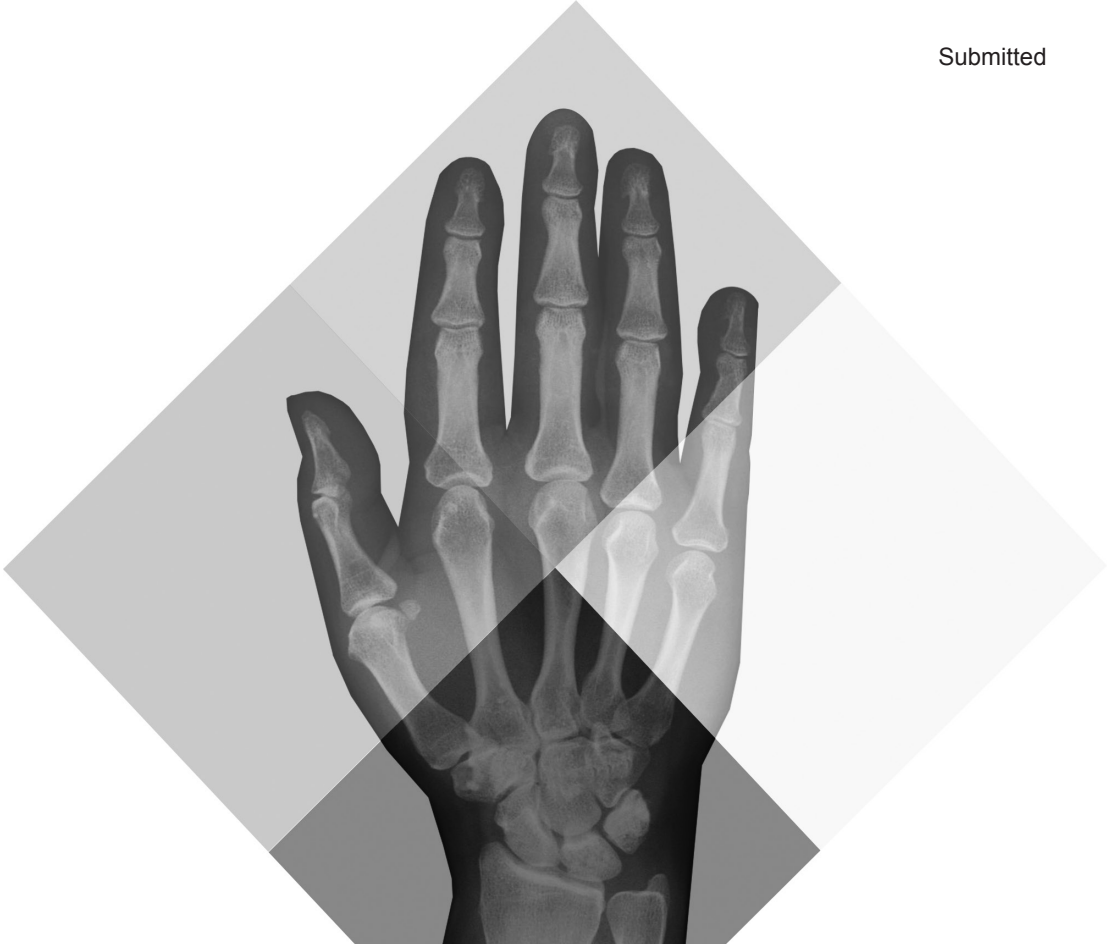

ABSTRACT

Objectives

To evaluate synovial inflammation on magnetic resonance (MR) imaging in chronic or recurrent gonarthritis and changes after intra-articular (i.a.) infliximab (IFX) or methylprednisolone (MP) treatment in relation to clinical response.

Methods

In the RIA study, a prospective double-blind trial, chronic or recurrent gonarthritis patients were randomized to i.a. IFX or MP. Changes in T1 contrast enhanced MR outcomes of the knee pre-injection and 4 weeks post-injection were compared for Hoffa synovitis (0-3) and joint effusion (0-3), and investigated in relation to early clinical response measured by the knee joint score (tenderness, swelling, patient's pain) after 4 weeks and late clinical response measured by relapse within 6 months.

Results

Sets of pre- and post-injection MR images were available for 26 injections (14 IFX, 12 MP) in 20 knees. Pre-injection, MR findings were not associated with patient or gonarthritis characteristics. Hoffa synovitis and effusion decreased in IFX injected knees ((2.5 (1.8;3.0) to 2.0 (1.0;2.3), p=0.021) (2.5 (2.0;3.0) to 1.0 (1.0;3.0), p=0.007), respectively). In IFX injected knees, but not in MP injected knees, MR improvement after 4 weeks was associated with clinical improvement. Relapse within 6 months occurred in all IFX and in half of MP injected knees, irrespective of MR or early clinical improvement at 4 weeks.

Conclusions

MR of chronic or recurrent gonarthritis, showed considerable signs of inflammation. IFX injected knees showed early clinical and MR improvement, this was not seen in MP injected knees. However at the long term MP injected knees showed less relapse than IFX injected knees.

INTRODUCTION

Isolated gonarthritis in daily practice is mostly treated with local corticosteroid injections, but this treatment is associated with a high recurrence rate.[1] An alternative treatment with intra-articular (i.a.) injections of infliximab (IFX), a tumour necrosis factor α blocker, has been tried in several studies.[2-5] These showed promising clinical responses, but were uncontrolled, open label and with relatively short follow up. To evaluate whether i.a. infliximab was superior to (retreatment with) i.a. corticosteroids in chronic gonarthritis that had persisted or recurred after previous i.a. corticosteroid treatment, we conducted the RIA study, a double-blind randomized controlled trial in patients with chronic gonarthritis to compare the 6 months clinical outcomes of i.a. infliximab and i.a. methylprednisolone (MP).[6] The results were disappointing: 100% of IFX injected knees showed persistence or recurrence of gonarthritis after 6 months, compared to 50% of MP injected knees.

We hypothesized that either the pre-treatment amount of inflammation was too high to (permanently) improve after local injection, or that initial improvement may have occurred but untreated disease mechanisms have resulted in recurrence of inflammation. To investigate this hypothesis, we assessed pre- and 4-weeks post-injection magnetic resonance (MR) imaging of the treated knees. MR imaging enables the evaluation of soft tissues as well as of bone in joints. Earlier studies showed that MR signs correlate well with histological findings of inflamed synovium [7,8] and that these signs may improve early after i.a. corticosteroid injection.[9] Here we report pre-injection inflammatory MR signs and their improvement after treatment with either i.a. IFX or MP injections in relation to clinical response in patients with chronic or recurrent gonarthritis.

PATIENTS AND METHODS

Study design and Patients

The RIA study (Remicade Intra Articularly), a prospective, randomized, double-blind trial, included 23 patients from the outpatient clinic of the Rheumatology department of the Leiden University Medical Center. These patients had clinically active monoarthritis of the knee and had been treated with i.a. corticosteroid injection at least once in the previous year. Exclusion criteria were gonarthritis caused by an infection, gout or osteoarthritis, hemorrhagic disease, participation in any other study that could be influenced by this study, use of oral prednisone >10 mg/day, change of disease modifying antirheumatic drug (DMARD) therapy ≤6 weeks before inclusion, i.a. injection with corticosteroid in any joint <2 months, hypersensitivity to methylprednisolone, lidocaine, or infliximab (or other murine proteins), active or latent tuberculosis, acute or chronic infection, multiple sclerosis, heart failure, pregnancy or lactation,

and malignancy. All patients were screened for (latent) tuberculosis including radiograph of the lungs and a tuberculin skin test. The study was approved by the hospital's Medical Ethics Committee and all patients gave written informed consent.
Patients were randomized to receive i.a. infliximab 100 mg or i.a. corticosteroid 80 mg in the knee. If gonarthritis recurred clinically within 3 months patients could receive a second injection with the other study medication in the same knee.
Study medication was prepared by a 'non-assessing' investigator who made sure that patient, rheumatologist and assessor remained blind for the injected medication. Prior to injection of the study medication, i.a. fluid was evacuated by aspiration as much as possible.

Outcomes
All patients were clinically evaluated at 4 weeks, 3 and 6 months. Outcome measures were event-free survival and/or non-improvement of the knee joint score. This arbitrary score (0-7) includes knee tenderness 0-3 (0 = no tenderness, 1 = tenderness when asked, 2 = tenderness on pressure and 3 = tenderness and wincing), knee swelling 0-3 (0 = no swelling, 1 = little swelling, 2 = moderate swelling and 3 = abundant swelling) and a patient's knee pain score 0-1 (visual analogue scale, VAS, measured in mm, 0=best possible, 100=worst possible, divided by 100). Event free survival was defined by time from i.a. treatment until local retreatment (joint aspiration or injection, arthroscopy, or (radio-) synovectomy) was performed due to recurrence or persistency of the gonarthritis (which will be referred to as 'relapse').

MR and scoring
A T1 gadolinium contrast enhanced MR (CE-MR) of the affected knee was performed at baseline preceding the i.a. injection and 4 weeks later. A 3 T Philips Achieva MR system (Philips Healthcare) using an eight-channel dedicated knee coil was used. In case of recurrent or persistent gonarthritis, patients entered the cross-over part of the study and CE-MR was again performed prior to and 4 weeks after the second injection. Per patient a decision was made to withhold gadolinium (8 pre-treatment MRs and 7 post-treatment MRs). The Guermazi score was therefore dropped from the analysis.
All MR images were scored by one trained reader. Since there is no validated scoring method to assess (changes in) MR signs in inflammatory gonarthritis, the MR images were assessed by 3 scoring methods more specific for osteoarthritis. Sagittal T2 proton density weighted images were used for the MOAKS [10] (MR Osteoarthritis Knee Score) was used to assess Hoffa synovitis (range 0-3, 0 = no synovitis, 1 = mild synovitis, 2 = moderate synovitis and 3 = severe synovitis). Axial and coronal T2 proton density weighted images were used for the KOSS [11] (Knee Osteoarthritis Scoring System) to assess joint effusion (range 0-3, 0 = no effusion, 1 = mild effusion, 2 = moderate effusion, 3 = severe effusion). Sagittal T1 CE-MR images were used for the Guermazi [12] scoring method to assess synovitis on 8 anatomical

sites in the knee: suprapatellar, infrapatellar, intercondylar, adjacent to the anterior cruciate ligament (ACL), parameniscal lateral, parameniscal medial, adjacent to the posterior cruciate ligament (PCL) (per anatomical site range 0-2 (0 = synovial thickness less than 2 mm, 1 = thickness between 2 and 4 mm, 2 = thickness above 4 mm) and if loose bodies were present, this site was scored in addition. A total score was calculated (0-16). Intra-observer reliability was measured by intraclass correlation coefficient (ICC) and ranged from a minimal value of 0.70 for the Hoffa synovitis score to a maximal value of 0.94 for the effusion score.

Statistical analysis

Differences between two consecutive MR images were compared between the randomization groups using Mann-Whitney *U* test, Wilcoxon signed ranks test and χ^2 test. As there was no statistical significant difference in the primary clinical endpoint (knee joint score) between the randomization arms, and no differences in MR scores pre-injection between once or twice injected knees between the randomization arms, we assumed no cross-over or carry over effects of treatments, and analyzed all interventions together. Statistical analysis were performed by SPSS 23.0.

RESULTS

MR images preceding injection

In the RIA study, 23 middle-aged, majority male patients, 35% were diagnosed with UA, were included, who in total received 41 i.a. knee injections: 15 single injections, 13 same-knee re-injections. Pre- and post-injection MR images were unfortunately not complete, due to patients' refusal, contra-indications to gadolinium, or rescheduling of MR appointments resulting in inadequate timing respective to the injections. In 21 patients MR images preceding 1st, 2nd or 3rd injections were obtained (table 1). At baseline (preceding the first injection) 18 MR images (4 had no post-injection MR images) were available, 12 MR images preceding the second injection (2 had no post-injection MR images) and 2 preceding the third injection.
Evident signs of inflammation of the knee were seen by a median knee joint score at inclusion of 3.7 (table 1). Median Hoffa synovitis score was 2 and effusion score was 3. Guermazi scores were missing in 9 patients, because these patients did not receive gadolinium. Median Guermazi synovitis total score was 7. The medians for the 8 different anatomical sites were approximately 1 (supplementary table 1) and only the score for 'loose body' was 0.
MR scores were comparable in knees with various diagnoses (data not shown).
Preceding the first injection, there were no differences in MR scores between MP and IFX injected knees (Hoffa synovitis score mean difference -0.69 (95% CI -1.44;0.05) and effusion score 0.31 (-0.33;0.95)), or in knees injected once or twice (in cross-over design) with study medication (data not shown).

Table 1. Baseline patient characteristics and MR signs on images preceding injections (n=32 interventions in 21 patients).

MR preceding 1st, 2nd or 3rd injection	Patients n=21
Age, years, mean (SD)	51 (12)
Female, n (%)	10 (48)
Diagnosis, n (%)	
UA	9 (42.9)
RA	4 (19)
PsA	5 (23.8)
SpA	2 (9.5)
JIA	1 (4.8)
Number of DMARDs, median (IQR)	1 (0;2)
Number of previous i.a. corticosteroid injections, median (IQR)	2 (1;3)
	Interventions n=32
Randomization MP/IFX, n (%)	15/17 (47/53)
Knee joint score at time of inclusion (0-7), median (IQR)	3.7 (3.3;4.8)
Knee tenderness (0-3), median (IQR)	1 (0.8;2)
Knee swelling (0-3), median (IQR)	2 (2;3)
Patient knee pain score (0-1), median (IQR)	0.40 (0.20;0.64)
Hoffa synovitis, n (%)	
Mild	6 (19)
Moderate	13 (41)
Severe	11 (34)
Effusion, n (%)	
Mild	3 (9)
Moderate	9 (28)
Severe	18 (56)
Guermazi score, median (IQR)	7 (5.8;10.3)

UA: undifferentiated arthritis; RA: rheumatoid arthritis; PsA: psoriatic arthritis; SpA: spondyloarthritis; JIA: juvenile idiopathic arthritis; DMARDs: disease modifying antirheumatic drugs; i.a.: intra-articular; IFX: infliximab; MP: methylprednisolone; VAS: visual analogue scale; SD: standard deviation; n: number; IQR: interquartile range.

Changes in MR scores

There were 26 sets of pre- and post-injection MR images. These comprised 14 sets around first injections (6 MP, 8 IFX), 10 sets around second injections (5 MP, 5 IFX), 8 in a previously injected knee, and 2 sets around third injections (1 with MP in a previously injected knee and 1 with IFX in the contralateral knee), thus making 12 sets of knee MR images pre-injection and post-injection with MP, and 14 sets of knee MR images pre-injection and post-injection with IFX. A second injection in the contralateral knee will further be considered to be a first injection in that knee. Thus there were 17 first injections (7 MP, 10 IFX) and 9 second injections (5 MP, 4 IFX). All 26 sets were combined in one analysis, although details about retreated knees will be presented.

There were no differences between IFX injected patients and MP injected patients in age, number of DMARDs, number of previous i.a. corticosteroid injections, distribution of diagnoses nor between injected knees in knee joint scores at the time of inclusion (table 2).

Table 2. Clinical characteristics of patients at inclusion classified per injection (n=26 injections).

	Total patients n=18	**MP n=10**	**IFX n=14**
Age, years, mean (SD)	51 (13)	51 (13)	50 (13)
Female, n (%)	8 (44)	2 (20)	7 (50)
Diagnosis, n (%)			
UA	6 (33)	2 (20)	4 (29)
RA	4 (22)	2 (20)	3 (21)
PsA	5 (28)	4 (40)	4 (29)
SpA	2 (11)	1 (10)	2 (14)
JIA	1 (6)	1 (10)	1 (14)
Number of DMARDs, median (IQR)	1 (0;2.3)	0.5 (0;2.3)	1 (0;2.3)
Number of previous i.a. corticosteroid injections, median (IQR)	2 (1;3)	2.5 (1;11.3)	2 (1;2.3)
	Total interventions n=26	**MP n=12**	**IFX n=14**
Knee joint score at time of inclusion (0-7), median (IQR)	3.7 (3.3;5)	3.7 (3.3;5)	3.6 (3.1;5)
Knee tenderness (0-3), median (IQR)	1 (0.3;2)	1 (1;2)	1 (0;2)
Knee swelling (0-3), median (IQR)	2 (2;3)	2 (2;3)	2 (2;3)
Patient knee pain score (0-1), median (IQR)	0.37 (0.20;0.67)	0.39 (0.32;0.58)	0.36 (0.13;0.74)
Hoffa synovitis, n (%)			
Mild	5 (19)	2 (17)	3 (21)
Moderate	11 (42)	7 (58)	4 (29)
Severe	9 (35)	2 (17)	7 (50)
Effusion, n (%)			
Mild	3 (12)	1 (8)	2 (14)
Moderate	7 (27)	2 (17)	5 (36)
Severe	15 (58)	8 (67)	7 (50)
Guermazi score, median (IQR)	8 (6;10.5)	6 (5;8)	9 (6.3;11)

IFX: infliximab; MP: methylprednisolone; UA: undifferentiated arthritis; RA: rheumatoid arthritis; PsA: psoriatic arthritis; SpA: spondyloarthritis; JIA: juvenile idiopathic arthritis; DMARDs: disease modifying antirheumatic drugs; i.a.: intra-articular; VAS: visual analogue scale; MOAKS: MR Osteoarthritis Knee Score; KOSS: Knee Osteoarthritis Scoring System; SD: standard deviation; n: number; IQR: interquartile range.

First we looked at changes in MR outcomes 4 weeks post-injection in relation to treatment. Following injection the Hoffa synovitis score improved by ≥1 point in 12/26 (46%) knees (4/12 (33%) MP injected knees and 8/14 (57%) IFX injected knees, p=0.302), while synovitis score remained stable in 13/26 (50%) knees (7/12 (58%) MP injected knees and 6/14 (43%) IFX

injected knees, p=0.302, incomplete data for 1 MP injected knee). Following injection, the effusion score improved by ≥1 point in 11/26 (42%) knees (3/12 (25%) MP injected knees and 8/14 (57%) IFX injected knees, p=0.227), while it remained stable in 14/26 (54%) knees (8/12 (67%) MP injected knees and 6/14 (43%) IFX injected knees, p=0.227, incomplete data in 1 MP injected knee). Irrespective of intra-articular medication, of 14 knees that showed improvement in Hoffa synovitis score or improvement in effusion score 9 showed improvement in both scores. In IFX injected knees, the mean decrease in Hoffa synovitis scores and effusion scores reached statistical significance (from 2.5 (1.8;3) to 2 (1;2.3), p=0.021 and from 2.5 (2;3) to 1 (1;3), p=0.007, respectively) but not in MP injected knees (from 2 (2;2) to 1.5 (1;2), p=0.157 and from 3 (2;3) to 2 (1;3), p=0.102, respectively) (table 3).

Second we looked at post injection MR outcomes in relation to early clinical response. Four weeks post injection, the knee joint score had improved by ≥1 point in 13/26 (50%) injected knees (6/12 (50%) MP injected knees and 7/14 (50%) IFX injected knees, p=1.000) with a median improvement from 3.7 (3.3;5) to 1.9 (0.8;3.6) in MP injected knees (p=0.012) and from 3.6 (3.1;5) to 1.7 (1;3.5) in IFX injected knees (p=0.038) (table 4). Early knee joint score improvement was associated with MR improvement only in IFX injected knees, where all knees with MR improvement also showed early clinical improvement. In MP injected knees, clinical improvement was seen more often in knees where no MR improvement was seen (table 4).

Six of twelve MP injected knees and all 14 IFX injected knees were defined as having a relapse 6 months after injection (p=0.04). MR changes nor early clinical improvement were related to clinical outcomes at 6 months (table 4). Median (IQR) Hoffa synovitis scores and effusion scores before injection were similar in MP injected knees that did or did not relapse (data not shown). Also the post-injection changes in Hoffa synovitis scores and effusion scores were similar (delta Hoffa synovitis scores 0 (-1.5;0.5) p=0.414 in MP injected knees with relapse and 0 (-1;0) p=0.157, in MP injected knees that did not relapse, delta effusion scores 0 (-1;0), p=0.157 in knees with relapse and 0 (-0.5;0) p=0.317, in knees without relapse). Knee joint score 4 weeks post-injection had decreased significantly in patients who had no relapse at 6 months (from 3.5 (3.4;4.7) to 1.1 (0.2;2.6), p=0.028) but less so in patients who did relapse (from 4.1 (3;5.4) to 3.9 (1.6;5.4), p=0.180) (table 5). These limited findings may suggest that there may have been a short term suppression of synovitis, but chronic inflammation then recurs.

Table 3. Clinical and MR outcomes before and 4 weeks after treatment and clinical outcome 6 months after treatment in the randomization groups.

Time point	MP n=12	p-value week 0 vs. 4 MP	IFX n=14	p-value week 0 vs. 4 IFX	p-value between MP and IFX
Total Knee joint score, median (IQR)					
Baseline	3.7 (3.3;5)		3.6 (3.1;5)		0.671
Week 4	1.9 (0.8;3.6)		1.7 (1;3.5)		1.000
Delta	-1 (-3.5;-0.8)	0.012	-1.6 (-3.1;0.03)	0.038	
Knee tenderness, median (IQR)					
Baseline	1 (1;2)		1 (0;2)		0.977
Week 4	1 (0;2.8)		0.5 (0;2)		0.582
Delta	0 (-1;0.3)	0.317	-0.5 (-1.3;0.3)	0.161	
Knee swelling, median (IQR)					
Baseline	2 (2;3)		2 (2;3)		0.755
Week 4	1 (1;2.8)		1 (1;2)		1.000
Delta	-1 (-2;-0.8)	0.009	-1 (-1.5;0)	0.014	
Patient knee pain score, median (IQR)					
Baseline	0.39 (0.32;0.58)		0.36 (0.13;0.74)		0.630
Week 4	0.31 (0.04;0.64)		0.26 (0.11;0.47)		0.923
Delta	-0.07 (-0.31;-0.02)	0.012	-0.06 (-0.38;0.04)	0.097	
Hoffa synovitis score, median (IQR)					
Baseline	2 (2;2)		2.5 (1.8;3)		0.288
Week 4	1.5 (1;2)		2 (1;2.3)		0.826
Delta	0 (-1;0)	0.157	-1 (-1.0)	0.021	
Effusion score, median (IQR)					
Baseline	3 (2;3)		2.5 (2;3)		0.286
Week 4	2 (1.3;3)		1 (1;3)		0.186
Delta	0 (-1;0)	0.102	-1 (-1;0)	0.007	
6 months					
Sufficient response*, n (%)	6 (50)		0		
Insufficient response, n (%)	6 (50)		14 (100)		0.004

IFX: infliximab; MP: methylprednisolone; n: number; IQR: interquartile range.
*no relapse before 6 months requiring therapeutic intervention

Of 9 patients who had a gonarthritis relapse within 6 months and received a second injection in the same knee, 6 patients had available MR sets for the first and the second injections. Four were first injected with IFX and then with MP (3 again relapsed), and 2 first with MP and then with IFX (all again relapsed). None of the reinjected knees showed a significant improvement in knee joint score 4 weeks post-injection (supplementary table 2). In 5 retreated knees (83%) the pre-second injection synovitis scores were again as they were 4 weeks pre-first injection or higher (median Hoffa synovitis scores pre-first injection 2.5 (IQR 1.8;3) and pre-second injection 2.5 (2;3), p=1.000). For effusion score this was seen in all 6 patients (median effusion scores pre-first injection 3 (1.8;3) and pre-second injection 3 (2.5;3), p=1.000).

Table 4. MR improvement after (≥1 points) 4 weeks in relation to early clinical improvement (delta knee joint score ≥1 points) at 4 weeks and relapse after 6 months by treatment with methylprednisolone or infliximab.

Treatment	MR improvement	Early clinical improvement		Relapse	
		yes	no	yes	no
	Hoffa synovitis				
MP*	**yes**	2[#]	2	2	2
	no	4	1	1	4
IFX	**yes**	6	0	6	0
	no	1	3	4	0
	Effusion score				
MP*	**yes**	2[#]	1	2	1
	no	4	2	1	5
IFX	**yes**	5	0	5	0
	no	2	3	5	0

MP: methylprednisolone (no data on early clinical improvement available for 3 injections); IFX: infliximab (no data on early clinical improvement available for 4 injections); MR: magnetic resonance imaging.
*: in 1 patient no Hoffa synovitis and effusion scores available.
[#]: these are the same patients.

Table 5. MRI outcomes and knee joint score in the MP group according to response after 6 months.

Time point	No relapse n=6	Relapse n=6	p-value no relapse vs relapse	p-value week 0 vs. 4 no relapse	p-value week 0 vs. 4 relapse
Hoffa synovitis, median (IQR)					
Baseline	2 (1;2)	2 (2;3)	0.056		
Week 4	1 (1;2)	1.5 (1;2)	0.614		
Delta	0 (-1;0)	0 (-1.5;0.5)		0.157	0.414
Effusion score, median (IQR)					
Baseline	2.5 (1.8;3)	3 (3;3)	0.080		
Week 4	2.0 (1;3)	1.5 (1;2)	0.617		
Delta	0 (-0.5;0)	0 (-1;0)		0.317	0.157
Knee joint score, median (IQR)					
Baseline	3.5 (3.4;4.7)	4.1 (3;5.4)	0.818		
Week 4	1.1 (0.2;2.6)	3.9 (1.6;5.4)	0.114		
Delta	-2.9(-4.3;-0.8)	-0.1 (-0.8;0)		0.028	0.180
Knee tenderness, median (IQR)					
Baseline	1 (1-2)	1 (0-2)	0.589		
Week 4	0.5 (0;1.3)	1 (0.3;2.5)	0.476		
Delta	-1 (-1.3;0.3)	0 (0;0.8)		0.157	0.317
Knee swelling, median (IQR)					
Baseline	2 (2;2.3)	3 (2;3)	0.180		
Week 4	1 (0;1)	2 (1.3;2.8)	0.038		
Delta	-1.5 (-2;-1)	-0.5 (-1;0)		0.024	0.157
VAS score, median (IQR)					
Baseline	0.39 (0.34;0.49)	0.37 (0.15;0.80)	0.818		
Week 4	0.15 (0.03;0.31)	0.35 (0.08;0.64)	0.352		
Delta	-0.24 (-0.46;-0.04)	-0.03(-0.08;-0.01)		0.043	0.109

n: number; IQR: interquartile range

DISCUSSION

We evaluated the signs of synovial inflammation on MR images in patients with chronic or recurrent non-osteoarthritic gonarthritis following intra-articular injection with either infliximab or methylprednisolone. Regardless of type of gonarthritis, similar signs of inflammation using the Hoffa synovitis score and the effusion score were identified in all knees. We found significant changes in MR scores four weeks following intra-articular injection with IFX, but not with MP. These changes appeared to be associated with early clinical response measured with a clinical Knee Joint Score. However, we found no association between pre-injection MR scores or post-injection MR score changes with the clinical response 6 months after either an i.a. IFX or MP injection. All IFX injected knees showed a relapse, compared to 50% of MP injected knees. Relapse was not associated with MR changes, but MP injected knees which showed early clinical improvement may be less likely to clinically relapse after 6 months.

Intra-articular treatment of inflamed joints may often result in rapid symptom reduction.[13-15] This is thought to be due to suppression of local inflammation. However, up to 50% of injected joints still show clinical signs of inflammation or will suffer a clinical relapse after initial improvement.[13] MR is an upcoming imaging tool to detect early stages of damage, arthritis and subclinical arthritis. We hypothesized that signs of inflammation on MR at baseline or after intra-articular injection may be different in knees that do or do not show clinical improvement and/or later relapse. We found that a single dose of 100 mg i.a. IFX appears to be effective on the short term, but is insufficient to induce long-lasting suppression of inflammation, whereas a single dose of 80 mg i.a. MP is less often effective on the short term, but may suppress inflammation possibly longer than IFX.

We can only speculate whether these observations may be related to the mode of action of the i.a. therapies used. Methylprednisolone can cross cell membranes [16] and works intracellularly in contrast to infliximab that binds to extracellular receptors. By inhibiting prostaglandin synthesis and reducing vascular permeability by altering physicochemical properties and the activities of membrane-associated proteins,[16] MP may act through more pathways than infliximab, activating cytokine genes, mediating proinflammatory action of tumor necrosis factor to suppress inflammation and blocking influx of new inflammatory agents.

As an alternative possible explanation of our findings, the dosage of IFX may have been too low to be effective. We used 100 mg IFX per injection as described in successfully treated case reports [2,3,5] but the therapeutic intra-articular dosage may need to be in range with the therapeutic dosage used intravenously.

To our knowledge this is the first study to study changes in signs of inflammation in relation to treatment in arthritic joints. We acknowledge that this was a small exploratory study, where several caveats are due. We included patients with recurrent gonarthritis of various known and unknown origins. Some types or stages of gonarthritis may be irresponsive to MP or IFX

or both. Lacking scoring methods for rheumatoid or other types of arthritis, we used scoring methods developed for osteoarthritis. We found more inflammation in our study compared to previous studies in osteoarthritis patients.[17,18] However, we did not include osteoarthritis patients in our study. We wanted to use gadolinium enhanced MR in all patients, but this was contraindicated or omitted in several patients, in particular in follow up MRs. As a result, we had insufficient data to evaluate possible changes in the Guermazi score. To evaluate clinical response after 4 weeks we used an arbitrary Knee Joint Score, and considered clinical improvement to be represented by a decrease in ≥1 point, which may be under- or oversensitive to measure clinical change in relation to treatment, although in the IFX injected joints it appears to match MR changes.

Our study showed that in patients with gonarthritis of various causes there is a considerable range in severity of features suggesting synovial inflammation as seen on MR and scored with Guermazi, MOAKS and KOSS. Our data suggest that these features are sensitive to change following intra-articular treatment, and that the MR scores originally developed for assessment of osteoarthritis can be used to detect these changes. Larger studies are needed to confirm this. Future studies may also reveal whether this is true for all gonarthritis types, or whether there are differences in relation to the underlying cause of gonarthritis. MR thus may be a promising tool to evaluate, understand and improve intra-articular treatment of our patients with gonarthritis.

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SUPPLEMENTARY FILE

Supplementary table 1: Guermazi MRI outcomes on MRIs preceding injections n=32

	Baseline MRI n=32
Suprapatellar, median (IQR)	1 (1;2)
Infrapatellar, median (IQR)	1 (1;1)
Intercondylar, median (IQR)	1 (0;2)
Adjacent to ACL, median (IQR)	1 (1;1)
Parameniscal lateral, median (IQR)	1 (1;2)
Parameniscal medial, median (IQR)	1 (0;1)
Adjacent to PCL, median (IQR)	1 (0;1)
Loose body, median (IQR)	0 (0;0)

MRI: magnetic resonance imaging; Suprapatellar site: 0.5-1 cm cranial to the superior patellar pole; Infrapatellar site: directly adjacent to the inferior patellar pole; Intercondylar site: at the surface of Hoffa's fat pad 1.5-2 cm distal to inferior patellar pole; ACL: anterior cruciate ligament; Adjacent to ACL site: directly anterior to the ACL close to its femoral attachment; Parameniscal lateral site: directly adjacent posterior to the posterior horn of the lateral meniscus; Parameniscal medial site: directly adjacent posterior horn of the medial meniscus; PCL: posterior cruciate ligament; Adjacent to PCL site: directly adjacent to the PCL at its mid-portion; Loose body: located posteriorly to the PCL; IQR: interquartile range.

Supplementary table 2: MRI outcomes in the 6 patients with cross over in the same knee according to the different randomization groups.

Time point	Total n=12	IFX n=6	MP n=6	p-value	p-value week 0 vs. 4 IFX	p-value week 0 vs. 4 MP
Hoffa synovitis, median (IQR)						
Baseline	2.5 (2;3)	3 (1.8;3)	2 (2;3)	0.476		
Week 4	2 (1;2.8)	2 (1;2.3)	1.5 (1;3)	0.932		
Delta	-1 (-1.5;0)	0 (-1.5;0)	-1 (-1.8;-0.3)		0.102	0.257
Effusion score, median (IQR)						
Baseline	3 (2.3;3)	3 (1.8;3)	3 (2.5;3)	0.598		
Week 4	2.5 (1;3)	2 (1;3)	2.5 (1.8;3)	0.600		
Delta	0 (-1;0)	0 (-1.5;0)	-0.5 (-1;0)		0.180	0.157
Knee joint score, median (IQR)						
Baseline	3.6 (3.2;4.4)	3.6 (2.9;4.5)	3.6 (3;4.6)	0.872		
Week 4	3.3 (2.3;4.2)	3.5 (2.3;4.2)	3.3 (0.8;4.1)	0.618		
Delta	-0.6 (-1;0)	-1 (-1.8;0.6)	-0.05 (-0.8;0)		0.461	0.180
Knee tenderness, median (IQR)						
Baseline	1 (0;1.8)	1 (0;2)	1 (0;1.3)	0.733		
Week 4	1 (0.5;2)	1 (0.5;2)	1 (0.3;1.8)	0.694		
Delta	0 (-0.8;0.8)	-0.5 (-1;0.8)	0 (0;0.8)		0.336	0.109
Knee swelling, median (IQR)						
Baseline	2 (2;3)	2 (2;3)	2.5 (2;3)	0.575		
Week 4	2 (1;2)	2 (1.5;2)	1.5 (0.3;2.8)	0.686		
Delta	-0.5 (-1;0)	-0.5 (-1;0)	-0.5 (-1;0)		0.458	0.458
VAS score, median (IQR)						
Baseline	0.34 (0.19;0.40)	0.27 (0.14;0.48)	0.35 (0.15;0.51)	0.687		
Week 4	0.28 (0.17;0.35)	0.26 (0.17;0.40)	0.31 (0.08;0.36)	0.623		
Delta	-0.03 (-0.08;0)	-0.05 (-0.09;0.05)	-0.03 (-0.05;-0.01)		0.498	0.686

IFX: infliximab; MP: methylprednisolone; n: number; IQR: interquartile range.