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Changes in pain and MRI-based synovitis in knee osteoarthritis following intraarticular glucocorticoids and exercise: a randomised controlled trial

Robert GC Riis[1,2], Marius Henriksen[1,3], Louise Klokker[1], Cecilie Bartholdy[1], Karen Ellegaard[1], Elisabeth Bandak[1], Henning Bliddal[1], Mikael Boesen[1,2]

1: The Parker Institute, Copenhagen University Hospital Bispebjerg-Frederiksberg, Copenhagen, Denmark

2: Dept. of Radiology, Copenhagen University Hospital Bispebjerg-Frederiksberg, Copenhagen, Denmark

3: Dept. of Physical & Occupational Therapy, Copenhagen University Hospital Bispebjerg-Frederiksberg, Copenhagen, Denmark

Corresponding author

Mikael Boesen, MD, PhD

Department of Radiology and the Parker Institute,

Copenhagen University Hospital Bispebjerg-Frederiksberg

email: mikael.boesen@gmail.com

Phone: +45 3816 4654

ABBREVIATIONS & ACRONYMS

BLOKS: Boston-Leeds Osteoarthritis Knee Score

(D)CE-MRI: (dynamic) contrast-enhanced MRI

EES: extravascular, extracellular space

Gd: Gadolinium-(chelated contrast agent)

iAUGC60: initial area under the Gadolinium curve over the first 60 seconds

IRE: initial rate of enhancement

KOA: knee osteoarthritis

KOOS: knee injury and osteoarthritis outcome score

Ktrans: volume transfer coefficient between plasma and EES

ME: maximum enhancement

MOAKS: MRI Osteoarthritis Knee Score

Nvoxel: the number of voxels with plateau or washout patterns (i.e. the highest perfused voxels)

PROMs: patient reported outcome measures

ROI: region of interest

TIC: time-intensity-curve

Ve: proportion of EES within a ROI/VOI

VOI: volume of interest (consisting of ≥2 ROIs)

INTRODUCTION

The present study is based on a randomised controlled trial investigating the benefit of intraarticular corticosteroids prior to exercise therapy in knee osteoarthritis (KOA)(1). In the present sub-study, the magnetic resonance imaging (MRI) data will be presented.

The aims of the present study are to: i) describe and compare the changes in MRI-assessments of synovitis following an exercise program preceded by an intraarticular injection of either glucocorticoid or isotonic saline and ii) investigate if any of the changes in the MRI-variables are associated with changes in patient reported outcome measures. We hypothesize that: i) the combination of steroid and exercise is more effective in decreasing (improving) synovitis assessed on MRI compared to the combination of isotonic saline and exercise MRI-based estimates of synovitis will decrease (improve) to a larger degree in the steroid-group compared to the placebo-group and ii) an improvement in the patient-reported outcome measures (PROMs) is paralleled by a decrease (improvement) in the MRI-assessments of synovitis.

METHODS

The hosting study is a double-blind randomised, controlled trial (EudraCT: 2012-002607-18). Patients diagnosed with knee osteoarthritis were randomised to one of two interventions: 1) intraarticular injection of glucocorticoids followed by a physiotherapeutic exercise programme, or 2) intraarticular injection of isotonic saline followed by a physiotherapeutic exercise programme. The 12-week training programme commenced 2 weeks after injection and 3 Tesla MRI was performed at baseline, after termination of the training programme (i.e. at 14 weeks) and after 12 weeks of follow-up (week 26). Patient reported outcome measures (PROMs) and MRI-based measurements of synovitis will be assessed at weeks 14 and 26 and the two groups compared (Figure 1). Please consult the original study protocol for additional details(1).

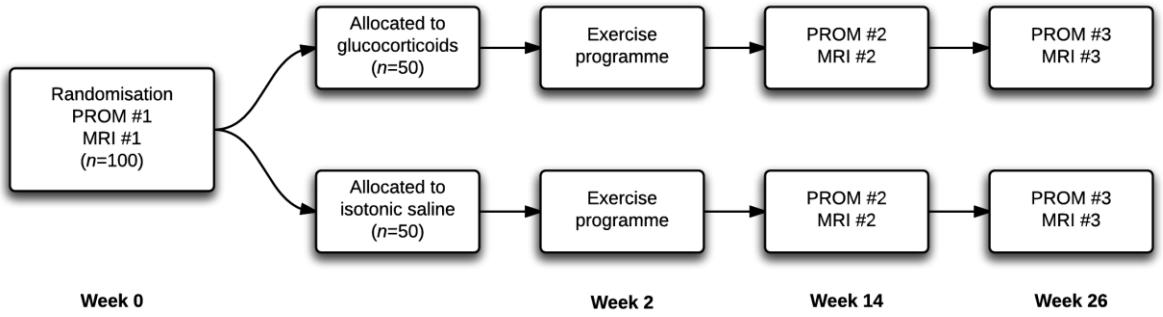

Figure 1. Trial profile

MRI acquisition

MRI of the target knee was performed on a 3 T Siemens Verio® system using a dedicated 15 channel send/receive knee coil. MRI was only acquired in participants without contraindications to MRI (e.g. metallic implants). The following MRI protocol was used: Gradient echo (GRE) scout (Slice thickness (ST) 8 mm, Field of View (FOV) 400 x 400 mm, TE 3.69 ms, TR 7.8 ms, scan time 17 sec); coronal T1-weighted (T1w) turbo spin echo (TSE) (ST 3.5 mm, FOV 150 x 150 mm, matrix resolution 0.6 x 0.5 x 3.5 mm, TE 17 ms, TR 790 ms, scan time 2 min 24 sec); coronal and sagittal short tau inversion recovery (STIR) (ST 3 mm, FOV 160 x 160 mm, matrix resolution 0.7 x 0.6 x 3 mm, TI 220 ms, TE 34 ms, TR 4350 ms, scan time 1min 29 sec); sagittal 3D proton density weighted (PDw) FS TSE SPACE (ST 0.6 mm ST, FOV 160 x 160 mm, matrix resolution 0.6 x 0.5 x 0.6 mm, TE 44 ms, TR 1000 ms, scan time 9 min 26 sec); sagittal GRE 3D T1w VIBE (ST 0.6 mm, FOV 160 x 160 mm, matrix resolution 0.6 x 0.6 x 0.6 mm, Flip angle (FA) 10 degrees, TE 5.39 ms, TR 11.6 ms, scan time 3 min 19 seconds). Just prior to and simultaneously with the intravenous injection of 0.2 ml/kg Gadoteridol (Prohance), a sequential sagittal custom made DCE-MRI GRE T1w VIBE sequence was performed using 4 mm slices every 9 seconds, with 30 repetitions using the following parameters: TE 1.86, TR 5.51, FA 15 degrees, FOV 160x160 mm, matrix resolution 256x256, scan time 4 min 40 sec covering the knee from medial to lateral and from above the suprapatellar recess to below the insertion of the patella tendon on the tibia. Following this the static 3D GRE T1w VIBE sequence was repeated. Total imaging time

varied between 30 and 40 min. (D)CE-MRI was not performed on participants with an estimated glomerular filtration rate < 60 ml/min/1.73 m^2.

MRI analyses

RR will perform all MRI analyses. On static, non-CE-MRI, synovitis will be assessed according to the MOAKS (MRI in OA Knee Score)(2) using the 3D PDw sequence: the two subscales, i.e. Effusion-Synovitis and Hoffa-Synovitis, each scored 0-3, will be summed to one single *MOAKS-Synovitis* score ranging from 0-6. On static, CE-MRI, synovitis will be assessed according to the whole-knee synovitis score as proposed by Guermazi et al. (3), using the sagittal and reconstructed axial post-Gd GRE 3D T1w VIBE. Furthermore, effusion will be assessed (0-3) on the same sequence according to the BLOKS (Boston-Leeds OA Knee Score)(4). As effusion can only be differentiated from synovitis on CE-MRI, the BLOKS-Effusion score will reflect only the joint effusion itself, whereas the MOAKS Effusion-Synovitis score (on non-CE-MRI) represents the combination of effusion and synovitis.

By using the subtraction function in the DICOM-viewer Osirix®, i.e. subtracting the first repetition of the DCE-MRI sequence (where the Gd has not reached the knee yet), from the last repetition (where the Gd has reached the knee), a new sequence depicting all enhancing voxels is created. Regions of interest will then be drawn around the enhancing synovium in the entire knee and automatically be transposed to the motion corrected DCE-MRI sequence. The ROIs will then be collapsed into one single volume of interest from which the perfusion variables are generated. All DCE-MRI analyses will be performed using Dynamika® v. 4.1 (www.imageanalysis.org.uk). Osirix® will be used to generate the subtraction sequence and score the aforementioned static MRI variables.

Outcome measures

Outcome measures were measured at baseline, week 14 (primary end point) and week 26. The primary outcome measure of the hosting study was the change in the pain subscale of the KOOS (knee injury and

OA outcome score) from baseline to week 14(1). In this exploratory MRI study, static non-contrast-enhanced (non-CE), static CE, and dynamic CE (DCE)-MRI assessments of synovitis were included.

Major outcome measure

The major outcome in the present MRI study will be the DCE-MRI variable *MExNvoxel*, a composite score reflecting both the volume of synovitis (Nvoxel) and degree of perfusion in the synovium (ME – maximum enhancement).

Minor outcome measures

The following variables will represent minor outcome measures:

- PROMs: The remaining 4 KOOS subscales (symptoms, sport/recreation, quality of life and function in daily living)
- From static, non-CE-MRI: MOAKS-Synovitis
- From static, CE-MRI: CE-Synovitis, BLOKS-Effusion
- DCE-MRI (heuristic): Nvoxel, IRExNvoxel, MExNvoxel and IRExME
- DCE-MRI (pharmacokinetic): Ktrans, Ve, iAUGC60

All outcome measures are summarised and explained in Table 1. In addition, the following basic characteristics were assessed: age, gender, BMI (body mass index), CRP (C-reactive protein) and Kellgren-Lawrence grade of the target knee.

PROM	*KOOS-Pain*	Pain subscale of the knee injury and OA outcome score (KOOS). 0 indicates extreme pain, 100 indicates no pain.
	KOOS-Symptoms	Knee related symptoms subscale of the knee injury and OA outcome score (KOOS). 0 indicates extreme symptoms, 100 indicates no symptoms.
	KOOS-ADL	Function in daily living subscale of the knee injury and OA outcome score (KOOS). 0 indicates poor function, 100 indicates unaffected function.
	KOOS-S/R	Sport and recreation subscale of the knee injury and OA outcome score. 0 indicates no sport and recreation activity, 100 indicates unaffected sport and recreation activity.
	KOOS-QOL	Quality of life subscale of the knee injury and OA outcome score. 0 indicates poor quality of life, 100 indicates unaffected quality of life.
non-CE-MRI	*MOAKS-Synovitis*	Sum score (0-6) of the Effusion-Synovitis (0-3) and Hoffa-Synovitis (0-3) subscales of the MRI in OA Knee Score (MOAKS)
CE-MRI	*BLOKS-Effusion*	Effusion subscale (0-3) of the Boston-Leeds OA Knee score (BLOKS)
	CE-Synovitis	The whole-knee synovitis score (0-22) according to Guermazi et al.
DCE-MRI (heuristic)	*Nvoxel*	volume (ml) of voxels with "plateau" or "washout" patterns, i.e. the most perfused voxels
	IRExNvoxel, MExNvoxel	As a voxel represents a volume, Nvoxel can be regarded as the volume of the highest perfused synovium whereas the IRE and ME represent the degree of perfusion. By multiplying Nvoxel with the mean IRE and mean ME respectively, we created two composite variables reflecting both the volume and degree of perfusion
	IRExME	The product of the mean IRE and mean ME, as we believed that the two are the most defining TIC-parameters characterizing the perfusion profile of the voxels
DCE-MRI (pharmacokinetic)	K^{trans}	Contrast transfer coefficient from blood to extracellular space over time (min^{-1}) and thus a measure of capillary permeability
	Ve	Proportion (between 0 and 1) of extra-vascular, extra-cellular space in the ROI
	iAUGC60	Initial area under the gadolinium curve over 60 seconds

Statistics

Statistical analyses were intended to be conducted on the intention-to-treat population, i.e. all randomized patients (*n*=100). However 5 patients did not undergo (D)CE-MRI at baseline, wherefore the analyses will be carried out on a modified intention-to-treat population (*n*=95). Missing data will be replaced using multiple imputations using age, gender, BMI, group allocation and baseline scores as predictors. For sensitivity purposes, we will repeat the analyses on the as observed population, i.e. no imputation for missing data.

The primary endpoint will be the first follow-up, i.e. week 14. The primary analysis will be to compare the difference in the mean changes in the MRI-assessments of synovitis (both static and dynamic) between the two groups (glucocorticoid v. placebo) from baseline to week 14 and 26 (aim no. 1). We will use analysis of covariance with the baseline value as covariate. To analyse the possible correlation between changes in synovitis on MRI and PROMs, simple bivariate correlations (Spearman) will be performed, followed by a linear regression model with the PROMs as dependent and MRI-assessments of synovitis as independent variables (aim no. 2). All MRI variables will undergo the same analyses. In order to detect changes in the MRI-assessments of synovitis, we will perform sub-group analyses on the participants with a *CE-Synovitis* score of above 4, i.e. exclude participants with normal/equivocal synovitis as defined by Guermazi et al.(3).

AUTHOR CONTRIBUTION

All authors will revise the manuscript and approve the final version.

Study conception and design: MH, RR, HB, MB

Acquisition, analysis, interpretation of data: RR, MH, LK, CB, EB, KE, HB, MB

Drafting of the manuscript: RR

Statistical analysis: RR, MH

Study supervision: MH, HB, MB

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