32.3). A significant positive interaction was found between severe pain at baseline and treatment effect (interaction coefficient 13.6, 95%CI 1.4-25.8). A non-significant overall interaction estimate was found for inflammatory signs 12.5 (95%CI -7.22-32.3). However, a strongly positive interaction estimate (45.3, 95%CI 24.4-66.1) was found for inflammation and treatment effect when analyzed in the studies where inflammation was measured by ultrasound.

Conclusions: Our results show that patients with severe pain at baseline do benefit significantly more from IA glucocorticoid injections than those with less severe pain and this could be used as a predictive measure of response in clinical practice. However inflammation defined by ultrasound provided an even more significant measure of a positive treatment response of IA glucocorticoids in patients with knee or hip OA. The differences in treatment response at short-term follow-up between IA glucocorticoid treatment and IA placebo were much larger when inflammatory signs, measured by ultrasound, were present compared to absence of inflammatory signs.

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BONE MARROW LESIONS MAY NOT RESPOND TO ANTI-INFLAMMATORY TREATMENTS IN KNEE OSTEOARTHRITIS(OA)

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Purpose: Intra-articular steroid therapy to the knee is associated with a reduction in pain in patients with symptomatic knee OA. The mechanism by which treatment is linked with a reduction in pain is unknown though thought in part to be related to a reduction in synovitis. Bone marrow lesions (BMLs) are poorly circumscribed lesions of water signal on MRI using fat suppressed pulse sequences; while BMLs may be caused by mechanical stress across the joint, their relation to inflammation is unknown though it is possible they may be a candidate target for steroid therapy as they are linked with knee pain and fluctuate over time. The aim of this analysis was to determine whether intra-articular steroid therapy is associated with a change in BMLs.

Methods: Men and women aged 40 years and older with painful knee OA, and who met American College of Rheumatology criteria for the disease, were recruited for participation in an ongoing open label clinical trial of intra-articular steroid therapy. Subjects who took part in the study had significant knee pain and knee OA of grade 2 (Kellgren-Lawrence) or higher. At baseline they completed also the Knee Injury and Osteoarthritis Outcome Score (KOOS). They had a Gadolinium(Gd)-enhanced MRI immediately prior to having an intra-articular steroid injection with repeat questionnaire and Gd-enhanced MRI scan at the post-injection visit usually within a 2 week period. Response was determined using the OARSI responder criteria. Those who responded were followed up by serial telephone call until their knee pain recurred or at 6 months at which point a further Gd-enhanced MRI was scheduled. The knee images were assessed semi-quantitatively for BML severity (score 0-45 using the WORMS method) at all three time points by an experienced MSK radiologist. Synovial tissue volume was assessed using manual segmentation and computer image analysis of the contrast enhanced images. We looked at mean change in BML severity score, between baseline and post-injection visit, and the mean change in BML score between baseline and the final scan. We looked also at change in synovial volume between baseline and the post injection scan.

Results: 100 patients with imaging data were included in this analysis. Their median age was 62.0 years (SD 10.4 years), and 48 were female. The median time between baseline and post-injection scan was 8 days (IQR 7 to 14 days). Among those who responded (67) pain recurred within 6 months in 46. The median BML score at baseline was 8.0 (IQR 4.0 to 12.0), post-injection visit 8.0 (IQR 4.2 to 12.0) and 7 (IQR 4.0 to 10.9) at final visit. The score did not differ between the baseline and post-injection scan (mean within person difference = 0.05 points; 95% CI -0.21 to 0.31 points; $p = 0.72$) however a slight difference was noted between the baseline and final scan (mean within person difference = -0.36 points; 95% CI -0.67 to -0.06 points; $p = 0.02$). This within-person difference reflects a reduction of 4.6% in the baseline BML score, which, while statistically significant, is a clinically small change. In contrast, synovial volume shrank between the baseline and post-injection visit (mean within person difference = -1082mm^3; 95% CI -1996 to -168mm^3; $p = 0.02$). This within-person difference reflects a reduction of 13.2% in the baseline synovitis score.

Conclusions: BMLs show little change in response to intra-articular steroid therapy in patients with symptomatic knee OA, suggesting they may not respond to anti-inflammatory treatments.

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DEVELOPMENT OF A NEW HYALURONIC ACID-CALCITONIN CONJUGATE FOR THE LOCAL TREATMENT OF OSTEOARTHRITIS

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Purpose: Salmon calcitonin (sCT) has been shown to exert beneficial metabolic actions on cartilage and bone turnover and may therefore be useful in the management of osteoarthritis (OA). A calcitonin-based oral treatment for knee OA recently failed to meet the primary endpoint for efficacy in a two-year placebo-controlled clinical trial, though demonstrating positive effects on pain and function. The objective of our project is to synthesize a new polymeric conjugate between hyaluronic acid (HA) and salmon calcitonin and to evaluate its potential as intra-articular treatment for OA. The rationale is to retain sCT in the joint cavity, thus maximizing and prolonging the local activity and avoiding the side effects related to a systemic administration.

Methods: HA was linked to sCT by means of a spacer having pendant aldehyde groups for selective conjugation at the N-terminus of the peptide.

The residual activity of conjugated sCT was investigated in rats by measuring the plasma calcium level after i.v. injection. Preliminary PK studies were performed by labeling HA-sCT and sCT with a fluorescent dye for the detection in blood samples after i.a. injection. In addition, blood samples were withdrawn at fixed times up to 24 hours and the total calcium levels were measured using a colorimetric calcium assay. Unilateral OA was surgically induced in the rabbit knees by anterior cruciate ligament transection (ACLT). Controls (PBS and HA), sCT and HA-sCT at 25, 100 and 400 UI, were administered by i.a. injection once a week at day 10, 17 and 24 post-surgery. The efficacy was evaluated by macroscopic examination of the treated joint, histopathological assessment of the synovial membrane and of the femoral condyles. The histopathological criteria score was based on the evaluation of four parameters: articular cartilage morphology, subchondral bone morphology, cartilage thickness, and arrangement of chondrocytes.

Results: The new HA-sCT conjugate was synthesized according to a patented technology that avoids the formation of heterogeneous and cross-linked products.

The potency of the conjugated sCT was evaluated by i.v. injection, showing that it maintains a comparable potency with respect to the free protein and sustains the hypocalcaemic action for a longer time.

Interestingly, after local administration, unlike free sCT, HA-sCT did not cause a systemic reduction of calcium concentration, suggesting a negligible extra-articular diffusion of the conjugated peptide.

The PK study with labelled sCT confirmed this encouraging result: while i.a. injection of HA-sCT led to very low and constant plasma peptide concentration, the local administration of free sCT resulted in high fluorescence in plasma, demonstrating a fast clearance of the peptide