were revealed to be more predictive of a patient receiving TKA than the other scores. Osteophyte, at least in patients with end-stage knee OA, may induce disability of daily living, associating the determination of the patients for receiving TKA. In conclusion, when we evaluate the structural changes due to knee OA by MRI, osteophytes score is only a predictor for receiving TKA.

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THE RESULTS OF MODIFIED DISTRACTION ARTHROPLASTY FOR DEGENERATED OSTEOARTHRITIS OF THE ANKLE

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Purpose: In the treatment of degenerated osteoarthritis of the ankle, we obtained good results in terms of preserving the joint functions and relieving pain by performing a procedure to reconstruct the anatomical structure of the ankle, accompanied by ROM exercises undertaken with the joint space kept pulled apart with a conventionally used external fixator.
Methods: A total of 43 patients (45 ankles; 28 ankles in 28 male patients and 17 ankles in 15 female patients) who underwent the procedure from 1998 to 2012 were enrolled in the study. The patients were 18-72 years old, with a mean age of 56 years at the time of the procedure. In regard to Takakura's classification, 6 ankles were classified as Stage 2, 21 as Stage 3a, 12 as Stage 3b, and 6 as Stage 4. The patients underwent debridement by the conventional method, including removal of bone spurs and synovectomy, combined with low tibial osteotomy, osteochondral graft, drilling and/or reconstruction of ankle lateral ligaments. As post-treatment, patients were started on active ROM exercises from the day after the surgery and started partial weight bearing at 6-8 weeks after the surgery. The external fixation device was removed to allow total weight bearing at 3 months. Follow-ups were performed for 1-8 years, with a mean of 4 years and 7 months.
Results: The pain severity did not change in 2 ankles. For the remaining 43 ankles in which the pain improved, no problems in daily life activities, but inability to undertake sports activities were observed for 31 ankles, while no problems in either physical work or sporting activities for 12 ankles. None of the patients took painkiller. Improvements of the ROM were seen in 10 ankles, while no change of the ROM was observed in the remaining 35 ankles. There were no patients who needed additional operations such as arthrodesis during the follow-up period.
Conclusions: Procedures such as arthrodesis, total ankle replacement and low tibial osteotomy are performed to treat degenerated osteoarthritis of the ankle, but each of these is associated with problems, including those related to the qualifying age, durability, and range of motion. It is difficult to select a proper treatment option, especially for relatively young patients. In contrast, there is no age requirement for the procedure described in this study, because joint functions are preserved by restoring the patients' own tissue and the patients suffered only mild postoperative limitation of the ADL. As demerits, this procedure is less effective for pain relief than arthrodesis and more abundant experience is required, because several kinds of surgical procedures have to be performed. However, it can be indicated for young patients in whom preservation of the joint functions and higher activity potential are required. In addition it is well applicable to degenerated osteoarthritis of the ankle that arises at a relatively early age, because future joint replacement or arthrodesis will not be difficult in patients who undergo this procedure.

Therapy- Intraarticular

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INTRA-ARTICULAR SUPPLEMENTATION WITH RECOMBINANT HUMAN GDF5 ARRESTS DISEASE PROGRESSION AND STIMULATES CARTILAGE REGENERATION IN THE RAT MEDIAL MENISCUS TRANSECTION (MMT) MODEL OF OSTEOARTHRITIS

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Purpose: Genome-wide association studies and investigation of osteoarthritis (OA) risk alleles suggest that reduced levels of functional Growth and Differentiation Factor 5 (GDF5) expression in tissues of the joint may be a precipitating factor contributing to OA. Therefore, we hypothesized that supplementation of rhGDF5 to the OA joint via intra-articular injection may represent a viable therapeutic approach.
Methods: We used a rat medial meniscus transection (MMT) model of OA which causes rapid and progressive OA-like pathology including the aggressive erosion of articular cartilage. Three studies were conducted (n = 15 / treatment group) to investigate the feasibility of rhGDF5 in either a preventative or therapeutic modality: (1) 6 weekly injections beginning on day 3 post MMT with termination on day 42 (preventative), (2) 6 weekly or 3 bi-weekly injections beginning on day 21 post MMT with termination on day 63 (therapeutic), and 3) a single injection, or a series of 2 or 3 bi-weekly injections, beginning on day 21, with termination on day 63 (therapeutic). rhGDF5 doses ranging from 0.3 to 100 μg were studied, using a glycine buffered trehalose vehicle (pH=3.0). Joints were harvested and processed for histological analysis following toluidine blue staining. Quantitative and semi-quantitative histopathological end points were used to evaluate the extent of OA progression in the medial tibial plateau cartilage.
Results: rhGDF5 demonstrated significant dose-dependent cartilage protection as a preventative therapy (Study 1). In particular, the width of significant tibial lesions was reduced by 11% by repeat treatment with 0.3 μg rhGDF5, 22% by 3 μg, 32% by 10 μg, and 49% by 30 μg injections when compared with vehicle controls. Study 2 demonstrated dose-dependent efficacy of rhGDF5 compared with vehicle controls when administered in a therapeutic modality beginning on day 21 post MMT. Following 6 weekly injections, the width of significant tibial lesions was reduced by 30% by a 10 μg rhGDF5 dose and by 47% by a 30 μg dose.

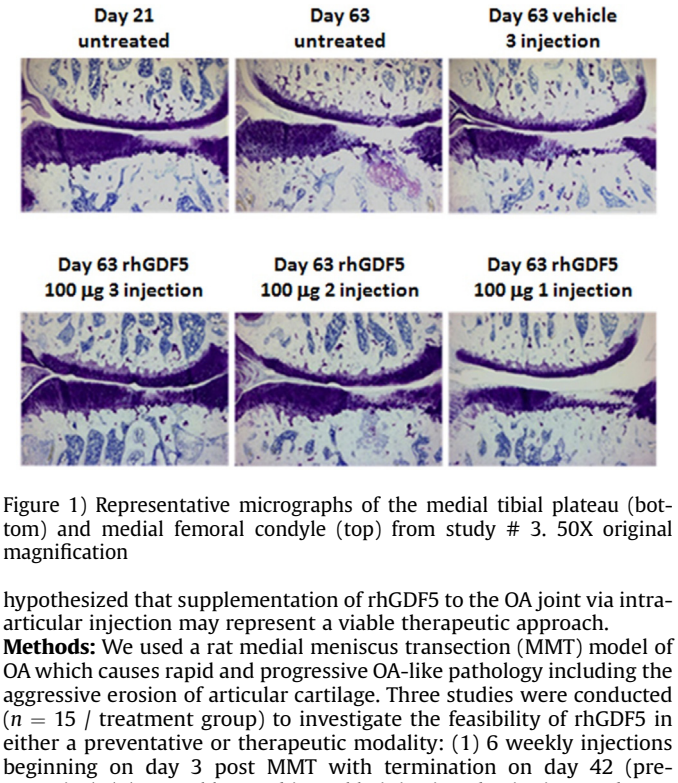

Figure 1) Representative micrographs of the medial tibial plateau (bottom) and medial femoral condyle (top) from study # 3. 50X original magnification

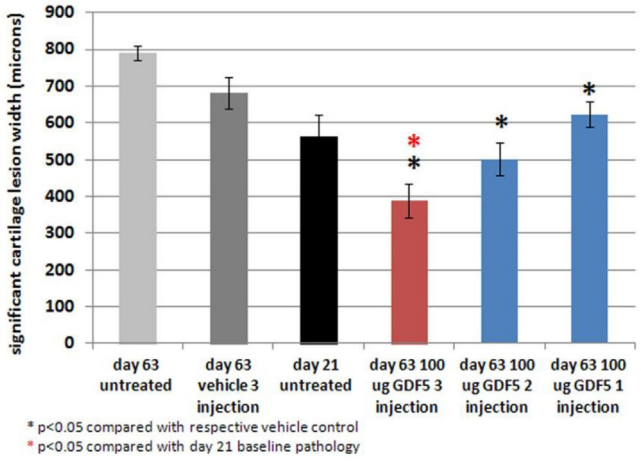

Figure 2) Quantitation of the effects of rhGDF5 intra-articular therapy on significant cartilage lesion width of the medial tibial plateau. Day 21 untreated group indicates the extent of cartilage erosion present at the onset of therapy. Data represent 15 rats/group from study # 3.

Following a 3 bi-weekly injection regimen there was a 28% and a 37% reduction in the width of significant tibial lesions, respectively, for 10 μg and 30 μg doses. This partial loss in efficacy by conducting 3 bi-weekly treatments rather than 6 weekly treatments was partially compensated for by increasing the 3 injection regimen rhGDF5 dose from 30 μg to 100 μg, which reduced lesion width by 41%. In Study 3, a single rhGDF5 injection on day 21 reduced the width of significant tibial lesions compared with vehicle controls by 13% and 19% for a 30 μg and 100 μg dose respectively. The 2 injection regimen administered on days 21 and 35 post MMT reduced tibial lesion width by 18% and 28%, and the 3 injection regimen reduced these lesions by 27% and 43%. After accounting for a modest vehicle effect, the level of Day 63 cartilage degeneration observed with 3 biweekly injections of rhGDF5 (30 or 100 μg) was significantly less than the untreated controls at day 21. This is indicative of disease arrest and cartilage regeneration with repeated injections of higher doses of rhGDF5.

Conclusions: Intra-articular delivery of rhGDF5 significantly protected the knee joint from MMT-induced OA disease in a dose and administration regimen dependent manner. Our data indicate that even a single injection of 100 μg rhGDF5 has significant therapeutic benefit. Additionally, rhGDF5 is able to arrest disease progression in a therapeutic modality with as few as 2 bi-weekly injections. Moreover, 3 bi-weekly injections of 100 μg rhGDF5 was able to stimulate cartilage regeneration in the MMT model. Collectively, these results clearly demonstrate the potential of rhGDF5 supplementation as a targeted therapeutic approach for treating OA.

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MAGNETIC RESONANCE IMAGING STRUCTURAL PARAMETERS DO NOT PREDICT RESPONSE TO INTRA-ARTICULAR STEROID THERAPY IN KNEE OA

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Purpose: Intra-articular steroid therapy is widely used in the management of osteoarthritis (OA) of the knee. Meta-analyses suggest treatment is linked with a significant reduction in pain at least in the short term (< 3 weeks). Steroids have marked anti-inflammatory effects and it is thought that their analgesic effect may be related in part to this.Some knees with OA have little if any synovitis whereas in others, synovitis, assessed as synovial volume, is similar to rheumatoid arthritis. It is not known, however, whether response to therapy is influenced by the degree of synovitis present nor of the presence of bone marrow lesions (BMLs), lesions also related to pain. The aim of this analysis was to determine the influence of synovitis, as assessed by synovial volume using magnetic resonance imaging (MRI), and also the summed score of BMLs, on the symptomatic response to treatment with intra-articular steroid therapy.

Methods: Men and women aged 40 years and older with painful knee OA who met the American College of Rheumatology (ACR) 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 (Kellgren-Lawrence grade 2 or more). At baseline they completed questionnaires about their symptoms including the Knee Injury and Osteoarthritis Outcome Score (KOOS) (0-100) with the lower scores indicating greater pain and also a VAS (0-10) for pain during a nominated activity (VASnA) with higher scores indicating greater pain. They subsequently had a gadolinium(Gd)-enhanced MRI scan immediately prior to having an intra-articular steroid injection (depomedrone 80 mg) with repeat questionnaires and Gd-enhanced MRI scan at follow-up visit usually within a 2 week period. To assess synovial tissue volume, sagittal (T1W Fat Suppressed images: TR 500ms, TE 17ms; FoV 15.9 x 15.9cm; slice thickness 3mm) scans were obtained. Manual segmentation of the synovial tissue layer was performed on the post-contrast knee image by a single observer. Using computer image analysis we excluded cartilage within the segmented space, by thresholding in the associated sagittal (3D WATSc: TR 20ms, TE 7.7ms, FoV 15cm, 288x288) scan. The rest of the segmented space is assumed to be a mixture of fluid and synovial tissue. We calculated the proportion of synovial tissue in every voxel and summarized these across voxels to compute a volume of synovium. BMLs were assessed semi-quantitatively by an experienced MSK radiologist using the WORMS method (range of possible scores 0-45) and this represented the BML score. In the analysis we looked whether the baseline structural parameters were associated with a change in both KOOS-pain and also VASnA.

Results: We studied 100 participants of mean age 62.0 years (SD 10.4 years) and of whom 48 were female. The median time between baseline and follow-up scan was 8 days (IQR 7 to 14 days). The mean synovial tissue volume at baseline was 10,033mm^3 (SD 6,495mm^3), and mean total BML score 8 (SD 5.0). Overall, pain significantly improved following steroid injection as indicated by an increase in KOOS (mean change at follow-up = 22.2 points; 95% CI 18.0 to 26.4; $p < 0.001$) and a reduction in VASnA (mean change at follow-up = -3.1cm; 95% CI -3.7 cm to -2.5 cm; $p < 0.001$). Neither synovial volume (r = 0.026; p = 0.80) nor BML score at baseline (r = -0.037; p = 0.72) were associated with the observed change in KOOS-pain. Similarly neither synovial volume (r = 0.064; p = 0.55) nor BML score at baseline (r = 0.098; p = 0.37) were associated with a change in VASnA. Overall, based on the OARSI criteria there were 67 responders and 33 non-responders. Baseline synovial tissue volume did not differ in those who did, compared to those who did not, subsequently respond (mean difference = -76mm^3; 95% CI -2831mm^3 to 2679mm^3; p = 0.96). Similarly, BML score did not differ between those who subsequently did, compared to those who did not, respond (mean difference = -0.41; 95% CI -2.53 to 1.71; p = 0.70).

Conclusions: Neither synovitis nor BML score predict response to intra-articular steroid injection in patients with symptomatic knee OA.

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ELECTROSTATIC INTERACTIONS ENABLE RAPID PENETRATION, ENHANCED UPTAKE & RETENTION OF INTRA-ARTICULAR INJECTED AVIDIN IN RAT KNEE JOINTS

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Purpose: Osteoarthritis affects individual joints necessitating the need for local therapy. Intra-articular (i.a.) injection of drugs remains inadequate due to rapid drug clearance from joint space. Local delivery into cartilage is further complicated by its complex architecture of dense