4 courses, and 760 (1.5%) received 5 courses or more. The time from diagnosis to when 50% of the subset received TKR was significantly longer (p1 year, an average of 9 months longer than those with no IA HA. Patients who received ≥5 courses had a delay in TKR by 3.6 years.
Conclusions: Among 182,022 patients with knee OA, those who received IA HA had a significantly longer time before TKR. More courses of IA HA injections were associated with a longer time to TKR. This study suggests a significant clinical benefit from use of IA HA for OA as delay in time to TKR can have important clinical and economic implications.

Median Time from knee OA diagnosis to TKR by number of courses of IA HA

	No IA HA	1	2	3	4	5+
Days to TKR	114	386	648	875	1054	1312
Years to TKR	0.3	1.1	1.8	2.4	2.9	3.6

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EVALUATION OF THE CLINICAL EFFICACY OF AUTOLOGOUS CONDITIONED SERUM IN PATIENTS WITH COXARTHROSIS

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Purpose: The aim of this open study was a comparative assessment of the effectiveness of local therapy with autologous conditioned serum (ACS) and low molecular weight hyaluronic acid (LHA) in patients with coxarthrosis.
Methods: The study included 60 patients with firm coxarthrosis in accordance with ACR criteria at the age of 55,5 ± 8,7. The main group (ACS treatment) consisted of 33 (55%) persons. Experimental group (LHA treatment) consisted of 27 patients who are comparable with the main group patients in terms of age, BMI, radiographic stage, disease duration and severity of clinical indicators. ACS was prepared in accordance with established method and injected intraarticularly (2.5 ml twice a week for three weeks). LHA treatment consisted of 3 weekly intraarticular injections of 40 mg sodium hyaluronate each. All intra-articular actions were performed with ultrasound control. Treatment efficiency was evaluated after 1,3 and 6 months after treatment, the following criteria were used: bodily pain dynamics in accordance with VAS, morning stiffness module and Womac index functional scale, and Lequesne index. “Area under the curve” (AUC) approach with estimation of treatment efficiency prolongation for 6 months (AUC6) was used for evaluation of clinical effect retention.
Results: A decrease in pain syndrome intensity according to VAS in hip joints at 1, 3 and 6 months of treatment in both compared groups was recorded.However, a significant regression was observed in the treatment of pain with ACS in comparison with LHA.After 1 month the decrease of pain severity in accordance with VAS was comparable (9.1%, $p = 0.40$), after 3 and 6 months, pain severity was higher in the LHA group compared with ACS group (+ 52.5%, $p = 0.009$ and + 33.1%, $p = 0.047$ respectively). AUC6 in case of ACS treatment was 35,6% ($p = 0,011$) higher compared with LHA treatment. Extension of the clinical effectiveness expressed via "morning stiffness" module of the Womac index AUC6 indicator was 55.9% ($p=0.003$) higher in case of ACS treatment compared with LHA treatment. Womac functional scale in case of ACS improved through all three control timepoints (-23.1% -28.5% -39.1%; $p = 0.001$). Same dynamics was observed in LHA group as well (-35.6%, -26.4%; $p = 0.001$ and -20.4%; $p = 0.005$), however after 6 months of monitoring more significant improvement of articular function was recorded within ACS group compared with LHA (18.3%, $p = 0.044$). The overall clinical efficacy in accordance with Lequesne index with a six-month monitoring was comparable in both groups, the difference came up to 8,8% ($p = 0,65$).
Conclusions: Intensity of pain, stiffness, functional status and overall clinical severity of coxarthrosis significantly and consistently decreased during therapy with ACS and LHA.However, favorable changes of local therapy with LHA were inferior in duration of conservation of treatment effect of ACS.

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REFINEMENT OF PRECLINICAL STUDIES FOR VISCOSUPPLEMENTATION THERAPY EVALUATION: INTEREST OF COMPLEMENTARY TECHNIQUES TO EVALUATE CARTILAGE IN A RABBIT MODEL OF EARLY OSTEOARTHRITIS

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Purpose: One of the major challenges of the viscosupplementation (VS) therapy is the development of more efficient formulations and, to this end, the use of animal models of osteoarthritis (OA) is still mandatory. The assessment of VS efficacy is challenging mainly since its structural effects are subtle. In order to refine preclinical VS efficacy studies and reduce the number of animals used, there is a crucial need for more sensitive and discriminant evaluation tools. In this study, we especially focused on complementary techniques to evaluate OA cartilage in a rabbit model of early OA.
Methods: Cranial cruciate ligament transection (ACLT) was performed in the left knee of white New-Zealand rabbits (n=12) to induce traumatic OA. One week post-ACLT and then weekly for 5 weeks, the operated knees of 6 rabbits were injected with a hyaluronic acid (HA) containing commercial formulation (Ostenil®, HA group). One group was injected with saline (operated-control group, n=6). The contralateral right knees (n=8) were used as unoperated-controls. End-point evaluation was done at the 6th week post-ACLT and included: gross and histological scoring of cartilage lesions, measurement of cartilage thickness by Equilibrium Partitioning Iodine Contrast micro-Computed Tomography (EPIC μ-CT) as well as the evaluation of the surface by Scanning Electron Microscopy (SEM).
Results: Gross and histological scorings showed statistical differences between operated and unoperated knees; however, no difference between the HA and operated-control groups was evidenced. SEM revealed that unoperated-control samples had normal smooth to rough surfaces with discreet cable-like structures. Cartilage from the operated knees presented rough surfaces and clearly visible cable-like structures, which might be the sign of cartilage matrix erosion. Finally, mean cartilage thickness and volume measured by EPIC μ-CT were comparable for the 3 groups. Interestingly, the use of the thickness distribution representation showed clear differences in the intact cartilage occurrences (i.e. thickness higher or equal to 0.9 mm). Indeed, intact cartilage proportion decreased statistically from 20% in the unoperated-control group to 10% in the operated-control group. In addition, intact cartilage proportion in the HA treated knees was equivalent to unoperated-control group, highlighting a moderate efficacy of HA which was detected neither by histology nor by SEM.
Conclusions: Complementary techniques were implemented to evaluate cartilage lesions in a rabbit model of early OA in order to refine preclinical VS efficacy studies. This study points out that classical evaluation tools (macroscopy and histology) are sensitive enough to discriminate between cartilage from unoperated and operated groups in early OA but that EPIC- μCT also permits the detection of the subtle structural effects of HA, validating this technique as a powerful evaluation tool.

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EVIDENCE OF *IN VIVO* DRUG DELIVERY VIA THE TAT PROTEIN TRANSDUCTION DOMAIN

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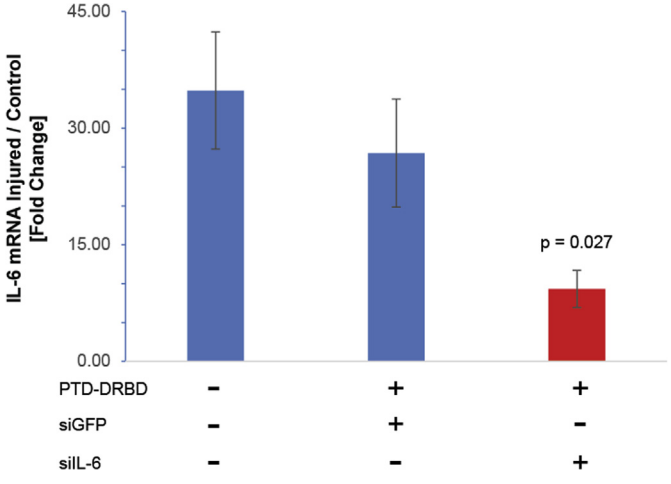
Purpose: Drug delivery to synovial joints is a major limitation for developing effective treatments for osteoarthritis (OA). Synovial joint anatomy includes large pores that allow direct transport between synovial fluid and fenestrated capillaries. This transport preferentially selects larger molecules to remain within the joint and exports smaller

molecules to circulation in order to maintain the high-viscosity needed for efficient lubrication by synovial fluid. One example of this challenge is that most contrast-enhanced clinical imaging protocols define cartilage defects by exclusion of systemically delivered small molecule contrast agents. This architecture presents a challenge to effective drug delivery for treating OA. We hypothesized that cationic TAT-PTDs (Peptide Transduction Domains) would enable in vivo drug delivery into synovial joints because of electrostatic attraction between the cationic TAT PTD and anionic cartilage glycosaminoglycans.

Methods: To address our hypothesis, we utilized a non-invasive in vivo model of post-traumatic OA. In this model, joints are subjected to a single mechanical overload which results in upregulation of IL-6 mRNA. 24 hours prior to injury, we treated the animals with siRNA complexed to a TAT-PTD fusion protein for delivery of siRNA. The fusion protein, TAT PTD-DRBD (Protein Transduction Domain coupled to a Double-stranded RNA Binding Domain), was complexed to siRNA at a 1:8 molar ratio of siRNA to protein. Controls included both untreated and off-target-treated joints. Therapeutic compounds and controls were delivered via 12 μL injection to the selected knee joint using a medial approach. Joints were injured by a single mechanical overload applied at 500 mm/s which results in a mid-substance tear of the ACL. Joints were harvested for qPCR 1 week after injury.

Results: Injury resulted in upregulation of IL-6 mRNA in the injured knee joint relative to the uninjured contralateral knee. There was significantly less upregulation of IL-6 mRNA in injured joints treated with the PTD-DRBD complexed to an anti-IL-6 siRNA ($p = 0.027$, Figure 1) while treatment treated with off-target siRNA complexes had no effect.

Conclusions: These data demonstrate the feasibility of in vivo bioactive drug delivery to synovial joints using the TAT Peptide Transduction Domain, in this example for delivery of siRNA to attenuate injury-induced expression of IL-6. Future studies may utilize TAT fusion proteins as well as the PTD-DRBD to advance both basic and translational studies of osteoarthritis.



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INTRA-ARTICULAR AUGMENTATION OF LUBRICATION WITH SILK MICROSPHERES

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Purpose: Osteoarthritis of the knee represents a large unmet clinical need. Deficits in synovial lubrication have been reported in osteoarthritis, and several strategies to augment lubrication have shown preclinical benefit. We hypothesized that augmentation of the boundary lubrication of synovial fluid by intra-articular administration of long-residence non-inflammatory lubricating silk microspheres could reduce mechanical injury and pain in an osteoarthritis animal model.

Methods: Silk microspheres with phospholipid coatings were prepared by a modified version of previously published methods. Osteoarthritis was induced in rats using the surgical instability model consisting of MCL tear and meniscectomy. One week following injury, affected knees were intra-articularly administered saline vehicle or silk microspheres (2.5mg). Serial body weights, knee effusion, gait analysis on Day 14, and Von Frey secondary allodynia testing on Days -1, 6, and 13 were measured. Severity of osteoarthritis was assessed by histopathologic analysis by a trained pathologist on Day 28 after injury.

Results: Silk microspheres with varying size distributions were synthesized and achieved coefficients of friction approaching 0.05 to 0.02. Intra-articular injection of silk microspheres was well tolerated in rats with no adverse reactions. Von Frey testing of secondary allodynia 6 days after injection indicated a trend towards a modest but sustained reduction of osteoarthritic pain.

Conclusions: Intra-articular silk microspheres offer a novel, biologically inert, non-inflammatory, and well tolerated potential therapy for osteoarthritis. These results motivate further formulation optimization of silk microsphere composition to tune synovial residence, degradation profile, lubrication properties, and potentially to provide prolonged delivery of active therapeutics. Augmentation of joint lubrication with silk microspheres merits further preclinical exploration as a novel therapy to address the unmet need in osteoarthritis.

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BMI, AGE, RADIOGRAPHIC SEVERITY AND ULTRASOUND GUIDANCE IMPACT THE RESPONSE TO HYALURONIC ACID INJECTIONS IN KNEE OSTEOARTHRITIS

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Purpose: While hyaluronic acid (HA) viscosupplementation has shown promise in the management of patients with knee osteoarthritis (KOA), mixed outcome data has led both individual physicians and subspecialty societies to question or eliminate its role in treatment algorithms. We examined clinical predictors of response to HA injections in a prospective study.

Methods: We screened consecutive patients at HA injections during routine clinical visits to rheumatology, orthopedics or physiatry at NYU Langone Medical Center, enrolling those ≥25 years old with KOA and pain for ≥1 month and a visual analog scale pain score ≥30mm. Baseline assessments included OA severity by the Kellgren-Lawrence (KL) scale on knee radiographs within the year prior, a history of comorbidities and prior KOA treatment, and patient-reported questionnaires including the Knee Injury and Osteoarthritis Outcome Score (KOOS), and the Western Ontario McMasters Universities Osteoarthritis Index (WOMAC) with a Likert scale calculated from the KOOS. We documented other variables such as the specific HA formulation, the anatomic approach, and use of ultrasound guidance. Patients are completing the questionnaires at 2, 6, 9 and 12 month intervals, but only continue past 2 months as long as there was still some benefit at the preceding visit.

Results: Thus far we have screened 194 patients with (ongoing) enrollment now at 107 (61% female, mean age 58 years ±11, range 27-84). To date, the cohort's mean BMI is 30.9 kg/m2±6.6, range 20.9-61.7, well distributed by BMI subgroup (&lt25, 25-30=overweight, 30-35=obese, and &gt35=morbidly obese). At baseline, the mean KOOS pain score (0=worst, 100=best) is 47.1 ±17.4, range 0-83.3, and the WOMAC index (0=best, 96=worst) is 45.1±17.8, range 12-96, without a significant difference between the 4 BMI strata. X-rays have been scored on 85 patients thus far (others are obtaining recent images from other institutions), but neither the KOOS pain nor WOMAC index at baseline trends with x-ray severity. Of 102 patients (5 withdrew), 38 have completed their 2 month followup visits. Patients with a BMI&lt30 (n=23) responded better than &gt30 (n=15), both by KOOS pain (+17.1 vs +9.2, p=0.09) and WOMAC index (-15.7 vs -9.2, p=0.14), with similar trends across other KOOS and WOMAC scores. The KOOS pain improvements were better for radiographic grades KL2 and KL3 than those seen for KL4 (+ 12.8 and +15.1 vs +5.9, p=0.13 for KL 3vs4), as were the WOMAC index scores (-19.3, -13.7 vs -6.5) The youngest quartile (ages 37-54) responded better than the middle 2 and the oldest quartile (ages 70-84) by KOOS pain (+18.2, +17.6, +12.3, +7.1, p=0.04