Title

SAFETY, TOLERABILITY, PHARMACOKINETICS, AND CLINICAL OUTCOMES FOLLOWING TREATMENT OF PAINFUL KNEE OSTEOARTHRITIS WITH SENOLYTIC MOLECULE UBX0101

Authors

Hsu, B
Visich, J
Lane, NE
et al.

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(-35.9 vs. -31.6, p=0.78) or function score (-90.7 vs. -92.8, p=0.97). In those without BMLs at baseline (n=105), annual change in tibial cartilage volume was significantly different between the atorvastatin and placebo groups [0.50% (95% CI -0.88% to 1.87%) vs. -1.19% (95% CI -2.09% to -0.30%)] where significant cartilage volume loss was observed in the placebo group but not in the atorvastatin group with a between-group difference of -1.69% (95% CI -3.36% to -0.02%, p=0.047) (Table 1). There were no significant differences in adverse events between groups.

Conclusions: Among participants with symptomatic knee osteoarthritis, oral atorvastatin 40 mg once daily did not reduce knee cartilage loss or knee pain over two years. However, atorvastatin reduced cartilage loss in those without BMLs, suggesting atorvastatin may have a disease-modifying effect in those with knee osteoarthritis and without BMLs.

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CLINICAL AND COST-EFFECTIVENESS OF ULTRASOUND-GUIDED INTRA-ARTICULAR CORTICOSTEROID AND LOCAL ANAESTHETIC INJECTION FOR HIP OSTEOARTHRITIS: A RANDOMISED CONTROLLED TRIAL (HIT)

Z. Paskins [1], K. Bromley [1], M. Lewis [1], G. Hughes [1], E. Hughes [1], A. Cherrington [1], A. Hall [1], M. Holden [1], R. Oppong [2], J. Kigozi [2], K. Stevenson [1], A. Menon [3], P. Roberts [4], G. Peat [1], C. Jinks [1], N. Foster [1], C.D. Mallen [1], E. Roddy [1]. [1] *Keele Univ., Staffordshire, United Kingdom;* [2] *Univ. Of Birmingham, Birmingham, United Kingdom;* [3] *Midlands Partnership NHS Fndn. Trust, Stoke-on-Trent, United Kingdom;* [4] *Univ. Hosp. North Midlands NHS trust, Stoke-on-Trent, United Kingdom*

Purpose: Evidence of the effectiveness of intra-articular corticosteroid injection for hip osteoarthritis (OA) is limited. The HIT trial compared the clinical and cost-effectiveness of an ultrasound-guided intra-articular hip injection (USGI) of 40mg triamcinolone acetonide and 4ml 1% lidocaine hydrochloride combined with best current treatment (BCT) with (i) BCT alone (primary objective) and (ii) an USGI of 5ml 1% lidocaine only combined with BCT (EudraCT: 2014-003412-37).

Methods: This was a pragmatic, three-parallel group, single-blind, randomised controlled trial in adults with moderate to severe painful hip OA recruited from community musculoskeletal services and primary care. Participants were randomised equally to: (1) BCT alone, (2) BCT plus USGI triamcinolone/lidocaine, or (3) BCT plus USGI lidocaine only. BCT comprised written information and individualised advice regarding weight loss, exercise, footwear, walking aids and analgesia. Outcomes were collected postally at 2 weeks, 2, 4 and 6 months. The primary outcome was self-reported current hip pain intensity (0-10 numeric rating scale (NRS)) over 6 months (repeated measures analysis). A wide range of secondary outcomes were measured at each follow-up point including pain and physical function (Western Ontario and McMaster University Arthritis Index, WOMAC), pain self-efficacy, participant's global impression of change, general health (EQ-5D-5L) and healthcare utilisation. Participants and clinicians were not blind to allocation to BCT alone or injection, however participants randomised to either injection arm were blind to the nature of injection. The research nurse involved in data collection and study statistician were blind to treatment allocation. 204 participants were required to detect a minimum difference of 1 point in mean pain NRS score between arms (1) and (2) with 80% power (5% two-tailed significance level, 15% loss to follow-up). Analysis was by intention-to-treat. To determine the cost-effectiveness of BCT plus USGI triamcinolone/lidocaine compared with BCT alone, a cost-utility analysis was conducted, adopting an NHS perspective. QALYs were calculated over a period of 6 months using the area under the curve approach.

Results: 199 participants were recruited (43% male, mean age 63 years), 67 to arm (1) and 66 each to arms (2) and (3). Primary outcome completion rates were 95% at 2 weeks, 94% at 2 months, 90% at 4 months, and 89% at 6 months. Greater mean improvement in hip pain intensity (0-10 NRS) over 6 months was seen with BCT plus USGI triamcinolone/lidocaine compared with BCT alone: -1.43 (95% CI -2.15, -0.72). Greater mean improvement in pain intensity was seen at 2 weeks (-3.17; -4.06, -2.28,) and 2 months (-1.81; -2.71, -0.92,), but not at 4 months (-0.86; -1.78, 0.05) or 6 months (0.12; -0.80, 1.04). Participants treated with BCT plus USGI triamcinolone/lidocaine compared with BCT alone had greater mean improvement in function (WOMAC-F -5.47; (-9.41, -1.53)) and pain self-efficacy (5.87; 2.30, 9.45) over 6 months. More participants reported being completely recovered/much better at 2 months with BCT plus USGI triamcinolone/lidocaine than with BCT alone (45.4% v 6.9%; relative risk=6.7; 2.5, 17.9). There was no statistically significant difference in hip pain intensity over 6 months between BCT plus USGI triamcinolone/lidocaine compared with BCT plus USGI lidocaine only (-0.52; -1.21, 0.18). However, a statistically significant difference was seen in favour of the group receiving USGI triamcinolone/lidocaine in comparison to USGI lidocaine alone for a range of secondary outcome measures, over 6 months (e.g. pain self-efficacy, function, and work presenteeism). There was one possible treatment-related serious adverse event: a participant with no signs of infection at randomisation died from endocarditis four months after USGI triamcinolone/lidocaine. BCT plus USGI triamcinolone/lidocaine was less costly (mean cost difference per participant £-161.59) and associated with significantly higher quality-adjusted life-years (QALYs) than BCT only over 6 months (mean difference 0.0477 (0.0257, 0.0699). Increased number of visits to NHS consultants and hip-related surgery in the BCT only group accounted for the majority of cost difference.

Conclusions: USGI triamcinolone/lidocaine combined with BCT leads to greater improvements in pain and function over 6 months in adults with hip OA than BCT alone, and was highly cost-effective. There was no significant difference in hip pain intensity over 6 months between the groups receiving USGI triamcinolone/lidocaine and USGI/lidocaine only raising the possibility of a degree of placebo effect.

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SAFETY, TOLERABILITY, PHARMACOKINETICS, AND CLINICAL OUTCOMES FOLLOWING TREATMENT OF PAINFUL KNEE OSTEOARTHRITIS WITH SENOLYTIC MOLECULE UBX0101

B. Hsu [1], J. Visich [1], N.E. Lane [2], L. Li [3], J. Mittal [3], M. An [1], R.-M. Laberge [1], J. Dananberg [1]. [1] *Unity Biotechnology, South San Francisco, CA, USA;* [2] *Univ. of California - Davis Hlth., Sacramento, CA, USA;* [3] *BioStat Solutions, Inc., Frederick, MD, USA*

Purpose: To report the Results of a Phase 1 study that assessed the safety, pharmacokinetics (PK), and clinical outcomes of single dose, intra-articular (IA) UBX0101 in patients (pts) with painful knee osteoarthritis (OA). In a previous observational biomarker study of patients with painful knee OA, the percentage of senescent cells (SnCs) in synovial biopsies positively correlated with disease severity, synovitis severity, and knee pain. UBX0101 is an MDM2/p53 interaction inhibitor that can induce apoptosis of senescent synovial fibroblasts. Reducing the number of SnCs from painful OA joints with UBX0101 may reduce pain and create a pro-regenerative environment.

Methods: This was a Phase 1, double-blind, randomized, placebo-controlled, single, ascending dose (SAD) study in 48 pts randomized 3:1 to IA UBX0101 (dose range of 0.1 to 4.0 mg) or placebo IA. Key eligibility criteria included knee OA by ACR criteria, Kellgren-Lawrence (KL) grade 1-4, and mean daily pain between 4-9 on a Numeric Rating Scale (NRS, 0-10). Clinical outcomes through 12 weeks included NRS and total WOMAC with pain, function, and stiffness sub-scores derived from the Knee Injury and Osteoarthritis Outcome Score (KOOS) Survey. PK modeling was used to pre-define low (0.1 to 0.4 mg) and high (1.0 to 4.0 mg) dose groups, predicted to achieve knee concentrations below and above 50% effective concentration (EC50) pharmacological thresholds for senolysis, respectively. The SAD study design and sample size were chosen for evaluation of safety. Statistical significance for efficacy endpoints in this Phase 1 SAD study size was considered to be $p<0.1$. WOMAC sub-scores were item-averaged (i.e., each was normalized to a 0-4 Likert scale). A minimal clinically important difference (MCID) for the WOMAC pain sub-score was considered to be a within-subject reduction in the pain sub-score of ≥ 0.5. In addition, the rate and extent of pain reduction was determined using the area under the effect curve (AUC) for both NRS and WOMAC pain sub-score. Odds ratios for achieving response were determined using logistic regression models controlling for baseline NRS score and baseline WOMAC sub-score.

Results: The SAD study population was balanced regarding patient characteristics and baseline outcome measure values; mean age was 62 years, 67% were female, 89.6% white, mean WOMAC pain sub-score at baseline was 1.96 ± 0.46. Single IA doses of UBX0101 up to 4 mg were well-tolerated. Most adverse events (AEs) were mild. No serious AEs occurred and no AEs led to discontinuation. The plasma PK of UBX0101 following single IA injection demonstrated minor inter-patient variability at all dose groups and systemic concentrations were low and

Clinical Outcomes at Week 12			
		UBX0101	
Endpoint	PlaceboInjection(n=14)	Low doses,0.1-0.4mg (n=16)	High doses,1.0-4.0mg (n=18)
WOMAC Pain (0-4)			
Baseline, mean	1.87	2.14	1.86
LSM Change from BL to Week 12 (95% CI)	-0.74 (-1.14, -0.34)	-0.49 (-0.89, -0.10)	-1.09 (-1.38, -0.80)
p-value		0.43	**0.07**
Mean Daily Pain NRS (0-10)			
Baseline, mean	6.47	6.29	6.31
LSM Change from BL to Week 12 (95% CI)	-1.96 (-3.14, -0.77)	-2.66 (-3.78, -1.55)	-3.95 (-4.74, -3.16)
p-value		0.42	**<0.01**
WOMAC Function (0-4)			
Baseline, mean	1.93	2.05	1.94
LSM Change from BL to Week 12 (95% CI)	-0.72 (-1.12, -0.31)	-0.49 (-0.88, -0.10)	-1.05 (-1.36, -0.74)
p-value		0.43	0.13

WOMAC= Western Ontario and McMasters Universities Osteoarthritis Index (Likert) 0-4, LSM= Least-squares mean, BL=Baseline, CI=Confidence Interval, NRS=Numeric rating scale 0-10

further minimized by an estimated 4-hour elimination half-life. Improvements in pain and function were dose-dependent, clinically meaningful, and durable through 12 weeks for the high doses group of UBX0101 (table). Greater proportions of pts in the high doses group achieved decreases from baseline in the WOMAC pain sub-score equivalent to the MCID, and twice the MCID, at Week 12 compared to the placebo and low dose groups. The odds ratio of 3.68 versus placebo of having a 70% reduction from baseline in the WOMAC pain sub-score in the high doses group was nearly statistically significant (p=0.106, alpha=0.1). The magnitude and duration of pain reduction as measured by the mean (standard deviation) WOMAC pain AUC from baseline to Week 12 was 4.94 (3.66) in the high doses group (p=0.034 vs placebo), 3.32 (3.62) in the low doses group, and 2.28 (2.35) in the placebo group.
Conclusions: Single IA doses of UBX0101 up to 4.0 mg were well-tolerated by patients with painful knee OA. Systemic exposure was well described by a one-compartment model with first order absorption. The activity of UBX0101 is supported by the dose-dependent, clinically meaningful, and durable improvements in pain and function observed. Senolysis with IA UBX0101 may be an important future therapeutic option for pts with knee OA.

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THE LONG TERM EFFECT OF INTRA ARTICULAR TRIAMCINOLONE-ACETATE ON KNEE JOINT PATHOLOGY IN A MODEL OF POST TRAUMATIC OSTEOARTHRITIS

S. Zaki [1,2], S. Nair [1], C. Blaker [2], C.B. Little [2]. [1] *SSVS Faculty of Sci., Univ. of Sydney, Camperdown, Australia;* [2] *RPRL Kolling Inst., Univ. of Sydney, St Leonards, Australia*

Purpose: The short medium term benefits of intra articular corticosteroids (IAC) are well reported. Recently, we demonstrated the predictive utility of the mouse destabilisation of the medial meniscus (DMM) model for therapeutic outcomes in humans, by measuring the analgesic effect of intra articular triamcinolone acetate (iaTA) when administered at different stages of OA disease. Importantly, the factors that modify efficacy in patients were reflected in this model (better response with more inflammation; less efficacy with worse radiographic OA pathology). Despite the symptom relieving benefits of IAC, the impact of this therapy on OA disease progression is still unclear. Previous animal studies have demonstrated both structural and metabolic effects on articular cartilage (AC). In vitro studies suggest IAC induce chondrocyte apoptosis and inhibit matrix protein expression, thereby promoting cartilage degeneration. However, clinical trials evaluating the effect of IAC on AC and OA progression have produced inconsistent findings. IAC are associated with an increased risk of OA progression, but little is known about how the stage of OA disease at the time of administration impacts long-term joint pathology. The aim of this study was to determine the effect of iaTA on long term joint pathology (OA progression) when administered at three distinct stages of OA disease (post-injury, early established OA, and progressive/chronic OA), using the DMM model of OA.
Methods: Male, 10 week C57BL6 mice had unilateral DMM surgery. At week 2, 4 or 8 post surgery, mice received 100mcg iaTA or intra articular saline (n=12 per treatment per time). At week 16 knee joints were harvested for histopathological assessment. Toluidine blue stained, sagittal sections of the tibiofemoral joint were examined microscopically. Global joint pathology was quantified by scoring individual tissue pathology changes. Pathology scores were determined for AC, synovium, subchondral bone (SCB), menisci and osteophytes.
Results: There was no significant difference in AC structural damage, cartilage proteoglycan (PG) loss, chondrocyte hyperplasia/apoptosis, SCB or osteophyte pathology, between the 3 time points for saline injection. iaTA did not significantly affect SCB or osteophyte pathology at any injection time, compared to saline injected mice. AC structural damage was significantly increased in week 2 iaTA injected mice, for femur (p=0.03); week 4 injected mice for tibia (p=0.02); and

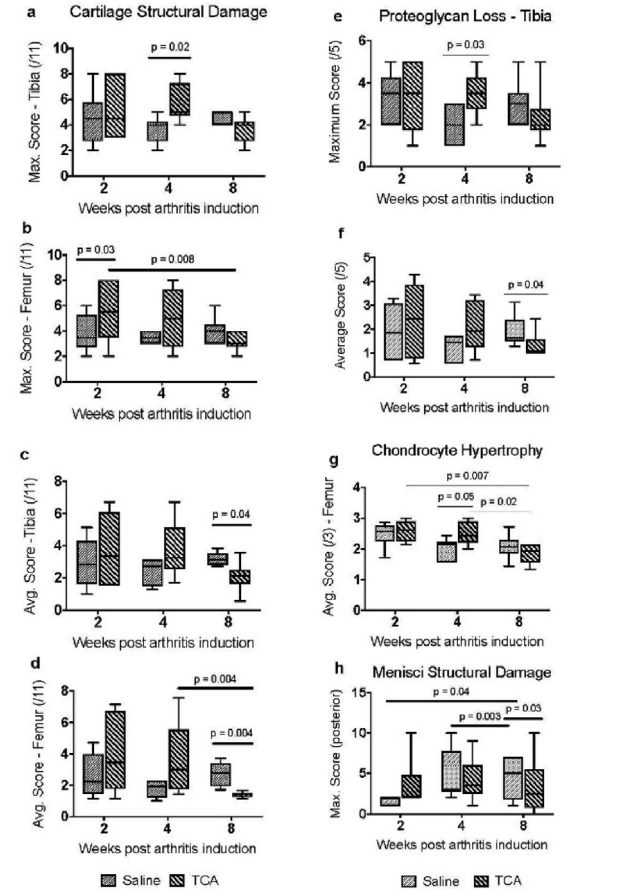

Figure 1: Joint tissue histopathology scores following intra-articular triamcinolone-acetate (iaTA) injection at week-2, -4, -8 post DMM in C57BL6 male mice. (a) cartilage structural damage maximum score-tibia, (b) cartilage structural damage maximum score-femur, (c) cartilage structural damage average score-tibia, (d) cartilage structural damage average score-femur, (e) Proteoglycan loss maximum score-tibia, (f) Proteoglycan loss average score-tibia, (g) chondrocyte hypertrophy average score-femur, (h) mnisci structural damage maximum score-posterior.