Table 1

Prediction Parameter	OR (95%CI)	P value
Maximal Medial BML Grade	7.07 (2.80-17.84)	<0.0001
Maximal Medial Meniscus Grade	1.08 (0.39-2.98)	0.88
WOMAC Pain	1.09 (0.97-1.23)	0.16
Valgus anatomic axis	0.20 (0.04-0.93)	0.04
Varus anatomic axis	1.52 (0.52-4.44)	0.44

(central medial femur) the denuded area appears to show the highest univariate relation to purported predictive risk factors of BML grade and meniscal morphology. For clinical trial planning screening for maximal BML grade and excluding knees with valgus alignment will afford the greatest opportunity to detect progression.

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COST EFFECTIVENESS OF TRADITIONAL CHINESE ACUPUNCTURE AS ADJUNCTIVE THERAPY IN OSTEOARTHRITIS OF THE KNEE

S. Yousuf[1], K.D. Frick[2], C. Spencer[3], L. Lao[1], B.M. Berman[1], D.M. Steinwachs[2], **M.C. Hochberg**[1]
[1]University of Maryland, Baltimore, MD; [2]Bloomberg School of Public Health, Baltimore, MD; [3]Bllomberg School of Public Health, Baltimore, MD

Purpose: There are significant health care costs associated with osteoarthritis (OA) of the knee due to several factors including both utilization of health care services and loss of productivity. We previously reported that traditional Chinese acupuncture (TCA) given in a tapering schedule over 26 weeks was associated with significantly greater improvement in pain and function when compared to both sham acupuncture and education alone (Ann Intern Med 2004;141:901-10). Herein, we report results of a cost effectiveness analysis of TCA in comparison to education alone as adjunctive treatment for knee OA.
Methods: This analysis was limited to the 190 and 189 patients randomized to the TCA and education alone groups, respectively; data on patients randomized to sham acupuncture were not used in this analysis. To estimate costs, we used self-reported data from the Health Assessment Questionnaire (HAQ) that was completed by participants at their 26 week close-out visit to determine health care utilization including medication use, hospitalizations, outpatient surgeries or procedures, emergency room visits and doctor or health care worker visits. In addition, we included the costs of providing the interventions. To measure effectiveness, we estimated quality adjusted life years (QALYs) gained, based on self-reported data from the EuroQoL (EQ-5D) completed at baseline, 8- and 26 weeks. The changes in health utility used to estimate gains in QALYs were calculated using generalized estimating equations to account for the multiple observations per study subject. Missing data were assumed to be missing at random. We used 1000 bootstrapped repetitions to describe the distribution of the cost-effectiveness results. In a secondary analysis, we also estimated the costs per additional OMERACT/OARSI responder.
Results: At 26 weeks, HAQ and EQ-5D data were available on 131 (92.3%) of 142 and 91 (84.3%) of 108 subjects who completed the entire study period in the TCA and education alone groups, respectively. Participants in the TCA group used fewer medications, had fewer hospitalizations (7.6% v 8.9%), outpatient surgeries (13.0% v 16.5%), emergency room visits (8.4% v 11.0%) and mean number of health care worker or doctor visits (7.1% v 7.9%), but slightly higher mean number of nights in hospital (0.61 v 0.58) than those in the education alone group. Over the 26-week study period, the TCA group gained 0.06 QALYs when compared to education alone group. The median cost-effectiveness was $32,000/QALY gained. The cost-effectiveness acceptability curve shows that 95% of 1000 repetitions were consistent with a cost-effectiveness result of less than $50,000/QALY gained (see Figure 1). As previously reported, 52% of the TCA group and 30% of the education alone group could be classified as OMERACT/OARSI responders. The cost per additional responder achieved in the TCA group was estimated as $30,000.

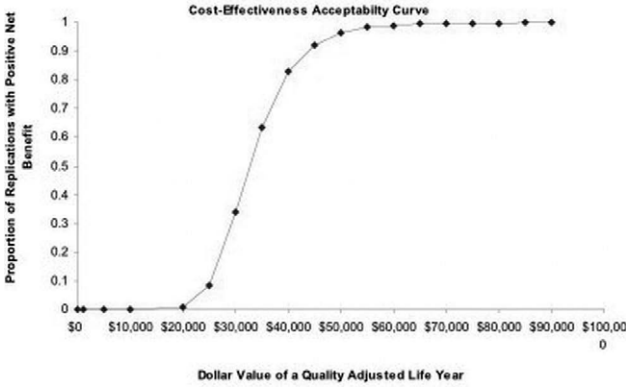

Figure 1

Conclusions: These analyses, based on data from a rigorous 26-week randomized controlled trial suggest that TCA is a cost effective modality when used as an adjunctive therapy in patients with symptomatic OA of the knee.

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EXPRESSION OF THE PATTERNING RECEPTOR CD36 IS CHONDROPROTECTIVE BY DISENGAGING INFLAMMATION FROM DYSREGULATED CHONDROCYTE DIFFERENTIATION AND FUNCTION

D.L. Cecil[1], C.G. Appleton[2], F. Beier[2], R. Terkeltaub[1]
[1]UCSD/VAMC, San Diego, CA; [2]University of Western Ontario, London, ON, Canada

Purpose: In Osteoarthritis (OA), low-grade cartilage and joint inflammation promotes dysregulated chondrocyte differentiation and cartilage catabolism. Inflammatory and pro-catabolic signals for human chondrocytes in OA are provided not only by traditional cytokines such as IL-1, TNFalpha, and chemokines, but also by moieties such as fibronectin proteolytic fragments and the calgranulins S100A11 and S100A4. The calgranulins are ligands of the patterning receptors RAGE (receptor for advanced glycation endproducts) and CD36. S100A11, as well as TNFalpha and CXCL8 (IL-8), induce RAGE signaling-dependent chondrocyte hypertrophy. CD36 is a scavenger receptor whose ligands other than calgranulins include thrombospondin and long-chain fatty acids. PPARgamma agonists induce CD36 expression in cells other than chondrocytes, and numerous studies have shown PPARgamma activation to be anti-inflammatory. Furthermore, the PPARgamma agonist, pioglitazone, reduces severity of experimental OA. Hence, we examined the expression and function of CD36 in chondrocytes in vitro and in situ in experimental OA.
Methods: We employed an in vivo OA model using male Sprague-Dawley rats that underwent joint destabilization surgery by anterior cruciate ligament transection and partial medial meniscectomy and forced mobilization of the joint. Since normal cultured chondrocytes did not express CD36, we transfected CD36 to assess “gain of function” in human chondrocytes.
Results: We demonstrated that both RAGE and CD36 expression became increased by 4 weeks in vivo. RAGE expres-

sion became uniformly increased in hypertrophic chondrocytes, whereas CD36 expression developed most robustly at sites of the most intense injury. We demonstrated that forced expression of CD36 blocked the capacity of S100A11, TNFalpha and CXCL8 to induced chondrocyte hypertrophy. CD36 also blocked the capacity of S100A11 to inhibit proteoglycans synthesis. Last, the PPARgamma agonist N-(2-Benzoylphenyl)-O-[2-(methyl-2-pyridinylamino)ethyl]-L-tyrosine hydrate induced CD36 expression without affecting RAGE expression in chondrocytes.
Conclusions: Early induction of CD36 expression by chondrocytes occurs at sites of cartilage injury as OA develops experimentally. PPARgamma ligation, which is chondroprotective, induces chondrocyte CD36 expression in vitro. Chondrocyte CD36 expression suppresses the capacity of not only its ligand S100A11, but also of TNFalpha and CXCL8 to induce chondrocyte hypertrophy, and CD36 expression promotes preservation of proteoglycans synthesis. We conclude that chondrocyte expression of CD36 is chondroprotective by disengaging responsiveness to inflammation from dysregulated chondrocyte differentiation and function.

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THE "ALARMIN" S100 A8: AN ACTIVATOR OF CHONDROCYTE MEDIATED CARTILAGE DAMAGE?

P. van Lent[1], L. Grevers[1], A. Blom[1], A. Sloetjes[1], T. Vogl[2], W. Nacken[2], J. Roth[2], W. van den Berg[1]
[1]Radboud University Medical Centre, Nijmegen, The Netherlands; [2]Inst of Experimental Dermatology, Muenster, Germany

Purpose: In a previous study we have shown that "alarmins" S100A8 and S100A9 which can form dimers and are predominantly produced by myeloid cells in the synovial fluid and synovial membrane are involved in MMP-mediated cartilage destruction during experimental arthritis. S100A8 forms the active part which is stabilized by S100A9 and protects S100A8 from degradation. As MMP mediated cartilage destruction is particularly found around the chondrocyte this prompted us to investigate whether S100A8 and A9 are produced by chondrocytes and whether these "alarmins" are actively involved in MMP-mediated chondrocyte activation.
Methods: S100A8 and A9 proteins were detected in knee joints of murine arthritis and osteoarthritis using immunolocalisation. Murine chondrocyte cell line H4 was stimulated with pro-inflammatory cytokines (100 ng/ml) to investigate rS100A8 and A9 production or by recombinant S100A8 (0.2, 1 and 5 μg/ml) to investigate MMP and cytokine production.mRNA and protein levels were measured using RT-PCR and blotanalysis. S100A8/A9 dimers and cytokines were measured in culture supernatant using ELISA and Luminex. Breakdown of aggrecan on the pericellular surface of the chondrocyte was measured using VDIPEN and NITEGE (MMP and aggrecanase neoepitopes) antibodies and FACS analysis.
Results: Immunolocalisation of inflamed knee joints depicted that S100A8 and S100A9 proteins were abundantly expressed in chondrocytes. Expression was particularly found in the superficial layers of the cartilage surfaces at the margins of the joint. Stimulation of murine chondrocytes by pro-inflammatory cytokines IL-17, IL-18 and IFNγ caused strong upregulation of particularly S100A8 and in lesser extent S100A9 mRNA (S100A8: 24, 48 and 4 fold and S100A9: 4, 4 and 0 fold respectively). Stimulation of chondrocytes by rS100A8 caused a significant autoinduction of S100A8 and in lesser extend upregulation of S100A9 mRNA and protein levels. High concentrations of cytokines IL-6, KC and RANTES were measured in the culture supernatant whereas TNFα, IL-1α and β were below detection level. S100A8/A9 dimers could not be detected by ELISA confirming that S100A8 is the active component and can directly activate chondrocytes. Moreover MMPs (-2,-3,-9,-13) and ADAMTS(-4,-5) mRNA levels in the chondrocyte were strongly upregulated (maximal at 1 μg/ml (4, 4, 3, 16, 8 and 4 times respectively). VDIPEN and NITEGE neoepitopes on the pericellular membrane of chondrocytes were significantly elevated after stimulation with rS100A8 for 24 hours in a concentration (0,2, 1 and 5 μg/ml) dependent manner. (VDIPEN 17,67,108% and NITEGE 8, 33 and 67% respectively).
Conclusions: The alarmin S100A8 is produced by chondrocytes and directly activates MMP and aggrecanase mediated peri-cellular matrix degradation. S100A8 may be an important mediator of severe cartilage destruction.

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INTERLUKIN-7 STIMULATES SECRETION OF S100A4 BY ACTIVATING THE JAK-STAT PATHWAY IN HUMAN ARTICULAR CHONDROCYTES

R.R. Yammani, D. Long, R. Loeser
Wake Forest University School of Medicine, Winston-Salem, NC

Purpose: S100A4, a member of the S100 family of calcium binding proteins, has been shown to be increased in OA cartilage and to stimulate chondrocyte RAGE signaling resulting in increased expression of MMP-13. Members of S100 family are known to be secreted into the extra-cellular environment, however the mechanism(s) of secretion is not completely understood. The aim of this study was to determine the pathway involved in secretion of S100A4 in response to cytokines in chondrocytes.
Methods: Human articular chondrocytes isolated from normal ankle cartilage obtained from tissue donors were cultured in high density monolayers in media with 10% serum for 5-7 days. Confluent monolayers were then changed to serum free media 16-18hr prior to treatment with 10ng/ml of IL-7, IL-1β and TNF α. In some experiments, cells were pre-treated with a JAK-3 inhibitor or Brefeldin-A (BFA), a chemical inhibitor that blocks classical protein translocation. Immuno-blotting with phospho-specific antibodies was used to determine the activation of signaling proteins. Secretion of S100A4 was measured in the conditioned media by immuno-blotting with polyclonal antibodies to S100A4.
Results: Chondrocyte secretion of S100A4 was observed after treatment with IL-7 and TNFα but not with IL-1β. Treatment with IL-7 resulted in activation of the JAK/STAT pathway with increased phosphorylation of JAK-3 and STAT-3. IL-7 stimulation of S100A4 secretion was inhibited by pretreatment with a JAK-3 inhibitor. In addition, pretreatment with Brefeldin-A (BFA) didn't effect the secretion of S100A4 suggesting a pathway independent of Golgi-endoplasmic reticulum (classical pathway).
Conclusions: Our study demonstrates for the first time that IL-7 or TNFα but not IL-1β can stimulate chondrocyte secretion of S100A4 via activation of JAK/STAT signaling. We have recently found that OA chondrocytes produce IL-7 and others have shown TNFα. These cytokines may contribute to cartilage destruction through secretion of S100A4 which can function as an autocrine factor to stimulate MMP-13 production via RAGE.

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INFLAMMATORY GENE EXPRESSION IN EARLY KNEE OSTEOARTHRITIS PATIENTS

C.R. Scanzello, S. Rodeo, R. Marx, T. Miles, E. Umoh, M.K. Crow
Hospital for Special Surgery, New York, NY

Purpose: Synovial inflammation in osteoarthritis (OA) patients has been associated with increased pain, disability, and more