SAT0546 TOTAL OSTEOPHYTE SCORE IS A BIOMARKER OF CURRENT AND PERSISTENT PAIN IN KNEE OSTEOARTHRITIS SUBJECTS

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Background: X-ray and magnetic resonance imaging (MRI) demonstrated associations between osteophyte severity and current pain in knee osteoarthritis (OA) patients. Persistent pain over 5 years was also associated with x-ray osteophyte severity. A biomarker to identify knee OA subjects with persistent pain may reduce placebo response rates in clinical trials.
Objectives: To determine whether the total knee osteophyte score (TKOS), as measured by MRI Osteoarthritis Knee Score (MOAKS), is a biomarker of current and persistent pain severity in knee OA subjects.
Methods: Knee OA subjects from the Foundation for the National Institutes of Health Biomarker Consortium were longitudinally assessed over 4 years and categorized as pain and x-ray progressors (n=194), x-ray–only progressors (n=103), pain-only progressors (n=103), and non-progressors (n=200). Knee osteophyte severity was scored at baseline by MOAKS at 12 positions across the knee and summed to obtain the TKOS. TKOS was summarized as means and SDs in the 4 progression groups; each progression group TKOS was compared with the non-progression group using Wilcoxon rank sum tests (Table 1). The longitudinal Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scores were plotted and tested with a linear mixed model, by high and low TKOS status, defined as above and below the TKOS median of 6 (Figure 1). Subjects with persistent pain were defined based on WOMAC pain scores at 4 out of 5 time points higher than the thresholds listed in Table 2; at each threshold, mean differences in TKOS were tested using analysis of variance among those with and without persistent pain.
Results: The distribution of baseline TKOS differed by progression group, with the highest TKOS among pain and x-ray progressors (Table 1). In all 4 progression groups, baseline WOMAC pain scores were higher in subjects with high (>6) versus low (≤ 6) baseline TKOS status (P=0.0001, 0.0383, 0.0035, and 0.0466, respectively). The difference in WOMAC pain scores between TKOS high and low subgroups was constant over time (Figure 1; solid curves above and parallel to dashed curves with TKOS main effect always significant [$P<0.01$] in all 4 progression groups), but the TKOS$\times$Time interaction term in the longitudinal mixed model was not statistically significant, indicating that the pain difference between the TKOS high and low subgroups did not change over time. TKOS was highly associated with persistent pain, with TKOS higher at all thresholds (Table 2).

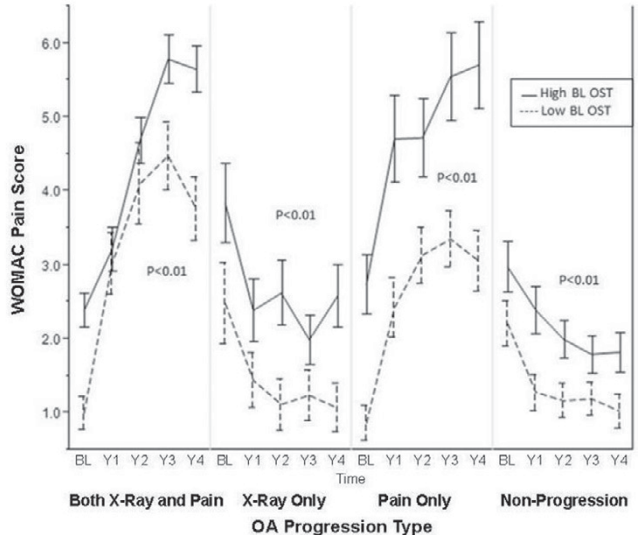
Table 1. Distribution Parameters of TKOS at Baseline by OA Progression Type

Progression Type	TKOS			*P* value)
	n	Mean	SD	
X-ray and pain	194	10.43	6.60	<0.0001
X-ray only	103	8.79	6.56	0.06
Pain only	103	8.03	5.91	0.22
None	200	7.32	6.07	–

Table 2. Group Sizes and TKOS Mean Differences for Different WOMAC Pain Thresholds for Persistent Pain

WOMAC Pain Threshold	Subjects With Persistent Pain, n	TKOS Difference for Subjects With Persistent Pain vs Those Without	*P* Value
2	211	2.5	<0.0001
3	150	2.4	<0.0001
4	112	2.4	0.0001
6	52	3.6	<0.0001
8	21	2.5	0.06

Figure 1. WOMAC pain score over 4 years stratified by baseline TKOS status and OA progression type.



Conclusions: TKOS is a candidate biomarker for current and persistent pain in knee OA patients and may be a predictive biomarker for reduced placebo response rates in clinical trials.
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SAT0547 THE INFLUENCE OF OSTEOARTHRITIS ON CLINICAL, LABORATORY AND ULTRASOUND PARAMETERS OF PATIENTS WITH EARLY RHEUMATOID ARTHRITIS

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Background: Osteoarthritis (OA) and rheumatoid arthritis (RA) are not infrequent in the general population. The two pathologic entities can overlap and the presence of OA can interfere with the evaluation of patients with RA.
Objectives: This study aims to evaluate the possible impact of OA on the clinical, laboratory and ultrasound parameters currently evaluated in patients with early RA (ERA).
Methods: We have evaluated the data obtained from patients with ERA referred to our Early Arthritis Research Center (EARC). Only data from patients who fulfilled EULAR/ACR 2010 criteria for RA (1) and had a symptom duration of less than 12 months were analyzed. 43 patients were diagnosed with ERA in the EARC between 2012 and 2016 and were enrolled in this study. Patients were evaluated at baseline and after 12 months. All patients underwent clinical examination, laboratory tests and ultrasound (US) examination. For the US examination we have calculated the score proposed by Naredo et al. considering that this simplified US score includes the evaluation of the hand and knee. (2)
Results: There was a clear predominance of women (62.8%). The mean age was 55.47±13.71 years. At baseline, 21 patients (48.8%) were diagnosed with OA. 15 patients (34.9%) presented hand OA and 9 patients (20.9%) presented knee OA. Hand OA didn't influence the values of DAS28, SDAI, patient's and physician's visual analogue scale (VAS) or ultrasound scores ($p>0.05$). For patients with knee OA, significantly higher values for DAS28 were observed at baseline (p=0.018) and were maintained significantly higher after 12 months of observation (p=0.031). All the other parameters were not influenced by the presence of knee OA ($p>0.05$). The median value and interquartile range for lab tests and for disease activity indices are shown in Table 1.

Table 1. Values for disease activity indices, laboratory tests and US scores for patients with ERA with/without OA

Lab test - Median (Interquartile range)	ERA patients with OA (n=21)	ERA patients without OA (n=22)	p
DAS28	5.07 (4.62–5.73)	4.94 (3.87–5.44)	0.280
SDAI	29.02 (24.95–36.59)	28.87 (16.18–33.97)	0.644
VAS patient (mm)	72.00 (55.00–81.00)	62.50 (50.50–72.25)	0.144
VAS physician (mm)	52.00 (40.00–66.50)	50.00 (33.75–57.00)	0.456
Naredo score - GS	8.00 (5.50–12.00)	9.00 (5.00–12.25)	0.932
Naredo score - PD	4.00 (0.00–6.50)	3.00 (0.00–4.00)	0.700

Conclusions: Significantly higher values of DAS28 were observed in patients with ERA who associated knee OA, while the values of SDAI were not influenced, suggesting that SDAI may be superior to DAS28 in evaluating patients with ERA and knee OA. Not the same tendency was observed in patients with ERA and hand OA. The values of patient's VAS were not influenced by the presence of hand or knee OA suggesting that these types of OA do not influence the patients' perception of the disease activity. Moreover, the values of ultrasound scores were not influenced by the presence of OA.
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SAT0548 PLASMA CGRP CONCENTRATIONS WERE NOT ASSOCIATED WITH PATIENT OA SYMPTOMS OR RESPONSE TO GALCANEZUMAB, A MONOCLONAL ANTIBODY AGAINST CGRP

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Background: The safety and efficacy of galcanezumab, a monoclonal antibody

directed against CGRP, were assessed in a phase 2 clinical trial NCT02192190 in patients with moderate to severe osteoarthritis (OA) knee pain. Patients were randomized to placebo, galcanezumab (5, 25, 120 and 300 mg subcutaneously every 4 weeks, at weeks 0 and 4) or celecoxib (200 mg once daily) for 16 weeks in a 2:1:1:1:1:1 ratio. The study was terminated after an interim analysis due to inadequate efficacy for OA pain.

Objectives: This study assessed the correlation of baseline plasma CGRP concentrations with signs, symptoms and radiographic severity of OA, and response to galcanezumab and celecoxib treatments.

Methods: Plasma samples were collected at baseline and weeks 4, 8, 12 and 16 after study drug treatment. CGRP concentrations were determined by a validated high sensitivity (HS) assay. Correlation of baseline CGRP levels to WOMAC scores, PGA and radiographic Kellgren-Lawrence (K-L) grades were assessed using Spearman's correlation and Wilcoxon test. Patients were stratified into high vs low groups by baseline CGRP concentrations and post-treatment changes from baseline WOMAC scores evaluated by mixed effect model repeated measures for each subset.

Results: At the interim analysis, baseline plasma CGRP samples were available for 262 patients with 54 patients providing samples at study termination through the week 8 visit. The median CGRP concentration at baseline was 1.07 pg/ml, range <0.78 to 33.91, and 31% of patients were below the level of quantitation (BLQ, <0.78 pg/ml). Median baseline CGRP levels were 1.0 pg/ml for K-L grade 2 (N=178), and 1.2 pg/ml for K-L grade 3 (N=84) (p=0.06). Correlations of WOMAC or PGA scores with baseline CGRP levels were all r <0.01 (showed no significant correlations). In OA patients receiving galcanezumab 300mg SC at week 0 and week 4, those with high baseline CGRP levels demonstrated a 14mm improvement in WOMAC Pain response at week 12, (95% CI 0, 29mm). The pain response to galcanezumab 300mg did not reach the magnitude of celecoxib response and no effects were seen at 5–120mg doses. Celecoxib treatment had larger pain reduction among patients with high baseline CGRP compared to low baseline CGRP levels. Treatment with celecoxib did not alter plasma CGRP concentrations.

Conclusions: At baseline, CGRP levels in OA patients were not associated with WOMAC or PGA scores. There was a modest association to radiographic K-L grade. Subgroup analyses of patients with high (>median) CGRP levels at baseline suggested a potential response to galcanezumab for the highest dose, 300mg, but not lower doses. Celecoxib response was greater in those with higher CGRP levels. However, interpretation was limited by small samples sizes at the latter time points. Further studies may determine if enriching the OA population for higher CGRP levels at baseline, or if increased or longer dosing of galcanezumab would improve pain responses or if CGRP blockade is relevant in relieving OA knee pain.

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SAT0549 ANTI-INFLAMMATORY PROPERTIES OF SM04690, A SMALL MOLECULE INHIBITOR OF THE WNT PATHWAY AS A POTENTIAL TREATMENT FOR KNEE OSTEOARTHRITIS

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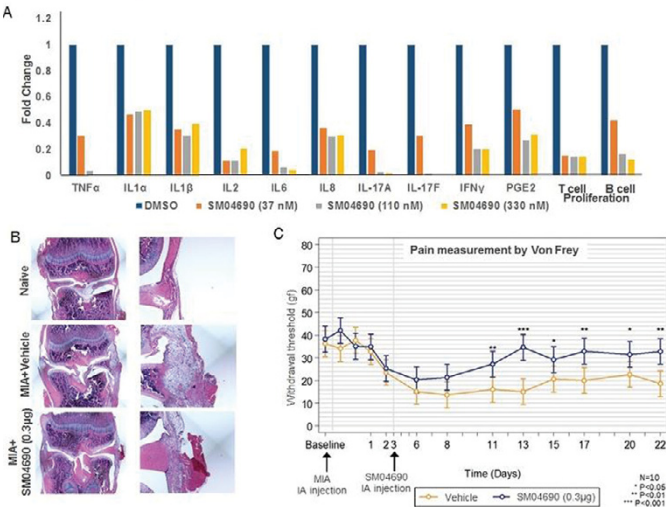
Background: Osteoarthritis (OA) is characterized by pain, deformity, and reduced function in the knee joint. Upregulated Wnt signaling affects the pathogenesis of OA through increased inflammation, increased subchondral bone and thinning cartilage. SM04690, a novel small molecule, was previously shown to inhibit the Wnt pathway and induce chondrogenesis *in vitro* and *in vivo*.[1]

Objectives: SM04690 was evaluated in preclinical studies to determine its capacity to reduce inflammation, and reduce pain in OA.

Methods: Anti-inflammatory activity was evaluated by measuring cytokine (IL-6 and TNF-α) secretion using ELISA with IL1-b stimulated synovial fibroblasts. A panel of pro-inflammatory cytokines (TNF-α, IL-1α, IL-1β, IL-2, IL-6, IL-8, IL-17A, IL-17F, IFN-γ and PGE2) was evaluated by ELISA; T and B cell proliferation by flow cytometry in peripheral blood mononuclear cells (PBMCs), and T and B cell co-cultures stimulated with super-antigen (SAg) or lipopolysaccharides (LPS), compared to vehicle or benchmark immunosuppressant or steroid (cyclosporin A and prednisolone). SM04690 effects on LPS-induced expression and phosphorylation of JNK, NFkB, Erk, cJun, Akt, Stat3 in THP-1 cells were measured by qPCR and Western Blot. *In vivo* SM04690 activity was evaluated in a rat monosodium iodoacetate (MIA) injection-induced OA model, immediately followed by a single intra-articular SM04690 or vehicle injection. Joint inflammation was evaluated by measuring synovial thickness and infiltrating cells histology; inflammatory cytokines (IL-1α, IL-1β, IL-2, IL-5, IL-6, IL-8, TNF-α and IFN-γ) by qPCR and ELISA and cartilage protection by qPCR for matrix metalloproteinases (MMPs). Pain was measured as paw withdrawal threshold using Von Frey apparatus.

Results: SM04690 inhibited IL-1b-induced TNF-α and IL-6 secretion in synovial fibroblasts (EC_{50} @30nM). SM04690 significantly inhibited ($p<0.01$) SAg and LPS stimulated pro-inflammatory cytokine production (TNF-α, IL1-α, IL1-β, IL-2, IL-6, IL-8, IL-17A, IL-17F, IFN-γ, PGE2), T and B cell proliferation in PBMCs and T and B cell co-cultures (Figure A), with activity comparable to or better than cyclosporin A and prednisolone. SM04690 treatment specifically decreased LPS-induced gene expression ($p<0.01$) and phosphorylation of NFkB in THP-1 cells with no effect on JNK, Erk, cJun, Akt and Stat3. Compared to vehicle in the rat MIA OA model, SM04690 injection reduced inflammatory cells, decreased synovial thickness ($p<0.05$,Figure B), inhibited production of pro-inflammatory cytokines and MMPs ($p<0.05$). SM04690 increased ($p<0.01$) paw withdrawal threshold in treated rats compared to vehicle at multiple time points (Figure C).

Figure. SM04690 inhibited inflammatory cytokine production *in vitro* and decreased inflammation and pain in the MIA model of OA



Conclusions: SM04690 demonstrated potent anti-inflammatory properties, comparable to or greater than cyclosporin A and prednisolone. In a rat knee OA model, SM04690 injection reduced inflammation, protease production and pain compared to vehicle. The anti-inflammatory properties of SM04690 may provide beneficial effects in the treatment of OA. Clinical studies are ongoing.

References:

[1] Hood et al. OAC 2016, s187.

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SAT0550 NEUROPATHIC PAIN AMONG PATIENTS WITH PRIMARY KNEE OSTEOARTHRITIS- RESULTS OF A CROSS SECTIONAL STUDY FROM A TERTIARY CARE CENTRE IN SOUTHERN INDIA

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Background: Pain in osteoarthritis (OA) is generally believed to be nociceptive because of local structural pathology and joint failure which so characterizes OA. However, there is often a discordance between the radiographic knee OA and pain, suggesting that the pain can be contributed by other mechanisms other than nociception.[1] Recently it is shown that pain in knee OA may have a neuropathic component.[2]

Objectives: The objective of the study was to assess the level of neuropathic pain in patients with knee OA, and identify the clinical and socio-demographical factors associated with neuropathic pain

Study design: Cross sectional study.

Setting: Medicine and Orthopaedic outpatient department (OPD) of a tertiary care centre located in southern India

Methods: One-hundred and sixty-one patients with knee OA satisfying the American College of Rheumatology 1986 clinical and radiographic classification criteria for knee OA were studied. Neuropathic pain was assessed by the Douleur Neuropathique in 4 questions (DN4) questionnaire;[3] score of 4/10 or more was classified as diagnostic for neuropathic pain. The Indian version of Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[4] was used to assess pain, stiffness and physical function of the patients. Factors associated with neuropathic pain were explored.

Results: Mean age was 55.7±8.8 years. The mean total Indian WOMAC was