SAT0490 GENOME-WIDE DNA METHYLATION PROFILING OF OSTEOARTRHITIS PERIPHERAL BLOOD MONONUCLEAR CELLS REVEALS SLOWED EPIGENETIC AGING AMONG RAPID RADIOGRAPHIC PROGRESSORS: DATA FROM THE OSTEOARTHRITIS INITATIVE (OAI)

A. Rivas[1], M. Jeffries[1,2]. [1]*Rheumatology, Immunology, and Allergy, University of Oklahoma Health Sciences Center;* [2]*Arthritis & Clinical Immunology Program, Oklahoma Medical Research Foundation, Oklahoma City, United States*

Background: Extensive evidence has correlated epigenetic alterations in articular tissues with both the presence and progression of human osteoarthritis, but few analyses of blood cell epigenetic patterns have been done in OA.
Objectives: We examined the DNA methylation aging rate in peripheral blood mononuclear cells (PBMCs) at baseline from knee OA patients with rapid radiographic progression compared to well-matched nonprogressors enrolled in the Osteoarthritis Initiative (OAI).
Methods: PBMC DNA was obtained from baseline blood draws of 64 OA patients enrolled in the OAI longitudinal study. All patients had baseline symptomatic and radiographic OA. 32 rapidly-progressive OA patients, defined as $\geq$1.0mm radiographic joint space loss within 24 month follow-up were compared to 32 non-progressive patients. There were no differences in age, sex, race, BMI, baseline K/L grade, or calculated PBMC subset composition between rapid- and non-progressors. DNA methylation was quantified with Illumina HumanMethylation 450k arrays. Preprocessing was performed in GenomeStudio and normalized to internal controls. Epigenetic age was estimated with the algorithm described by Horvath et. al., using 353 age-associated CpG sites. This epigenetic age was compared to chronological age to calculate epigenetic-chronological age discordance (ΔAge) and group differences compared with a Student t-test. ΔAge was correlated with individual CpG methylation sites of rapid progressors, and Pearson values calculated. Correlation was considered significant if Pearson's r values were $\leq$-0.55 or $\geq$0.55 ($p \leq 0.001$). Pathway analysis of correlated genes was performed with the Ingenuity Pathway Analysis (IPA) system.
Results: The baseline DNA methylation aging rate in rapidly progressive (RP) knee OA patients was decelerated compared to nonprogressors (NP) and to chronological age (ΔAge-RP: -4.9±1.4 vs. ΔAge-NP: -0.071±1.3 mean±SEM years less than chronological age, p=0.015). 1165 CpG sites were correlated with ΔAge in rapid progressors, corresponding to 755 genes. Ontologic analysis of highly correlated genes showed association of the STAT3 pathway (p=6E-4), Notch signaling (p=1E-3), axonal guidance signaling (p=7E-3), CREB signaling (p=2E-2), NFAT signaling (p=2E-2), and autophagy (p=4E-2) among others. Associated upstream regulators included FGF2 (p=3E-5), SMAD4 (p=9E-4), SMAD5 (p=1E-3, TNF (p=4E-3), and TGFB1 (p=4E-3), among others
Conclusions: Our data reveal that a decelerated peripheral blood differential DNA methylation age epigenotype is present at baseline in rapidly progressive knee OA patients, but not in nonprogressive knee OA patients. The genes correlated with this methylation age deceleration cluster in pathways previously associated with OA in articular tissues, suggesting that these pathways may systemically epigenetically dysregulated. Our data reinforce the notion that OA is a heterogeneous disease composed of distinct subgroups, and suggests that future epigenetic investigation of immune cell subsets may be beneficial in unraveling OA pathogenesis.
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SAT0491 USE OF HISTAMINE H1-RECEPTOR ANTAGONISTS IS ASSOCIATED WITH DECREASED PREVALENCE OF RADIOGRAPHIC KNEE OSTEOARTHRITIS: A CROSS-SECTIONAL ANALYSIS OF OSTEOARTHRITIS INITIATIVE DATA

I. Shirinsky, V. Shirinsky. *Institute of Fundamental and Clinical Immunology, Novosibirsk, Russian Federation*

Background: Mast cells are prevalent in osteoarthritis (OA) synovial tissue and their presence is associated with structural damage [1]. H1-receptor antagonists block the action of histamine, which is the major mediator of mast cells, on specific receptors. Therefore, H1 receptor blockade may represent a way to prevent and treat OA. Currently, there is a lack of data investigating the effects of H1-receptor blockade on knee OA in humans.
Objectives: To evaluate cross-sectional association between the use of histamine H1-receptor antagonists and radiographic knee OA.
Methods: For the current analysis we used data from the publically available Osteoarthritis Initiative (OAI). We compared cross-sectionally the knees of OAI participants taking H1-receptor antagonists at baseline with knees of control participants. We used logistic regression models to assess the association between radiographic knee OA (defined as KL$\geq$2 and JSN) and the use of H1-receptor antagonists. Generalized estimating equations (GEE) were used to adjust for the correlation between knees. The models were adjusted for multiple covariates including age, race, and body mass index.
Results: A sample of 4377 OAI participants (8753 knees) was analyzed, 457 of them (914 knees) used histamine H1-receptors at baseline. The use of histamine H1-receptor antagonists was associated with lower prevalence of radiographic knee OA in both crude (OR 0.77, 95 CI 0.64–0.91, $p<0.01$) and adjusted (OR 0.79, 95 CI 0.66–0.95, p=0.01) analyses.
Conclusions: Histamine H1-receptor antagonists are associated with decreased prevalence of knee OA. Further studies are warranted to determine whether H1-receptor blockade may be of benefit in the prevention and treatment of knee OA.
References:
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SAT0492 INTRAMUSCULAR CORTICOSTEROID INJECTION VERSUS PLACEBO INJECTION IN HIP OSTEOARTHRITIS: A 12- WEEK BLINDED RANDOMIZED CONTROLLED TRIAL

D. Dorleijn[1], P. Luijsterburg[1], M. Reijman[2], M. Kloppenburg[3], J. Verhaar[2], P. Bindels[1], K. Bos[2], S. Bierma-Zeinstra[1]. [1]*General Practice;* [2]*Orthopeadics, Erasmus MC, Rotterdam;* [3]*Rheumatology, LUMC, Leiden, Netherlands*

Background: Several international guidelines recommend intra-articular (IA) corticosteroid injections for patients with hip OA experiencing moderate to severe pain and no responding to oral analgesics. Previous research has shown a systemic effect of an intramuscular (IM) gluteal corticosteroid injection in patients with subacromial impingement shoulder pain. A clinically relevant effect of IM corticosteroid injections would offer a less complex, alternative treatment for patients' episodes of increased pain in hip OA.
Objectives: The trial aim was to assess the efficacy of an IM gluteal corticosteroid injection compared to a placebo injection on patients' reported hip pain severity in patients with hip OA, who were not responding on oral analgesics.
Methods: Patients in primary and secondary care were included if they met the clinical ACR and radiographic (KL score $\geq$2) criteria for hip OA and scored a severity of hip pain $\geq$3 on a scale of 0–10 (0=no hip pain). Patients were randomized to receive either 40mg of triamcinolone acetate or saline (placebo) with an IA injection into the ipsilateral gluteus muscle. Primary outcome was severity of hip pain at 2 weeks, measured with numerical rating scale (NRS) in rest and during walking (0–10;0=no pain) and with the WOMAC pain subscale (0–100;0=no pain). Secondary outcomes included hip pain severity (NRS, WOMAC pain, ICOAP), function (WOMAC function), stiffness (WOMAC stiffness), adverse events, and medical co-interventions at 2, 4, 6, and 12 weeks follow-up. Statistical analyses were performed based on the intention to treat principle. Linear mixed models with repeated measurements were used to analyze between group differences. The models were adjusted for variables that changed the effect estimate >10%.
Results: 107 of 422 screened patients were randomized. After informed consent, one randomized patient did not show up at the appointment for baseline measurement and subsequent injection and could, because of lack of data, not be included in the analyses. Finally, 52 patients in the corticosteroid injection group, and 54 in the placebo injection group were included in the analyses. 68% of the patients were female, and 25% were recruited by orthopedic surgeons. Mean age was 64 years (SD 11) and duration of OA was $\geq$1 year for 70%. At 2 weeks follow-up (table), the corticosteroid injection was statistically significant and clinically relevant associated with hip pain reduction at rest (coefficient -1.3, 95% CI -2.3 to -0.3) compared to placebo. The corticosteroid injection was also associated with significant hip pain reduction at 4, 6 and 12 weeks. Moreover, at almost all follow-up measurements the estimates showed significant differences in favor of the corticosteroid injection on WOMAC pain, function, stiffness and total score, and ICOAP. No significant differences between groups were found for adverse events and medical co-interventions.

Table. Results of the multivariable linear mixed model analyses with repeated measurements regarding primary outcomes between corticosteroid and placebo group.

				Adjusted mixed model	
		Corticosteroid (n=52)	Placebo (n=54)	Between group difference * (95% CI)	p- value
Outcome; Mean (SD)					
NRS pain (rest) (0-10)	baseline	4.3 (2.4)	4.2 (2.5)		
	2 w	2.6 (2.3)	3.9 (2.5)	-1.3 (-2.3 to -0.3)	0.01
	4 w	2.8 (2.1)	3.9 (2.5)	-1.2 (-2.1 to -0.2)	0.01
	6 w	2.6 (2.3)	4.0 (2.6)	-1.4 (-2.4 to -0.5)	<0.01
	12 w	3.2 (2.4)	4.2 (2.8)	-1.2 (-2.3 to -0.2)	0.02
NRS pain (walking) (0-10)	baseline	5.4 (2.1)	5.1 (2.3)		
	2 w	3.5 (2.4)	4.2 (2.5)	-0.9 (-1.9 to 0.1)	0.07
	4 w	3.5 (2.2)	4.5 (2.5)	-1.1 (-2.0 to -0.2)	0.01
	6 w	3.4 (2.2)	4.6 (2.5)	-1.4 (-2.3 to -0.4)	<0.01
	12 w	4.0 (2.5)	5.0 (2.7)	-1.3 (-2.2 to -0.3)	0.01
WOMAC pain (0-100)	baseline	43 (17)	43 (17)		
	2 w	35 (18)	39 (17)	-6.1 (-13.4 to 1.2)	0.10
	4 w	34 (19)	39 (18)	-7.0 (-14.4 to 0.4)	0.06
	6 w	32 (18)	40 (20)	-9.9 (-17.7 to -2.2)	0.01
	12 w	33 (18)	40 (23)	-9.6 (-18.0 to -1.2)	0.03

Models adjusted for baseline hip KL-score, ethnicity, hip stiffness, and patients expected effect; * placebo group is reference group; SD = standard deviation; 95%CI = 95% confidence interval; WOMAC = Western Ontario and McMaster Universities Index (0 = no pain); NRS = Numerical Rating Scale (0 = no pain); ICOAP = Intermittent and Constant OsteoArthritis Pain (0 = no pain); w = weeks

Conclusions: An IM gluteal corticosteroid injection was effective in hip pain reduction compared to placebo injection in patients with hip OA at 2 weeks