OP0168 A PHASE 2A, PLACEBO-CONTROLLED, RANDOMIZED STUDY OF ABT-981, AN ANTI-INTERLEUKIN-1ALPHA AND -1BETA DUAL VARIABLE DOMAIN IMMUNOGLOBULIN, TO TREAT EROSIVE HAND OSTEOARTHRITIS (EHOA)

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Background: No approved OA therapies reduce pain and slow joint damage. Mouse data suggested that inhibiting IL-1α and -1β with ABT-981 would reduce pain and slow structural progression in EHOA.
Objectives: To test the efficacy and safety of ABT-981 in EHOA.
Methods: Subjects with HOA per ACR criteria, ≥3 inflamed IP joints (tender, swollen, or both), hand pain ≥6 (scale 0–10), and ≥1 erosive IP joint on X-ray (Verbruggen-Veys) were randomized to placebo (PBO) or ABT-981 200 mg SC every 2 wk for 26 wk. The primary outcome was AUSCAN hand pain at 16 wk. Subjects had radiographs of both hands and MRI of the index hand at baseline and 26 wk. Both radiographs (Verbruggen-Veys, GUSS™, OARSI, Kellgren-Lawrence [KL]) and MRIs (HOAMRIS) were read by 2 independent central readers. A modified intent-to-treat population (ie, randomized and treated) was analyzed. Continuous efficacy endpoints were assessed using ANCOVA models with treatment and country as main factors and baseline measurements as covariates with LOCF imputation for the primary endpoint.
Results: Of 131 treated subjects (85% women; mean age 66 y), 61/67 randomized to PBO and 49/64 to ABT-981 completed the study; subject characteristics were well matched. AUSCAN pain was not significantly different vs PBO at wk 16 (*P*=0.39; Table 1, Figure); X-ray data and other endpoints also were not statistically different vs PBO (Table 1). ABT-981 significantly decreased hsCRP, neutrophils, IL-1α, and IL-1β. Immunogenicity had no impact on ABT-981 pharmacokinetics. Besides injection site reactions and neutropenia, ABT-981 was well tolerated and safety was similar vs PBO, with no serious infections (Table 2).

Table 1

	PBO	ABT-981	PBO	ABT-981	*P*
1° Endpoint	Baseline, mean±SD		LS, mean change±SE at Wk 16		
AUSCAN pain (0–50)	39±7	38±6	–10.7±2.4	–9.2±2.3	0.39
2° Endpoints	Baseline, mean±SD		LS, mean change±SE at Wk 26		
AUSCAN function (0–90)	69±15	71±13	–14.3±4.2	–16.4±4.0	0.49
Tender joints (0–30)	12±6	12±7	–4.7±1.2	–5.8±1.2	0.32
Swollen joints (0–30)	6±6	6±5	–1.8±0.8	–2.2±0.9	0.64
X-ray erosive joints (0–16)	2±2*	3±2*	0.26±0.08†	0.18±0.08†	0.33
KL score (0–80)	41±13	46±13	0.13±0.19	0.10±0.19	0.87
OARSI JSN (0–58)	28±10	32±9	0.14±0.19	0.03±0.19	0.51
OARSI osteophytes (0–58)	23±11	26±10	0.25±0.15	0.14±0.16	0.45
HOAMRIS synovitis (sum score; 0–52.5)	11±4	10±4	0.92±0.48	0.85±0.51	0.89
HOAMRIS erosive damage (sum score; 0–105)	18±9	17±10	0.26±0.64	0.10±0.67	0.80
HOAMRIS BML (sum score, 0–105)	7±5	5±4	0.11±0.64	0.44±0.66	0.60

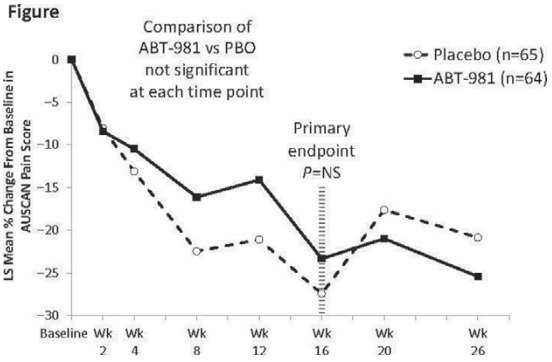
*Verbruggen-Veys, erosive phase (E) + erosive with remodeling (E/R) or† new E or E/R or R.

Table 2

	PBO (n=67)	ABT-981 (n=64)
Any AE/serious AE, %	88/3	91/3
Death, %	0	0
Infection/serious infection, %	51/0	41/0
Injection site reaction, %	16	36
Neutropenia by NCI CTCAE grade, n		
G2 (1000 to <1500/mm^3)	0	9
G3 (500 to <1000/mm^3)	0	3
G4 (<500/mm^3)	0	0

Conclusions: Despite adequate pharmacodynamics results, targeting IL-1 may be ineffective in EHOA, as ABT-981 did not improve outcomes.
Acknowledgements: AbbVie funded the study (NCT02384538); participated in study design, data collection, analysis, and interpretation and in abstract writing, review, and approval; and funded writing support by M. Theisen of CPS.
Disclosure of Interest: M. Kloppenburg Grant/research support from: Pfizer, Consultant for: AbbVie, GlaxoSmithKline, Merck, Levicept, C. Peterfy Shareholder of: Spire Sciences, Inc. (which provides imaging services for clinical trials to multiple pharmaceutical companies), Employee of: Spire Sciences, Inc. (which provides imaging services for clinical trials to multiple pharmaceutical companies), Speakers bureau: Amgen, I. Haugen Consultant for: AbbVie, F. Kroon: None declared, S. Chen Shareholder of: AbbVie, Employee of: AbbVie, L. Wang Shareholder of: AbbVie, Employee of: AbbVie, W. Liu Shareholder of: AbbVie, Employee of: AbbVie, G. Levy Shareholder of: AbbVie, Employee of: AbbVie, R. Fleischmann Grant/research support from: AbbVie, Consultant for: AbbVie, F. Berenbaum Consultant for: AbbVie, Pfizer, Regeneron, D. van der Heijde Consultant for: AbbVie, Amgen, Astellas, AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Daiichi, Eli-Lilly, Galapagos, Gilead, Janssen, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi, UCB, Employee of: Director of Imaging Rheumatology bv., J. Medema Shareholder of: AbbVie, Employee of: AbbVie, M. Levesque Shareholder of: AbbVie, Employee of: AbbVie
DOI: 10.1136/annrheumdis-2017-eular.4947

Figure



OP0169 EARLY OSTEOPHYTES DETECTED BY MRI ARE ASSOCIATED WITH CHANGES IN KNEE PAIN AND STRUCTURES IN OLDER ADULTS: A POPULATION-BASED COHORT STUDY

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Background: Early stage of osteophyte (OP) formations are hard to be detected by radiography, but can be detected by magnetic resonance imaging (MRI). Their subsequent developments on structural and clinical abnormalities are still unknown.
Objectives: To describe the prevalence of early osteophytes (OPs) that were detected by magnetic resonance imaging (MRI) but not by X-ray in older adults and to evaluate the longitudinal associations with knee pain and structural changes.
Methods: 837 participants (mean age 62 years, 50% female) were randomly selected from local community at baseline. T1- or T2-weighted fat suppressed MRI was used to assess knee OPs, cartilage volume, cartilage defects and bone marrow lesions (BMLs) at baseline and after 2.6 years. Knee pain was assessed by self-administered Western Ontario and McMaster Osteoarthritis (WOMAC) Index questionnaire at baseline and after 5 years. X-ray-detected OPs were assessed at baseline using the Osteoarthritis Research Society International atlas. OPs detected only by MRI but not by standard X-ray were defined as early OPs. OPs detected by both MRI and X-ray were defined as definite OPs.
Results: The prevalence of early OPs was 75% while the prevalence of definite OPs was 10% in total knee at baseline. Compared with participants without any OPs, participants with early OPs and with definite OPs had greater cartilage volume loss and increased cartilage defects and BMLs over 2.6 years. Presence of early medial tibiofemoral OPs predicted decreases in total knee pain over 5 years, while definite OPs predicted increases in total knee pain, after adjustment for relevant covariates.

Table 1. Longitudinal associations of OP phenotype status and WOMAC knee pain changes

	Adjusted* β (95% CI)	Adjusted** β (95% CI)
Total		
No OPs (n=103)	*Ref.*	*Ref.*
Early OPs (n=481)	-0.23 (-1.33, 0.88)	-0.28 (-1.40, 0.84)
Definite OPs (n=62)	2.20 (0.51, 3.89)	1.96 (0.17, 3.76)
Medial tibiofemoral		
No OPs (n=447)	*Ref.*	*Ref.*
Early OPs (n=155)	-1.25 (-2.2, -0.30)	-1.51 (-2.50, -0.52)
Definite OPs (n=43)	2.91 (1.21, 4.60)	2.54 (0.74, 4.35)
Lateral tibiofemoral		
No OPs (n=287)	*Ref.*	*Ref.*
Early OPs (n=332)	0.12 (-0.70, 0.94)	-0.05 (-0.91, 0.81)
Definite OPs (n=27)	1.08 (-1.11, 3.27)	0.35 (-1.95, 2.66)

Results of this table are generated from a linear regression model. *Adjusted for age, sex and BMI. **Further adjusted for BMLs and cartilage defects.

Conclusions: Although early OPs are associated with knee abnormal structural changes, they predict decreases in knee pain over time suggesting an adaptive response.
References:
[1] Centers for Disease C, Prevention. Public health and aging: projected prevalence of self-reported arthritis or chronic joint symptoms among persons aged >65 years–United States, 2005–2030. MMWR Morb Mortal Wkly Rep 2003; 52: 489–491.
Acknowledgements: The authors thank the participants who made this study possible, and acknowledge the role of the staff and volunteers in collecting the data, particularly research nurses Boon C and Boon P. Warren R assessed MRIs and Dr Srikanth V and Dr Cooley H assessed radiographs.

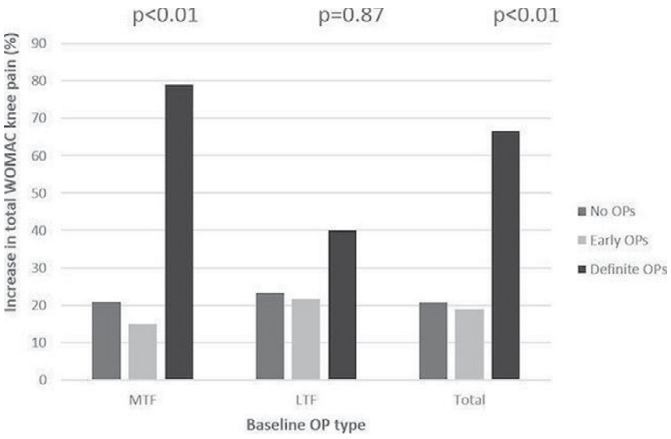

Figure 1

Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.1060

OP0170 LEPTIN AND ADIPONECTIN MEDIATE THE ASSOCIATION BETWEEN BODY MASS INDEX AND HAND AND KNEE OSTEOARTHRITIS

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Background: Associations between adiposity and osteoarthritis (OA) in non-weight-bearing joints suggest that besides mechanical factors also systemic influences contribute to OA. Systemically active substances secreted by adipose tissue, including leptin and adiponectin, are hypothesized to play a role in OA.
Objectives: To examine whether leptin and adiponectin mediate the association between body mass index (BMI) and hand and knee OA.
Methods: Cross-sectional data of a population-based study were used. Participants completed questionnaires and underwent standardized physical examination of hands and knees to define OA according to clinical American College of Rheumatology criteria. Fasting serum leptin and adiponectin were measured with immunoassays. Potential mediation was investigated using the Baron and Kenny framework. Four assumptions were investigated: associations between (1) BMI and OA (pathway *C*), (2) BMI and adipokines (pathway *A*), (3) adipokines and OA (pathway *B*), and (4) attenuation of the total association between BMI and OA after including adipokines (pathway *C'*). No exposure-mediator interaction and mediator-outcome confounding was assumed. Assumptions were investigated using logistic and linear regression analyses as appropriate. Odds Ratios (ORs) were calculated per standard deviation (SD) difference in BMI, and per ten and five units difference in leptin and adiponectin, respectively. Percentage mediation with 95% confidence intervals (CIs) was estimated, only when all four assumptions were fulfilled. Models were adjusted for age, ethnicity and education, and stratified by sex.
Results: In 6462 participants (56% women, median age 56 years (range 45–65), mean BMI 26.3 kg/m^2), prevalence of hand OA, knee OA and combined hand and knee OA were 8%, 10% and 4%, respectively. Median leptin and adiponectin concentrations were 7.1 ug/L (range 0.9–60.9) and 6.0 mg/L (0.5–23.7) in men, and 19.1 ug/L (0.5–262.0) and 10.5 mg/L (0.5–98.6) in women. BMI was positively associated with OA presence and serum leptin in both men and women (Table). A negative association was observed between BMI and serum adiponectin (-0.73 mg/L per SD BMI, 95% CI -0.55;-0.91). Leptin was positively associated with most OA types, except knee OA in men. Leptin partially mediated the association of BMI with hand OA in men (9% mediation, 95% CI 5;17) and women (30%, 13;198), and the association of BMI with knee OA in women (15%, 12;21). Similar analyses for adiponectin revealed a negative association of adiponectin with hand OA in men and partial mediation of the association of BMI with hand OA in men (19%, 12;37), whereas mediation was absent in other subgroups.
Conclusions: Leptin partially mediated the association of BMI and hand OA in both men and women, as did adiponectin in men. In addition, mediation by leptin for the association of BMI and knee OA was demonstrated in women. These findings suggest that systemic mediators contribute to hand OA, and to a lesser extent to knee OA.

Table. Associations of BMI with leptin and different types of OA (OR, 95% CI)

MEN	Pathway A BMI – log leptin* β (95% CI)		Pathway B Leptin – OA OR (95% CI)	Pathway C BMI – OA OR (95% CI)	Pathway C' BMI – OA OR (95% CI)	Mediation % % (95% CI)
SD BMI: 3.72	1.70 (1.64 – 1.77)	Hand OA	1.30 (1.13 – 1.50)	1.39 (1.18 – 1.64)	1.34 (1.06 – 1.70)	8.6 (5.4 – 17.2)
		Knee OA	1.14 (0.98 – 1.43)	1.25 (1.06 – 1.48)	^	^
		Hand and knee OA	1.28 (1.07 – 1.52)	1.59 (1.31 – 1.93)	1.82 (1.39 – 2.39)	^
WOMEN	Pathway A BMI – log leptin* β (95% CI)		Pathway B Leptin – OA OR (95% CI)	Pathway C BMI – OA OR (95% CI)	Pathway C' BMI – OA OR (95% CI)	Mediation % % (95% CI)
SD BMI: 4.88	1.82 (1.77 – 1.88)	Hand OA	1.08 (1.01 – 1.15)	1.18 (1.01 – 1.37)	1.12 (0.89 – 1.40)	30.3 (13.3 – 198.2)
		Knee OA	1.21 (1.14 – 1.29)	1.62 (1.42 – 1.85)	1.50 (1.25 – 1.81)	15.4 (11.7 – 21.3)
		Hand and knee OA	1.13 (1.05 – 1.22)	1.48 (1.26 – 1.74)	1.55 (1.25 – 1.93)	^

BMI, body mass index; CI, confidence interval; OA, osteoarthritis; OR, Odds Ratio; SD, standard deviation. Adjusted for age, ethnicity and education. *logarithmic transformation performed to obtain normal distribution. ^Mediation not calculated (no association within pathway B). ^Mediation not calculated (no attenuation of the total association of BMI and OA after including leptin in the model).

Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.3394

OP0171 SIGNAL INTENSITY ALTERATION WITHIN INFRAPATELLAR FAT PAD PREDICTS TOTAL KNEE ARTHROPLASTY WITHIN FOUR YEARS: DATA FROM THE OSTEOARTHRITIS INITIATIVE

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Background: Osteoarthritis (OA) is a common joint disease that frequently affects the knee and is the leading cause of total knee arthroplasty (TKA) in Western countries. The most common reason for TKA is to ease pain and disability. Investigation on prognostic factors associated with TKA could be a possible way to find therapeutic targets to slow disease progression and delay the time for knee replacement.
Objectives: To investigate whether infrapatellar fat pad (IPFP) signal intensity (SI) alteration predicts the occurrence of TKA in patients with knee OA over 4 years.
Methods: Participants with symptomatic knee OA were selected from the Osteoarthritis Initiative (OAI) study. Case knees (n=127) were defined as those that received TKA during 4 years follow-up visit. They were matched by gender, age and radiographic status measured at baseline with a control knee. We used T2 weighted MR images to measure IPFP SI alteration using a newly developed algorithm in MATLAB. The measurements were assessed at OAI baseline (BL), T0 (the visit when TKA was reported), 1 year prior to T0 (T1). Conditional logistic regression was used to assess the relationship between cases and control knees and assess the risk of TKA in regard to SI alteration.
Results: Participants (n=237) were mostly female (57%), with average age of 63.7±8.5 years old and mean BMI of 29.5±4.7 kg/m^2. In multivariable analysis, standard deviation of IPFP SI [sDev (IPFP)] and the ratio of high SI region volume to whole IPFP volume [Percentage (H)] measured at BL were significantly associated with TKA after adjustment for BMI, knee bending activities, self-reported knee injury and surgery history (HR: 3.5, 95% CI 1.1 to 11.4; HR: 8.9, 95% CI 1.2 to 67.2). IPFP SI alterations measured at T1 including sDev (IPFP), Percentage (H) and clustering effect of high SI [Clustering factor (H)] were significantly associated with TKA (HR: 4.0, 95% CI 1.2 to 13.2; HR 10.9, 95% CI 1.9, 63.6; HR: 1.8, 95% CI 1.1 to 2.9). All measurements including mean value of IPFP SI [Mean (IPFP)], sDev (IPFP), mean value of IPFP high SI [Mean (H)], standard deviation of IPFP high SI [sDev (H)], median value of IPFP high SI [Median (H)], upper quartile value of IPFP high SI [UQ (H)], Percentage (H), Clustering factor (H) were significantly associated with TKA at T0.
Conclusions: IPFP SI is an important predictor for TKA in knee OA patients. Targeting IPFP SI could be a potential way to reduce the need for future TKA.
Acknowledgements: Special thanks go to the participants who made this study possible, the OAI investigators, staff, participants and the funding of POMA study.
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.1163

THURSDAY, 15 JUNE 2017

Cellular drivers of inflammation in rheumatic disease

OP0172 EXPANDED T-CELL CLONES PRESENT IN SYNOVIUM AT ONSET OF RHEUMATOID ARTHRITIS ARE ALREADY PRESENT IN THE SYNOVIUM IN THE SEROPOSITIVE "AT RISK" STAGE

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Background: T-cells are thought to be key players in the initiation and progression