THU0104 BOTH MRI AND HAQ-DI CAN PREDICT RELAPSES FOLLOWING ALL TREATMENT WITHDRAWAL IN MTX-NAÏVE PATIENTS WITH RA IN REMISSION AFTER 12 MONTHS OF ABATACEPT THERAPY IN THE AVERT TRIAL

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Background: Factors predictive of relapse need to be identified to aid therapy withdrawal decisions for patients with RA achieving remission with treatment. AVERT (NCT01142726) was a Phase IIIb, randomized, active-controlled trial in patients with early RA.[1] After a 12-month, double-blind treatment period with abatacept + MTX, or abatacept or MTX monotherapy, patients with DAS28 [CRP] <3.2 could enter a 12-month withdrawal period (all treatment stopped).
Objectives: To evaluate *post hoc* whether MRI scores, patient characteristics and disease activity at Month 12 were predictors of clinical relapse at Month 18 and Month 24 after treatment withdrawal in AVERT.
Methods: Synovitis, erosion and bone oedema in the dominant hand and wrist MRI were scored at Month 12 using the RA MRI scoring system (RAMRIS). Patient characteristics (pain, age, weight, HAQ-DI) and disease measures (CRP, SJC28, TJC28, DAS28 [CRP], CDAI, SDAI) were recorded at Month 12. The influence of these factors on the proportion of patients who relapsed (doubling of TJC28 and SJC28, and DAS28 [CRP] ≥1.2 increase relative to Month 12) by Month 18 and Month 24 was assessed.
Results: A total of 172 patients achieving DAS28 remission (DAS28 [CRP] <2.6) at Month 12 in any treatment group were included in the analysis. Numbers of patients who relapsed at Month 18 and Month 24 were 100 and 113, respectively. Of the patient characteristics, disease activity and imaging factors analysed at Month 12, only MRI synovitis, erosion and oedema scores, as well as HAQ-DI scores, were significantly associated ($p<0.05$) with relapse status at both Month 18 and Month 24 (Table).
Conclusions: MRI and HAQ-DI scores in patients in DAS28 remission predicted clinical relapses 6 and 12 months after complete drug withdrawal in the AVERT trial. The clinical decision on whether to withdraw therapy in MTX-naïve patients with RA in remission may benefit from an assessment of imaging and physical function prior to drug withdrawal.
References:
[1] Emery P, et al. Ann Rheum Dis 2015;74:19–26.
Disclosure of Interest: H. Ahmad Shareholder of: Bristol-Myers Squibb, Employee of: Bristol-Myers Squibb, J. Baker: None declared, M. Østergaard Grant/research support from: AbbVie, Bristol-Myers Squibb, Janssen, Merck, Speakers bureau: AbbVie, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Eli Lilly, Centocor, GSK, Hospira, Janssen, Merck, Mundipharma, Novartis, Novo Nordisk, Orion, Pfizer, Regeneron, Schering-Plough, Roche, Takeda, UCB, Wyeth, P. Emery Grant/research support from: AbbVie, Merck, Pfizer, Roche, Consultant for: AbbVie, Bristol-Myers Squibb, Merck, Pfizer, Roche, Lilly, Novartis, Samsung Bioepis, T. Huizinga Grant/research support from: EU & Dutch Arthritis Foundation, Consultant for: Abbott Laboratories, Biotest AG, Bristol-Myers Squibb, Crescendo Biosciences, Inc, Novartis Pharmaceuticals Corporation, Pfizer Inc, Roche, sanofi-aventis, Schering-Plough, UCB, Inc., Eli Lilly, Speakers bureau: Abbott Laboratories, Biotest AG, Bristol-Myers Squibb, Novartis Pharmaceuticals Corporation, Pfizer Inc, Roche, sanofi-aventis, Schering-Plough, J. Ye Shareholder of: Bristol-Myers Squibb, Employee of: Bristol-Myers Squibb, S. Banerjee Shareholder of: Bristol-Myers Squibb, Employee of: Bristol-Myers Squibb, P. Conaghan Grant/research support from: Bristol-Myers Squibb, Consultant for: AbbVie, Lilly, Novartis, Pfizer, Speakers bureau: AbbVie, Bristol-Myers Squibb, Roche
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THU0105 PREDICTION OF RESPONSE TO CERTOLIZUMAB-PEGOL IN RHEUMATOID ARTHRITIS (PRECEPRA) BY FUNCTIONAL MRI OF THE BRAIN – AN INTERIM ANALYSIS OF AN ONGOING INVESTIGATOR INITIATED PHASE III TRIAL

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Background: Tumor necrosis factor inhibitors (TNFi) signify a major advance in the treatment of rheumatoid arthritis (RA). However, treatment success initially remains uncertain as one third of patients do not respond adequately to TNFi.
Objectives: We investigated whether brain activity associated to arthritis measured by functional magnetic resonance imaging (fMRI) can function as a predictor of response to TNFiin RA patients.
Methods: This is an interim analysis of the first 50 patients of the PreCePRA trial, a multi-center, double-blind, placebo-controlled fMRI trial on patients with RA. [1] [2] Active RA patients failing csDMARDs with a DAS28-ESR >3.2 and at least three tender and/or swollen joints received a baseline brain BOLD fMRI scan upon joint compression at screening. Patients werethen randomized into a 12-week double-blinded treatment phase with placebo (arm 1) or 200mg certolizumab-pegol eow (arm 2; fMRI Bold signal>2000 voxel i.e. $2cm^3$, arm 3; fMRI Bold signal <2000 voxel). LDA 3mo. Primary end point was DAS28-ESR low disease activity at 12 weeks. A 12 weeks follow-up phase in which patients were switched from the placebo to the treatment arm folowed the blinded phase. fMRIwas carried out at baseline as well as after 12 and 24 weeks of or placebo.
Results: In 31 patients (responders) baseline signal volume i.e. sum of significantly coupled voxels after the FDR thresholding was significatly higher compared to 19 patients (non-responders) ($p<0.001$) allowing discrimination between the two groups prior to treatment. In responders we detected an persitent decrease of the BOLD volume from baseline to week 12 and week 24 ($r^2=0.561$) whereas the BOLD volume in non-responders persitently increased ($r^2=0.589$).

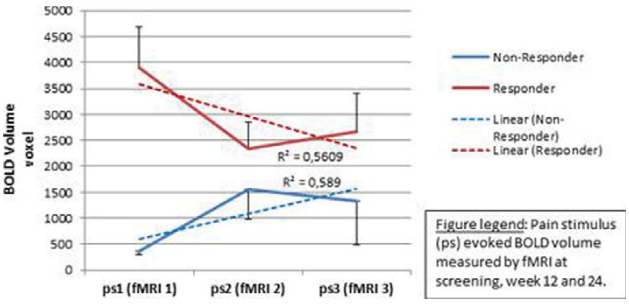

Figure legend: Pain stimulus (ps) evoked BOLD volume measured by fMRI at screening, week 12 and 24.

Conclusions: Based on this interim analysis we conclude that high BOLD volumes in fMRI, indicating high-level brain representation of pain in arthritis. These data represent the first encouring signal of the PreCePRA brain fMRI study supporting the concept that increased RA-related brain activity is related to response to TNFi.
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THU0106 ROUTINE CLINICAL ASSESSMENT OF JOINT DAMAGE TO EVALUATE OUTCOME IN RHEUMATOID ARTHRITIS

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Background: Early treatment of rheumatoid arthritis (RA) with treat-to-target strategies aims to reduce disease activity and to prevent joint damage. Assessment of the quality of care is commonly based on measurements of disease activity, functioning and well being. In clinical trials, radiographic scores are widely used to assess structural joint damage, but these are not applicable in routine care and limited to hands and feet. Only a few studies evaluated clinical assessment of irreversible joint damage (e.g. surgery) as outcome. The RA articular damage (RAAD) score counts structural damage in all joints that that are affected by RA[1]. It correlates with radiographic damage[2]. We have applied this score since 2014 in routine care.

Abstract THU0104 – Table 1. MRI and HAQ-DI Scores at Month 12 in Patients With vs Without Relapse by Month 18 and Month 24*

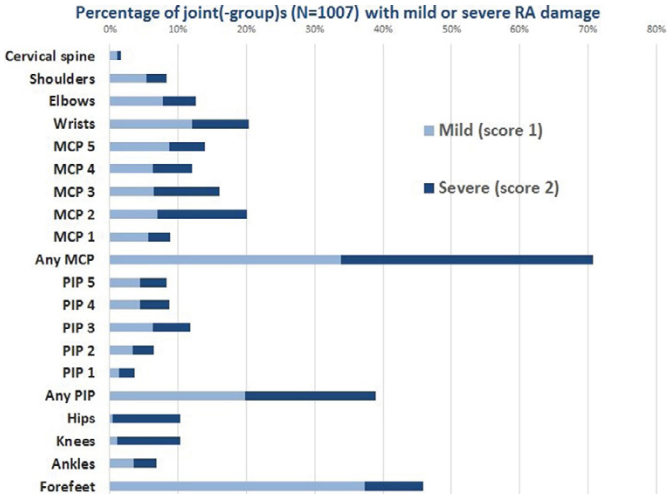
	Patients with vs without relapse at Month 18		Patients with vs without relapse at Month 24	
Score	Estimated difference in scores at Month 12 (95% CI)	p value	Estimated difference in scores at Month 12 (95% CI)	p value
MRI synovitis	1.051 (0.291, 1.810)	0.0070	1.088 (0.256, 1.920)	0.0107
MRI erosion	3.244 (1.694, 4.795)	<0.0001	3.076 (1.550, 4.601)	0.0001
MRI oedema	1.503 (0.650, 2.356)	0.0007	1.423 (0.644, 2.202)	0.0004
HAQ-DI	0.194 (0.050, 0.338)	0.0088	0.201 (0.050, 0.353)	0.0095

*Month 18: 92 with relapse, 63 without relapse; Month 24: 103 with relapse, 52 without relapse.

Objectives: Evaluate the feasibility of a simple clinical joint damage score and describe the increment over time in RA patients with varying disease duration.
Methods: Cross-sectional study in all patients with a clinical diagnosis of RA visiting the outpatient clinic in 2015 and 2016. Rheumatologists and nurses from the outpatient department of a large regional hospital received a single training to perform the RAAD score. Scores of 0 (no damage), 1 (mild) or 2 (severe: ankylosis, luxation or joint surgery) were assigned to 35 joints (maximum score: 70) with a disease activity score, and stored in the electronic patient record system. Baseline data including ACR 2010 criteria were also registered.
Results: In 1007 (67.3%) of 1496 RA patients seen over 2 years RAAD-scores were performed. 652 (64.7%) were female, average age (SD, range) was 62.6 (13.1, 19–95), disease duration 9.9 (9.6, 0–65) years. Rheumatoid factor and ACPA were positive in 70.6% and 70.3% respectively.
RAAD scores related to disease duration illustrate that at disease onset 86%, and after 20 years 37% of the patients has no joint damage (Table). Distribution over joints shows the classical predominance of damage in MCP, PIP and MTP joints (Image). Structural damage in shoulders or elbows was present in 8.3% and 12.5%, in knees and hips in 10,3% each. Despite current treatment strategies, irreversible joint damage of more than 5 joints is present in 6.3% within 10 years.

Table 1. Accumulation of irreversible joint damage score with disease duration, number (%)

RAAD-score	1st year (N=69)	2–4 yrs (N=228	5–9 yrs (N=253)	10–19 yrs) (N=239)	≥20 yrs (N=218)
0 (no joint damage)	59 (86)	158 (69.3)	145 (57.3)	81 (33.9)	80 (36.7)
1–5	8 (12)	65 (28.5)	92 (36.4)	103 (43.1)	42 (19.3)
6–10	2 (3)	4 (1.8)	11 (4.3)	34 (14.2)	28 (12.8)
11–20			4 (1.6)	13 (5.4)	36 (16.5)
>20		1 (0.4)	1 (0.4)	8 (3.3)	32 (14.7)
Average (range)	0,4 (0–6)	0,9 (0–23)	1,6 (0–37)	2,2 (0–18)	9,0 (0–59)



Conclusions: Clinical assessment of joint damage is a feasible parameter of long term outcome in RA. Reflecting overall joint damage, the RAAD-score provides a broader view than radiographic scoring of hands and feet and is easy to apply in routine care. Given the slow increment a single assessment per 5 years may suffice to compare structural joint damage across cohorts of patients.
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THU0107 ASSOCIATION OF GLOBAL DNA METHYLATION WITH MTX RESPONSE AND ADVERSE EVENTS IN EARLY RHEUMATOID ARTHRITIS

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Background: Methotrexate (MTX) is a first-line therapy in early Rheumatoid Arthritis (RA). However, ~30% of treated patients do not respond to the medicine or need to abrogate treatment because of severe adverse events. Since MTX interferes with the folate cycle and thereby influences the methylation cycle, we hypothesize that methylation status at start therapy is associated with response and adverse events after three months of MTX treatment enabling personalized medicine.
Objectives: Examine global methylation status of early Rheumatoid Arhtritis patients before and after 3 months of MTX use between responders and non-responders and patients that do or do not experience adverse events.
Methods: To assess global methylation status, DNA was isolated at baseline from whole blood of 120 patients from the Treatment in the Rotterdam Early Arthritis Cohort (tREACH), a multicenter, stratified single-blind clinical trial of patients with early RA. Methylation status of 7 CpG sites within Long-interspersed nuclear elements (LINE-1) were analyzed and quantified by Matrix Assisted Laser Desorption Ionization time of flight Mass Spectrometry (MALDI-TOF MS). Results were compared between MTX responders and non-responders based on a low disease activity (DAS28 <3.2) at three months of treatment and patients experiencing ≤2 or ≥3 adverse events. Gastrointestinal adverse events were assessed separately.
Results: No statistical differences in the mean of 7 LINE-1 CpGs were observed between responders and non-responders, nor in patients experiencing ≤2 or ≥3 adverse events. However, methylation status of specific CpG sites within LINE-1 did show significant changes. Baseline CpG_2 methylation levels were positively correlated with the DAS28 score at t3 (p=0.018) and baseline methylation levels in CpG_5 and CpG_8.9 were significantly higher in patients experiencing ≥3 adverse events (p=0.018 and p=0.034, respectively). Besides, CpG_5 methylation levels were particularly increased in patients experiencing gastrointestinal adverse events (p=0.038).
Conclusions: Global methylation status is associated with non-response and adverse events to MTX in early RA patients and can therefore be implemented in future prediction models.
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THU0108 SUBCLINICAL CENTRAL NERVOUS SYSTEM DAMAGE IN PATIENTS WITH RHEUMATOID ARTHRITIS: DISEASE ACTIVITY AND CYTOKINES

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Background: We aimed in this study to investigate blood-brain barrier (BBB) dysfunction in RA patients who had no neurological symptoms, and were receiving synthetic DMARD treatment.
Objectives: We investigated correlations between cranial MRI images and brain specific proteins (S100 Beta, GFAP), cytokines (IL-1 beta, IL-17) in plasma which had important roles in disease activity.
Methods: In our study, 57 patients (46 females and 11 males) were included included in RA group, and 34 patients (24 females and 10 males) in the control group. All of RA patients were receiving synthetic DMARD treatment. Demographic characteristics of all patients were recorded. Disease activity was evaluated by using DAS-28. Mini-mental test (MMT) was used for evaluation of cognitive functions, and Fazekas scale was used to evaluate cranial MR lesions. S100 beta, GFAP, claudin, IL-17, and IL-1 beta levels were measured in peripheral blood of both groups.
Results: Demographic characteristics were similar between the groups, and there was no statistically significant difference in gender, age, and body mass index (BMI) between patient and control groups (p>0.05). S100 beta, and GFAP levels were significantly higher in RA group (p<0.05). No difference was determined in hyperintense lesions diagnosed in cranial MR between patient and control groups (p>0.05). There were positive correlations between IL-17 S100 beta and GFAP, and IL-1 beta and S100 beta.
Conclusions: In our study, we have shown that blood-brain barrier may be damaged subclinically in RA patients, brain specific proteins related to BBB dysfunction may be increased in the peripheral blood, and BBB dysfunction may be related to cytokines which play an important role in disease pathogenesis. In conclusion, cytokines which circulate in the peripheral blood in RA may cause subclinical BBB damage. Further large scale studies with long-term follow-up are required which will support this hypothesis.
Disclosure of Interest: None declared
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THU0109 UPDATED ESTIMATION OF THE EQ5D QUALITY OF LIFE QUESTIONNAIRE UTILITY VALUES THROUGH HAQ-DI MAPPING FOR SPAIN

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Background: Rheumatoid arthritis (RA) deeply affects the quality of life (QoL) of patients. The preferred approach to evaluate treatment efficiency is to value health as patient preferences known as utilities, and subsequently, calculate Quality-Adjusted Life Years gained. A new 5-level of severity EQ5D has recently released and a new tariff proposed for Spain (Ramos-Goñi,2016). Although QoL questionnaires are not of routine use in clinical practice, it is possible to estimate it using the Health Assessment Questionnaire Disability Index (HAQ-DI)
Objectives: To develop a function that allows the estimation of EQ5D-5L utility values from HAQ-DI updated to the newest proposed tariff for Spain