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FRI0113 VALIDATION AND RESULTS OF THE SYMPTOMS IN PERSONS AT RISK OF RHEUMATOID ARTHRITIS (SPARRA) QUESTIONNAIRE

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Background: A range of symptoms can be present in persons at risk of rheumatoid arthritis (RA). However, information on the nature, location, timing, severity and predictive value of these symptoms is largely lacking. The Symptoms in Persons At Risk of Rheumatoid Arthritis (SPARRA) questionnaire has been developed with support from EULAR, informed by data from a qualitative study¹ and with input from patient research partners.

Objectives: To test the psychometric properties of the SPARRA questionnaire in an international group of arthralgia patients at risk of RA and to quantify these symptoms.

Methods: The SPARRA questionnaire contains questions about presence, severity, impact and location of 13 symptoms. 240 individuals (69% rheumatoid factor and/or ACPA positive, 23% seronegative with clinically suspect arthralgia and 8% first degree family members of patients with RA) completed the questionnaire in the Netherlands (N=125), United Kingdom (N=70), Sweden (N=15), Austria (N=11) and Switzerland (N=19). Individuals had no history or presence of clinically diagnosed arthritis at the time of first physical examination. Reliability (test-retest) and validity (face, content and construct validity) were tested.

Results: Face validity was tested by a group of experts on the at-risk phase of RA and feedback on the questionnaire was asked and received from 30 arthralgia patients, leading to only minor comments. The test-retest within 7–14 days (N=51) showed moderate to good agreement (kappa mean 0.565, range 0.309–1; agreement mean 71%, range 59–100%). The content validity was high, in line with the fact that the items were derived from a qualitative study in seropositive arthralgia patients. In contrast, the construct validity (relation to visual analog scale scores (VAS) for pain and well-being) was low (R-square 0.040–0.199), suggesting that the questions measure different elements in different time frames and grasp symptom content not captured with regular VAS pain/well-being. Most symptoms were present in a high percentage of individuals, with pain, stiffness and fatigue as the most common ones. When a symptom was present, it was usually experienced as moderate to severe, and with moderate impact. ACPA positive individuals reported lower presence of symptoms than ACPA negative individuals (mean 47% for ACPA-positive (N=118), 41% for only RF positives (N=53) and 59% in seronegative individuals (N=69)), but functional impact was higher in ACPA positive individuals (51%, versus 42% in seronegatives, NS). Note that the inclusion criteria for the seronegative individuals was presence of symptoms.

Conclusions: This study provides evidence of good psychometric properties of the SPARRA questionnaire, except for low construct validity. This means the questionnaire adds information to currently available clinical measures in persons at risk of RA. Future studies are needed to evaluate whether SPARRA data can help to improve the prediction of RA.

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FRI0114 ALLOGRAFT INFLAMMATORY FACTOR 1 (AIF1) POLYMORPHISMS RS4711274 (G/A) AND RS2269475 (C/T) MAY PREDICT ETANERCEPT PLUS METHOTREXATE RESPONSE IN FRENCH CAUCASIAN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Several risk loci for Rheumatoid Arthritis (RA) have been identified by Genome Wide Association Studies (GWAS), but they do not include Allograft Inflammatory Factor 1 (AIF1). Nevertheless, a few studies have shown that AIF1 rs2269475 (C/T) is associated with RA^{1,2}.

Objectives: We propose 1) To examine associations in French Caucasian patients with RA, of the seven most described AIF1 SNPs; 2) To study their linkage disequilibrium with HLA-DRB1 alleles; 3) To evaluate whether AIF1 single nucleotide polymorphisms (SNPs) could predict first line treatment responses in RA.

Methods: We amplified the AIF1 gene region containing the 7 SNPs and sequenced PCR products on a total of 469 individuals, including 95 Anti-Citrullinated Protein Antibody (ACPA) positive RA patients, 146, patients with scleroderma, 132 healthy controls and 96 additional healthy controls selected from a large database of volunteer bone marrow donors (VBMD) for carrying at least one RA-associated allele. Patients and controls were HLA-DRB1 genotyped. Patients with RA were divided into 2 groups, a first group called “non responders” was defined as patients who did not respond to first-line methotrexate (MTX) combined with Etanercept and a second group called “good responders” was defined as patients who did respond to methotrexate combined with Etanercept.

Results: Two SNPs were associated with RA: rs4711274 (G/A) and rs2269475 (C/T). The frequency of minor allele carriers was respectively 37% (A) and 36% (T) in patients with RA versus 18% among controls (p=0.0014 and p=0.001). Furthermore, patients with RA-associated HLA-DRB1 alleles carried more often minor alleles for both SNPs (p=0.0005). Preliminary clinical data show that 56% of non-responders (N=16) carried the minor alleles of both rs4711274 and rs2269475 compared to only 21% of good responders (N=24, p=0.02).

Conclusions: AIF is an inflammation-responsive protein encoded within the HLA class III region on chromosome 6 (6p21.3). As already described in British and Polish Caucasians, we found a significant AIF1 Rs2269475 association with RA. We also found an association with Rs4711274 in linkage disequilibrium with the former. The increased frequency of minor AIF1 alleles in RA was not associated with a particular HLA-DRB1 allele, but to any HLA-DRB1 allele carrying the shared epitope.

Finally, patients who failed to respond to Etanercept and MTX carried more often minor alleles of the 2 described AIF1 SNPs.

Further analysis on a larger groups of patients is required to confirm whether AIF1 SNPs can predict response to therapy with Etanercept and Methotrexate.

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FRI0115 EVER-SMOKING IS ASSOCIATED WITH DISEASE SEVERITY AND OPIOID USE IN RHEUMATOID ARTHRITIS

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Background: Cigarette smoking, both current and past, is a risk for incident rheumatoid arthritis (RA), even for those with low exposure rates of 1–10 pack years. Current smoking is also associated with severity of disease and poorer response to treatments. It is however not known whether any exposure to cigarettes impacts disease expression, especially for those who have discontinued smoking.

Objectives: To assess the disease severity in RA according to smoking status (ever-, past-, current-, non-smoker).

Methods: As part of a study to examine cigarette and marijuana smoking in rheumatic disease patients, consecutively attending rheumatology patients completed an anonymous self-administered questionnaire including: pain severity on visual analog scale (VAS), patient global assessment (PtGA) and cigarette or marijuana smoking status. Concomitant physician recorded information included: sociodemographics, co-morbidities, treatments for RA, physician global assessment (PGA). Patients were categorized according to smoking status. Categorical variables were compared between groups with the Chi-Square test and continuous variables with the Student's t-test. Variables showing a statistical trend (p<0.15) in univariate analysis were considered in multivariate logistic regression.

Results: Over a 2-month period (April-May 2014), there were 248 (25%) RA attendees of 1000 participants. Significant differences were observed between current, past and non-smokers in regard to age [mean (SD): 59.5 (10.0) vs. 65.2 (10.6) vs. 61.0 (18.2) years; $p=0.034$], gender (male: 23.9% vs. 30.3% vs. 14.6%; $p=0.027$), unemployment due to disability (13.3% vs. 3.1% vs. 4.9%; $p=0.044$), number of RA medications [mean (SD): 2.3 (1.1) vs. 2.1 (1.1) vs. 1.8 (1.1); $p=0.019$], DMARD use (78.3% vs. 82.8% vs. 64.1%; $p=0.008$), opioid use (19.6% vs. 10.1% vs. 3.9%; $p=0.009$), pain [mean (SD): 5.0 (3.3) vs. 4.0 (2.9) vs. 3.7 (2.6) cm; $p=0.040$] and PGA [mean (SD): 3.8 (2.8) vs. 3.1 (2.8) vs. 3.0 (2.4); $p=0.039$]. Recreational marijuana was used by 3 non cigarette smokers only, with 1 also reporting medicinal marijuana use. Ever smokers vs. non-smokers used a greater number of RA medications [mean (SD): 4.3 (3.0) vs. 3.7 (2.6); $p=0.081$], were more likely to use DMARDs (81.4% vs. 64.1%; $p=0.003$) and opioids (13.1% vs. 3.9%; $p=0.014$), and showed a trend towards more pain [mean (SD): 4.3 (3.0) vs. 3.7 (2.6); $p=0.081$]. In multivariate analysis, male gender (OR=2.193; $p=0.025$) and DMARD use (OR=2.376; $p=0.010$) were significantly associated with ever smoking while opioid use (OR=2.784, $p=0.103$ for ever smoking; OR=3.561, $p=0.074$ for current smoking) showed a statistical trend.

Conclusions: Current, but also ever cigarette use, was associated with worse RA disease as indicated by the use of more drug categories, and more likely use of DMARDs to treat RA, and a trend to more pain and opioids. The combination of opioids and cigarettes may be a manifestation of a patient "chemical coping" strategy in RA patients.

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FRI0116 A HIGH LEVEL OF CLINICAL RESPONSE BASED ON COMPOSITE INDICES IS ASSOCIATED WITH IMPROVED HEALTH-RELATED QUALITY OF LIFE: ANALYSES FROM A PHASE 3 CLINICAL TRIAL IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Rheumatoid arthritis (RA) is a chronic disease associated with inflammatory activity and joint damage that result in disability, pain, and other impairments. The current recommendation is to assess disease activity based on composite indices with objective signs of inflammation (e.g. synovitis, acute phase reactants) and patient's assessment of disease activity. The patient's perception of disease impact and its treatment also facilitate shared decision-making about treatment.

Objectives: To compare patient-reported outcomes (PROs) for RA patients who achieved low disease activity (LDA) or remission based upon the DAS28-ESR compared to those with moderate and high disease activity (MDA and HDA) in this post-hoc analysis of a randomized, double-blind phase 3 clinical trial, RA-BEAM¹.

Methods: 1305 patients were randomized to placebo (N=488), adalimumab (N=330) or baricitinib 4 mg (N=487). Patients with observed DAS28-ESR values at Week 24 (N=1,010) were divided into 4 disease activity groups: HDA (DAS28-ESR>5.1), MDA (3.2<DAS28-ESR≤5.1), LDA (2.6≤DAS28-ESR≤3.2), or remission (DAS28-ESR<2.6). Change from baseline to Week 24 were assessed for the pain visual analogue scale (VAS, 0–100 mm), Health Assessment Questionnaire-Disability Index (HAQ-DI) and SF-36 physical and mental component score (PCS and MCS) for the intent-to-treat (ITT) patients.

Results: Patients with HDA and MDA at Week 24 had greater baseline pain and HAQ-DI scores and lower PCS and MCS scores than patients achieving LDA or remission at Week 24. Lower disease activity at Week 24 was associated with improvement in pain, HAQ-DI, SF-36 PCS and MCS at Week 24. Among patients who achieved remission, residual pain was observed, with close to 40% still experiencing some level of pain and 20% of patients in remission at Week 24

Table 1. Improvement in disease activity is associated with improved PROs.

PRO Measures	Outcomes at Week 24	Disease Activity at Week 24			
		HDA DAS28-ESR>5.1 N=210	MDA 3.2<DAS28-ESR≤5.1 N=490	LDA 2.6≤DAS28-ESR≤3.2 N=142	Remission DAS28-ESR<2.6 N=168
Pain VAS	Baseline	65.8	61.3	56.6	51.9
	LSM Change	-10.6	-31.0 ^a	-43.2 ^{ab}	-46.7 ^{ab}
	Pain VAS≤10, %	1.4	19.0 ^a	48.6 ^{ab}	60.7 ^{ab}
	Pain VAS≤20, %	7.6	37.1 ^a	70.4 ^{ab}	79.2 ^{ab}
HAQ-DI	Baseline	1.8	1.6	1.4	1.2
	LSM Change	-0.3	-0.7 ^a	-1.0 ^{ab}	-1.0 ^{ab}
SF-36 PCS	Baseline	29.7	32.1	34.3	37.2
	LSM Change	3.3	8.0 ^a	12.9 ^{ab}	13.6 ^{ab}
SF-36 MCS	Baseline	44.3	46.2	46.7	49.8
	LSM Change	1.8	4.1 ^a	5.6 ^a	5.2 ^a

^avs0.05 compared to DAS28-ESR>5.1; ^bvs0.05 compared to 3.2<DAS28-ESR≤5.1; LSM=least squares mean

had a residual pain score>20. Sensitivity analyses using other clinical measures (DAS28-CRP, SDAI, CDAI) to define disease activity confirmed the findings.

Conclusions: Improving patient disease activity is associated with improved health-related quality of life. Patients who achieved remission had greater improvement in PROs but residual pain remained. Further research is needed to understand the treatment differences in the association between disease activity and PROs among different therapies.

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FRI0117 CHRONOLOGICAL CHANGES IN ACHIEVING J-HAQ REMISSION IN PATIENTS WITH EARLY-STAGE RHEUMATOID ARTHRITIS IN THE IORRA COHORT

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Background: With the introduction of biologic disease-modifying antirheumatic drugs (DMARDs) and the increase in the approved maximum dose of methotrexate in our country, the treatment of rheumatoid arthritis (RA) has advanced dramatically in the past 2 decades. Consequently, many patients were able to achieve clinical remission and low radiographic progression rates¹⁻³. In view of these dramatic changes in RA treatment, we investigated whether the Japanese version of the Health Assessment Questionnaire (J-HAQ) improved chronologically due to improved treatment over time.

Objectives: To investigate chronological changes in achieving J-HAQ remission and the factors related to J-HAQ remission in Japanese patients with an early stage of RA.

Methods: RA patients who enrolled in the IORRA cohort for the first time between 2000–2002 (Term 1), 2005–2007 (Term 2), and 2010–2012 (Term 3) and were within 2 years of disease onset were examined. For each patient in Term 3, one patient was extracted from Term 1 and Term 2 by matching the sex, age, and J-HAQ score. Among them, patients with J-HAQ >0.5 at study entry (baseline) were selected; the time to achieve J-HAQ remission (J-HAQ ≤0.5) and the J-HAQ remission rate at 3 years were analyzed. Multivariate analysis was performed to assess factors related to achieving J-HAQ remission.

Results: In each term, 348 RA patients were extracted. At baseline, the average J-HAQ of all 1,044 patients was 0.52. Baseline characteristics of 408 patients with baseline J-HAQ >0.5 were as follows: female, 89.0%; mean age, 56.3 years; anti-cyclic citrullinated peptide (anti-CCP) antibody positivity, 78.0%; mean Disease Activity Score with 28-joint count (DAS28), 4.37; and mean J-HAQ, 1.11. The mean time from baseline to achieving J-HAQ remission became significantly shorter chronologically (Term 1: 2.2 years; Term 2: 1.8 years; Term 3: 1.7 years; $p<0.005$, Fig.1). J-HAQ remission rates significantly increased in both Term 2 (55.2%) and Term 3 (57.4%) compared with Term 1 (37.5%; $p<0.005$). The factors significantly related to achieving J-HAQ remission at 3 years were younger age (OR 1.02; 95% CI 1.00–1.04) and enrollment in Term 2 (OR 2.0; 95% CI 1.2–3.5) or Term 3 (OR 2.3; 95% CI 1.3–4.1) compared with enrollment in Term 1.

Conclusions: Along with the improvement in RA treatment, patients were able to achieve J-HAQ remission more frequently and more quickly.

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