Rheumatoid arthritis - prognosis, predictors and outcome

SAT0037 | **THE EFFECTS OF B CELL DIRECTED THERAPY ON DISEASE RELEVANT BIOMARKERS IN SUBJECTS AT RISK OF RHEUMATOID ARTHRITIS**

D. Gerlag[1], M. Safy[2], K. Maijer[2], T. Ramwadhdoebe[2], S. Tas[2], N. de Vries[2], M. Starmans-Kool[3], A. van Tubergen[4], M. Janssen[5], S. Eyre[6], L. Klareskog[7], K. Zwinderman[2], P-P. Tak[2]. [1]*Amsterdam Rheumatology and Immunology Center;* [2]*Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands, Amsterdam;* [3]*Zuyderland Medical Center, Heerlen;* [4]*Maastricht Medical Center, Maastricht;* [5]*Rijnstate Hospital, Arnhem, Netherlands;* [6]*Arthritis Research UK Centre for Genetics and Genomics, Manchester, United Kingdom;* [7]*Karolinska Institute, Stockholm, Sweden*

Background: Exploration of the mechanism underlying the delay of development of clinical signs of seropositive rheumatoid arthritis (RA) observed after B cell directed therapy in individuals at risk of developing autoantibody positive RA may offer insights into the mechanism of disease and may assist the development of preventive strategies.

Objectives: To explore the effects of a single infusion of rituximab (anti-CD20 antibody) on the observed delay of the onset of clinically manifest arthritis in individuals at risk of developing autoantibody positive RA.

Methods: In a study of 81 subjects positive for both anti-citrullinated protein antibodies (ACPA) and rheumatoid factor (RF) with arthralgia who never had clinically manifest arthritis and never used disease-modifying antirheumatic drugs, a 55% reduction of the risk of developing arthritis was observed 12 months after receiving a single iv infusion of 1000 mg rituximab when compared to placebo. In this group there was a delay in the development of arthritis of 12.0 months (12 months placebo vs 24 rituximab group) at the 25% quartile (75% free of arthritis) of the cumulative arthritis-free survival. Explorative analysis of disease-related biomarkers was performed in subgroups to better understand the mechanisms of the observed delay of clinical disease onset.

Results: Baseline levels of ESR (mm/h; HR 1.03; p=0.016), the total number of B cells in peripheral blood (HR 1.48; p=0.047), the presence of anti-alpha-enolase 1 (anti-CEP1) antibodies (HR 3.71; p=0.004) and the percentage of regulatory B cells (HR 1.04; p=0.002) were related to arthritis development over time. Importantly, genetic analysis of 100 RA associated SNPs showed that the top SNP associated with arthritis development in the rituximab-treated group (OR=7, MAF in cases 60% compared to 17% in unaffected) was in the PLCL2 gene, described to play a role in B cell signaling[1]. In individuals treated with rituximab, B cell numbers and subtypes mainly of the memory and regulatory compartment as well as serum levels of IgM-RF (p<0.0001), IgA-RF (p=0.003), total IgM (p=0.001), and anti-CCP (p=0.035) showed statistically significant changes over time compared to individuals who received placebo. Exploratory analysis showed trends for multiple biomarkers in the B cell compartment that appeared predictive of the development of arthritis.

Conclusions: A single infusion of 1000 mg rituximab significantly affects B cell numbers and subsets of memory and regulatory B cells as well as a reduction of disease-related antibodies and immunoglobulin levels in individuals at risk of RA. The changes coincide with a decrease in risk and a delay in development of arthritis in this population. PLCL2 gene polymorphism was associated with arthritis development in rituximab-treated individuals.

References:
[1] Takenaka K, Fukami K, Otsuki M, Nakamura Y, Kataoka Y, Wada M, Tsuji K, Nishikawa S, Yoshida N, Takenawa T. Role of phospholipase C-L2, a novel phospholipase C-like protein that lacks lipase activity, in B-cell receptor signaling. Mol Cell Biol. 2003 Oct;23(20):7329–38.

SAT0038 | **SERUM B LYMPHOCYTE CHEMOATTRACTANT PROTEIN 13 (CXCL 13) AND MUSCULOSKELETAL ULTRASONOGRAPHIC FINDINGS IN EARLY RHEUMATOID ARTHRITIS**

E. Baraka, S. Egila, G. Hamad, M. Khalil. *Rheumatology, Rehabilitation and Physical medicine, Benha Faculty of Medicine, Benha University., Cairo, Egypt*

Background: Patients in clinical remission may continue to have synovitis detected by the musculo skeletal ultrasonography (MSUS).Recently,B-lymphocyte chemoattractant chemokine (CXCL13) has reported to be upregulated and risen to be a possible new marker of disease inflammation in RA

Objectives: to detect early synovitis by grey scale and power Doppler MSUS, measure serum levels of CXCL13 and to correlate these levels with both clinical and ultrasonographic disease activity in early RA patients

Methods: RA was assessed by the modified disease activity score (DAS28).Hands and feet plain radiography were evaluated by Laresn score. A semi-quantitative score (0–3) was used to score synovial effusion (SE), synovial proliferation (SP) and power Doppler (PD) signals by MSUS in 6 synovial sites in 3 joints bilaterally: wrist (dorsal radiocarpal recess). 2nd MCPJ (dorsal and palmar side) and knee

(suprapatellar recess) according to the European Leauge Against Rheumatism guidelines. A total MSUS score is the sum of scores for SE, SP and PD signals of the six joints in each patient (0–54).Quantitative detection of serum (CXCL13) levels of all subjects was done by ELISA.

Results: The mean serum CXCL13 values were highly significantly higher in fifty RA patients than in 30 age and sex matched control subjects with a mean of (388.86±283.63 pg/ml) and (62.96±32.5 pg/ml) respectively (p<0.001) and were significantly positively correlated with morning stiffness durations (p<0.001), Tender Joint Counts (p<0.001), Swollen Joint Counts (p<0.001), VASs (p<0.001), ESR 1st h values (p<0.001) and the platelets count (p<0.05), negatively correlated with disease durations (p<0.05) and HB concentrations (p<0.05) and showed no differences according to presence of extra-articular manifestations or CRP, RF or ACCP seropositivity.(p>0.05). In our RA patients' group, MSUS detected either synovial effusion and /or synovial hypertrophy with or without PD signal in 132 (65%) joints out of 203 clinically silent joints and and detected erosions in 93/300 joints (31%) compared to 27/300 joints (9%) detected by x ray.the serum CXCL13 levels were highly significantly positively correlated with the total MSUS score for each patient (p<0.001),SP and SE gradings (p<0.001) and (p<0.05) and were significantly higher in RA patients with MSUS detected erosions but were not correlated with either PD gradings (p=0.11) or Larsen scores (p>0.05).

Conclusions: MSUS is more sensitive than clinical assessment and conventional radiology in detecting synovitis and erosions in RA. Serum CXCL13 levels correlated with MSUS and DAS 28 scores and can be used as a marker for activity and severity of RA.Screening early RA patients by MSUS for more precise evaluation of synovitis activity, severity and better management of the disease and follow up patients to detect if elevated CXCL13 affect RA disease progression or patient disability are recommended.

References:
[1] Naredo E, Valor L, De la Torre I, Martinez-Barrio J, Hinojosa M, Aramburu F, et al., (2013): Ultrasound joint inflammation in rheumatoid arthritis in clinical remission: how many and which joints should be assessed? Arthritis Care Res.;65.

[2] Perricone C, Ceccarelli F, Modesti M, Vavala C, Di Franco M, Valesini G, et al., (2012): The 6-joint ultrasonographic assessment: a valid, sensitive-to-change and feasible method for evaluating joint inflammation in RA. Rheumatology; 51(5):866–73.

SAT0039 | **LARGE TENDER JOINTS HAVE THE GREATEST IMPACT ON LONGITUDINAL TRAJECTORIES OF FUNCTION IN EARLY RHEUMATOID ARTHRITIS**

S.H.L. Lim[1], O. Schieir[2], S. Bartlett[3], G. Boire[4], B. Haraoui[5], E. Keystone[2], D. Tin[6], C. Thorne[6], J. Pope[7], V. Bykerk[8], C. Hitchon[1] on behalf of Canadian Early Arthritis Cohort (CATCH) Investigators. [1]*University of Manitoba, Winnipeg;* [2]*University of Toronto, Toronto;* [3]*McGill University, Montreal;* [4]*Universite de Sherbrooke, Sherbrooke;* [5]*Institut de Rhumatologie de Montreal, Montreal;* [6]*Southlake Regional Health Center, Newmarket;* [7]*Western University, London, Canada;* [8]*Hospital for Special Surgery, New York, United States*

Background: Physical function remains suboptimal in patients with early rheumatoid arthritis (ERA) despite adequate disease control. Hence, factors impacting function need further evaluation. Large weight bearing joints are more likely to impact overall function than small non-weight bearing joints although the magnitude of impact may be task dependent. By weighting large joints more than small joints, the Lansbury Articular Index (LAI) may have stronger associations with function than standard joint counts that give equal weight to small and large joints.

Objectives: 1) To compare the correlations of weighted and non-weighted arthritis joint measures with physical function over time; and 2) to determine the impact of large compared to small joint involvement on the trajectory of HAQ in ERA.

Methods: ERA participants had <1 year symptom duration at enrolment in a multicentre Early Arthritis Cohort and were followed prospectively. Arthritis activity measures (DAS28, tender 28 joint count (TJC28), swollen 28 joint count (SJC28), function (Health Assessment Questionnaire; HAQ) were captured at each visit. The LAI weighted 28 joint count (LT28) and swollen joint count (LS28) were calculated based on the standard 28 joint sites. Correlations of trajectories were calculated using joint modeling for each of the following: DAS28, TJC28,SJC28,LS28 LT28 with the HAQ (2 trajectories/model). Unadjusted effects of large joints (shoulders, elbows, hips knees, ankles) and hand joints (time-varying) on the HAQ trajectory were estimated with a series of generalized estimating equations (GEE). GEE models were adjusted for baseline age, sex and education.

Results: ERA subjects (n=2125, 73% female; baseline mean (SD) age 53 (15) years, DAS28 5.1 (1.4)), were followed for median (IQR) 24 (10,48) months. At their last visit 44% were in remission (DAS28<2.6). HAQ over time was highly correlated with the following: DAS28 (r=0.83), LT28 (r=0.83), and TJC28 (r=0.85) and moderately with the LS28 (r=0.59) and SJC28 (r=0.61) trajectories. Each increase in joint involvement was associated with increase in HAQ: large tender joint (0.110 (95% CI 0.102–0.116)); large swollen joint (0.109 (0.099–0.120)); tender hand joint (0.036 (0.032–0.039)); swollen hand joint (0.035 (0.032–0.039)).

In multivariable modeling, after adjusting for age, sex, and education, large joints had greater effects (tender 0.074 (0.065–0.084), swollen 0.027 (0.014–0.04)) on HAQ than hand joints (tender 0.013 (0.009–0.017), swollen 0.008 (0.003–0.013)).

Conclusions: Both Lansbury and standard joint count trajectories correlate similarly with HAQ in ERA. The weighting of large joints in LAI was insufficient to reflect the full impact of large joint involvement in ERA probably because HAQ questions emphasize large joint activities. The effects of large joint swelling may be under recognized due to difficulty in measuring hip, shoulder or elbow swelling. Overall, tender joints had a greater impact on function than swollen joints and large tender joints had the most impact on function.

SAT0040   **ASSESSING 5-YEAR RADIOGRAPHIC PROGRESSION IN RHEUMATOID ARTHRITIS PATIENTS WITH MODERATE DISEASE: FINDINGS FROM A UK MULTI-CENTRE PROSPECTIVE OBSERVATIONAL STUDY**

L. Carpenter [1], S. Norton [2], E. Nikiphorou [3], K. Jayakumar [4], D.F. McWilliams [5], J. Dixey [6], P. Kiely [7], D.A. Walsh [5], A. Young [4] on behalf of ERAS and ERAN. [1]*Life and Medical Sciences, University of Hertfordshire;* [2]*Psychology Department, Institute of Psychiatry;* [3]*Department of Rheumatology, Whittington Hospital NHS Trust, London;* [4]*Department of Rheumatology, St Albans City Hospital, St Albans;* [5]*Arthritis UK Pain Centre, University of Nottingham, Nottingham;* [6]*Department of Rheumatology, New Cross Hospital, Wolverhampton;* [7]*Department of Rheumatology, St Georges University Hospitals NHS Foundation Trust, London, United Kingdom*

Background: Early, intensive treatment to achieve remission, or at least low disease target (Treat-to-Target, T2T), is advocated to prevent and/or reduce structural joint damage and disability in early Rheumatoid Arthritis (RA). A recent study shows how patients with moderate disease exhibit similar rates of functional disability and orthopaedic surgical interventions to those patients with high disease[1]. To our knowledge, no study has looked at longitudinal observational data to investigate the progression of structural joint damage in these patient sub-groups.

Objectives: To investigate the long-term progression of radiographic joint damage in patients with sustained moderate disease activity.

Methods: Demographic, clinical, laboratory and radiographic data from the Early Rheumatoid Arthritis Study (ERAS) was available for 1,465 patients. Radiographic damage was scored using the modified Sharp/van der Heijde (SvdH) method. The original three variable 44 joint count Disease Activity Score (DAS-44) was used. Mean DAS-44 over the first 5 years was estimated for patients with at least two DAS-44 scores. Patients were stratified based on EULARs thresholds of low (<2.4), moderate (2.4–3.7) and high (>3.7) disease. Mixed-effects negative binomial regression modelled patients' radiographic progression over 5 years, whilst controlling for key confounders, including age at onset, sex, rheumatoid factor status and baseline functional disability.

Results: A total of 1,110 patients with 3,751 observations over the 5 year period (mean =3.4 observations per patient) were analysed. 396 (36%), 363 (33%) and 351 (32%) patients were classified in the low, moderate and high DAS-44 groups respectively. The low group had lower SvdH scores at 1 year compared to the moderate group (12.9 vs. 19.2, p<0.001). Furthermore, the low group also experienced half the annual rate of change over the 5 years compared to the moderate group (3.6 vs. 7.4, p=0.002). In contrast, the high group had similar SvdH scores at year 1 compared the moderate group (20.4 vs. 19.2, p=0.884), but increased annual progression over the 5 years (10.0 vs. 7.4, p=0.010). Despite the increased annual progression rate, the difference in SvdH scores between the moderate and high groups remained non-significant at 5 years.

Conclusions: Sustained moderate disease over the first five years of RA indicates similar levels of radiographic progression compared to sustained high disease.

Progression of Total SvdH Score
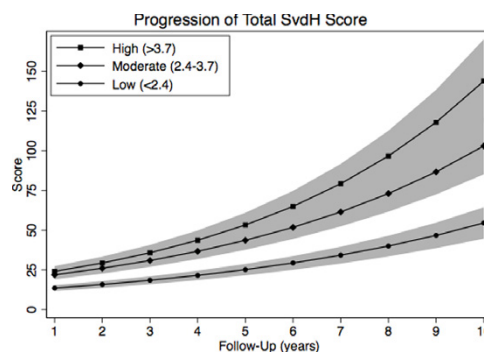
This study provides support on the importance of tight treatment control with early and aggressive therapy according to T2T principles. Preventing sustained moderate disease activity states can help reduce radiographic progression and consequently joint destruction, minimising the risk of disability in the long-term.

References:
[1] Nikiphorou, E. et al. Association between rheumatoid arthritis disease activity, progression of functional limitation and long-term risk of orthopaedic surgery: combined analysis of two prospective cohorts supports EULAR treat to target DAS thresholds. Ann. Rheum. Dis. annrheumdis–2015–208669 (2016).

SAT0041   **EFFICACY OF ABATACEPT VERSUS ADALIMUMAB IN PATIENTS WITH SEROPOSITIVE, EROSIVE EARLY RA: ANALYSIS OF A RANDOMIZED CONTROLLED CLINICAL TRIAL (AMPLE)**

R. Fleischmann [1], M. Weinblatt [2], H. Ahmad [3], M. Maldonado [3], E. Alemao [3], J. Ye [3], M. Schiff [4]. [1]*University of Texas Southwestern Medical Center, Dallas;* [2]*Brigham and Women's Hospital, Boston;* [3]*Bristol-Myers Squibb, Princeton;* [4]*University of Colorado, Denver, United States*

Background: Patients (pts) who are anti-citrullinated protein antibody (ACPA) positive tend to develop more severe erosive disease than ACPA-negative pts.[1] The presence of seropositivity and erosions have been noted in EULAR treatment guidelines as poor prognostic factors to identify pts with RA who require early and aggressive clinical intervention.[2] Since the disease in pts with seropositive, erosive early RA is mostly driven by immunological features, response to RA therapy may vary based on therapeutic mechanism of action (MOA).

Objectives: To investigate the efficacy of abatacept (ABA) vs adalimumab (ADA) in pts with seropositive, erosive early RA.

Methods: AMPLE (NCT00929864)[3] was a 2-year, Phase IIIb study in which biologic-naïve pts with RA were randomized 1:1 to either SC ABA 125 mg weekly or SC ADA 40 mg biweekly, both with background MTX. This *post hoc* analysis of AMPLE compared clinical outcomes between treatment groups in a subpopulation of pts with specified baseline criteria: disease duration ≤6 months, RF or ACPA seropositivity and >1 radiographic erosion. Disease activity and patient-reported outcomes were evaluated at Weeks 26, 52 and 104. Endpoints were compared between ABA and ADA groups using chi-square test for categorical variables, analysis of covariance model (ANCOVA) controlling for baseline covariates and DAS28 (CRP) stratification for continuous variables.

Results: Of 318 and 328 pts in the ABA and ADA groups, respectively, 38 and 45 pts had all specified baseline characteristics (Cohort 1) and 280 and 283 pts had an absence of at least 1 of the specified characteristics (Cohort 2). Overall, the baseline characteristics, including anti-cyclic citrullinated peptide titres, were well balanced between the groups, with the exception of weight. For Cohort 1, adjusted mean change (95% CI) from baseline DAS28 (CRP) with ABA vs ADA was −2.18 (−2.61, −1.75) vs −1.56 (−2.01, −1.11) at Week 26, −2.58 (−2.99, −2.17) vs −1.68 (−2.10, −1.25) at Week 52 and −2.50 (−2.97, −2.03) vs −2.0 (−2.49, −1.50) at Week 104. Similar trends of increased efficacy with ABA vs ADA were observed for changes from baseline CDAI, SDAI, HAQ-DI, pain and fatigue; no differences in radiographic progression were observed. For Cohort 2, no differences in clinical outcomes between ABA and ADA groups were observed. Given the differences in baseline weight between ABA and ADA groups in Cohort 1, sensitivity analyses that excluded pts >100 kg and adjusted for baseline weight were performed and demonstrated minimal effect of weight on treatment efficacy.

Conclusions: This *post hoc* analysis seems to indicate a trend of increased efficacy for abatacept in pts with seropositive, erosive early RA compared with the TNF inhibitor adalimumab. Given the small sample size, additional pre-specified randomized studies are needed to compare the benefit of biologic DMARDs with different MOAs in pts with early, rapidly progressing RA.

References:
[1] Combe B, et al. Ann Rheum Dis 2016 Dec 15. doi: 10.1136/annrheumdis-2016–210602.