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## SAT0044 A 10-YEAR FOLLOW UP STUDY OF EARLY SERONEGATIVE ARTHRITIS DIAGNOSED AT AN ADULT AGE

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**Background:** Up to 20–30% of patients enrolled into RA cohorts and clinical trials are seronegative. However, in studies examining predictors, prognosis, and response to treatment, seropositive and seronegative groups of patients seem to behave differently. Only a few studies have focused on the long term follow up of seronegative arthritis.
**Objectives:** To investigate long-term outcomes of patients with seronegative arthritis during a 10-year follow-up period including clinical outcomes and reclassification of diagnosis when applicable.
**Methods:** A total of 1046 patients were classified as early RA in 1997–2005 at single rheumatology center and scheduled for a ten year follow-up, including 434 seronegative patients who are subjects of the present analysis. Follow-up examinations were carried out for at least 2 years and then at 5 and 10 years by the treating specialist including complete clinical examination and patient reported outcomes. In addition, case –reviews were performed, with re-classification of the cases when applicable
**Results:** Among the 434 seronegative patients (69,4% women, mean age 58), 271 subjects were seen for the 10 year visit with the mean disease activity DAS28 of 2,3 (SD 1,02) and the mean HAQ of 0,71 (SD 0,72). Out of the remaining 146 patients, 88 had died and 53 did not attend the 10-year visit due to altered diagnosis, refusal or comorbidity. Five patients had dropped out and files of 17 patients were missing. During the follow-up of 10 years, 12/434 (2,7%) patients could be classified as seropositive or erosive RA: 4 turned seropositive (2 for ACPA and 2 for RF [>2x normal level]) and 8 developed erosions typical for RA. Reclassification revealed 70 (16,1%) cases of polymyalgia rheumatica, 47 (10,8%) cases of osteoarthrosis without evidence of inflammatory disease, 47 (10,8%) cases of psoriatic arthritis, 39 (9,0%) cases of spondylarthritis and 16 (3,7%) cases of plausible reactive arthritis. Few cases were reclassified as gout (11 cases (2,5%)) and pseudogout (3 cases (0,7%)). Also paraneoplastic arthritis (6 cases (1,4%)), juvenile arthritis (5 cases (1,2%)), hemochromatosis (2 cases (0,5%)), ankylosing spondylitis (2 cases (0,5%)) and temporal arteritis (2 cases (0,5%)) were revealed during follow up. One case of each reflex sympathetic dystrophy, trauma-induced arthritis, meniscal injury, optional Nasu Hakola disease, microscopic polyangiitis (MPA), granulomatous polyangiitis (GPA), antisynthetase syndrome and colitis ulcerosa were also found. The remaining 147 patient (33,8%) could not be reclassified in any clear cut diagnosis. A total of 44 of these undifferentiated cases had transient arthritis, 43 cases had features of seronegative spondylarthritis and 57 cases remained totally unspecified, while three patients had features of inflammatory connective tissue disease (SLE and Sjögren's syndrome), but they did not meet available classification criteria. In addition, files of 17 (3,9%) patients were missing from the analyses.
**Conclusions:** Over a 10-year period, 97% of seronegative patients remained seronegative and did not develop RA-like erosions. Reclassification revealed significant heterogeneity in the diagnosis of seronegative RA. Therefore, seronegative arthritis should not be studied as a homogenous disease entity.
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## SAT0045 11 YEARS' FOLLOW-UP OF A DANISH 2-YEAR TREAT-TO-TARGET RANDOMIZED CONTROLLED TRIAL IN PATIENTS WITH EARLY RHEUMATOID ARTHRITIS: BASELINE PREDICTORS OF FUNCTIONAL AND RADIOGRAPHIC OUTCOMES

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**Background:** Few RCTs have investigated long-term (>10 years (yrs)) outcomes of goal-directed synovitis suppression in early rheumatoid arthritis (RA). The CIMESTRA trial was a 2-year double-blinded Danish multicenter study on aggressive treatment with csDMARDS (methotrexate (MTX) versus MTX and cyclosporine) in combination with intra-articular glucocorticoids (1+2). Disease control after 2 yrs was excellent with ≈50% in remission and halted radiographic progression in both groups. We present 11 yr follow-up data.

| Baseline predictors of: | | | |
|---|---|---|---|
| **-Functional status ($HAQ_{10}$-)*** | **Coefficient** | **95% CI** | **p-value** |
| DAS28 (per unit increase) | 0.10 | 0.02-0.18 | 0.02 |
| Anti CCP (positive) | 0.24 | 0.02-0.46 | 0.03 |
| **-Radiographic progression ($\Delta TSS_{0-10}$-)*** | **Coefficient** | **95% CI** | **p-value** |
| Anti CCP (positive) | 7.69 | 0.91; 14.47 | 0.03 |
| MRI bone marrow edema (per unit increase) | 0.87 | 0.19; 1.55 | 0.01 |

*: Initial baseline variables in the $HAQ_{10}$- (§) and $\Delta TSS_{0-10}$-(#) multivariable linear models before backward selection were: Total Sharp-van der Heijde-Score (TSS)[§#]; Health Assessment Questionnaire score[§]; Disease Activity Score (28-joint count, 4 variables)[§]*; age[§]*; anti CCP[§]*; gender[§]*; MRI erosion score[§]*; MRI synovitis score[§]*; MRI bone marrow edema[§]*. CI, confidence interval; CCP, cyclic citrullinated peptide (dichotomized value); MRI, magnetic resonance imaging.

**Objectives:** The aims were to 1) investigate the clinical and radiographic status and 2) identify baseline predictors of functional status and erosive progression.
**Methods:** Of 160 patients (pts) included, 130 pts also had MRI of the wrist performed at baseline. 17 pts had died since baseline. All living pts were contacted and 120 signed informed consent to participate in a 11 yrs' follow-up visit assessing e.g. treatment, disease activity (DAS28, CRP, 4 variables), physical function (HAQ), X-ray of hands and feet. Baseline MRI was scored by OMERACT rheumatoid arthritis MRI scoring (RAMRIS) system, X-rays by Sharp-van der Heijde total Sharp Score (TSS). Multivariable linear regression analyses of a panel of baseline variables (see foot note in table) with backward selection were performed with HAQ at 11 yrs ($HAQ_{11}$) and radiographic progression since baseline ($\Delta TSS_{0-11}$) as dependent variables.
**Results:** 120 of 160 pts (75%) completed the 11 yrs visit. 96 pts with available baseline MRI and X-rays of both time points were included in the prediction models. Withdrawal analysis comparing the 160 pts with the 40 and 64 pts who were not included showed similar baseline characteristics except for higher DAS28 and HAQ score for withdrawers. Follow-up was after 11.6 yrs (10.7–12.2) (median (IQR)). Pts were 63 yrs (55–72) and 70% females. 20% received biologics (+/- csDMARD), 53% csDMARD alone, 27% were in drug free remission. DAS28 was 2.0 (1.5–2.6); pain score: 1 cm (0.3–3); pt. global: 1.1 cm (0.2–2.9); swollen joint count (28SJC): 0 (0–0); tender joint count (28TJC): 0 (0–1). 76% of pts were in DAS28 remission; HAQ-score was 0.25 (0–0.75); $\Delta TSS_{0-11}$(median (IQR)):4 (0–13); $\Delta TSS_{0-11}$(mean±SD): 10.9±16.9). The annual progression rate since baseline was median (IQR):0.4 (0–1.1); mean±SD:0.96±1.52. Multivariable linear regression analyses are shown in Table.
**Conclusions:** 11 years after diagnosis 75% were in DAS28 remission. HAQ-score was low, and mean radiographic progression was <1 TSS unit/year. High DAS28 and positive anti-CCP at baseline were independent predictors of poorer functional status. Baseline MRI bone marrow edema and anti-CCP positivity were independent predictors of radiographic progression.
**References:**
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**Disclosure of Interest:** M. L. Hetland Grant/research support from: AbbVie, BMS, MSD, Pfizer, Orion, Novartis, Biogen, Eli Lilly, K. Stengaard-Petersen: None declared, P. Junker: None declared, H. Lindegaard: None declared, T. Ellingsen: None declared, J. Pødenphant: None declared, H. Skjødt: None declared, A. Vestergaard: None declared, B. Ejbjerg: None declared, S. Jacobsen: None declared, N. S. Krogh: None declared, M. Østergaard Grant/research support from: Abbvie, BMS, Boehringer-Ingelheim, Celgene, Eli-Lilly, Centocor, GSK, Hospira, Janssen, Merck, Mundipharma, Novartis, Novo, Orion, Pfizer, Regeneron, Schering-Plough, Roche, Takeda, UCB, K. Hørslev-Petersen: None declared
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## SAT0046 TNF ANTAGONIST DRUG SAFETY ASSESSMENT BY PHARMACOVIGILANCE SIGNALING AND POST-MARKETING ADVERSE EVENT REPORTS

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**Background:** TNF antagonists have been equally effective in the treatment of immunoinflammatory diseases. However, differences in their characteristics and the introduction of biosimilars may be associated with different safety profiles.
**Objectives:** The main goal of this study is to compare the safety of infliximab (IFX), etanercept (ETN), and adalimumab (ADA), as well as of IFX-biosimilar.
**Methods:** We assessed the adverse events reported in the EudraVigilance database between 2004 and 2016. The MEdDRA® system was used to classify the adverse events according to the primary system organ class. For a direct

comparison of the data obtained, the adverse events reported for each drug were normalized using the number of treatments for the same period. The reporting odds ratio (ROR) and its 95% confidence intervals (CI) were calculated regarding the different categories of adverse events. The incidence of serious adverse events, serious infections, withdrawals due to adverse events and deaths were also calculated.

**Results:** The EudraVigilance database contains 851 882 adverse events reported for IFX, ETN, and ADA. During this period, the different TNF antagonists have shown almost the same safety profile. The reported adverse events were classified by systems organ class (SOC) and the most frequent were administration site conditions (28.8%) and infections and infestations (11.2%), Safety was not statistically different. The comparison between IFX originator and its biosimilar did not show statistically significant differences in safety (ROR 1.08 [0.80, 1.46]) during the initial 3-years after launch for both drugs. However, a small non-significant increase in immune reactions during administration was reported for IFX-biosimilar, which might reflect increasing attention for this class of drugs.

**Conclusions:** The comparison of reference IFX and IFX-biosimilar did not demonstrate statistically significant differences in safety. This pharmacovigilance study provides the first analysis of TNF antagonists from the EudraVigilance database and offers a framework for safety comparison between originators and biosimilar TNF antagonists.

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## SAT0047 PREDICTING MAINTENANCE OF RESPONSE BASED ON DISEASE CHARACTERISTICS AND EARLY CLINICAL RESPONSE IN RHEUMATOID ARTHRITIS PATIENTS UPON WITHDRAWAL OF ADALIMUMAB

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**Background:** Some patients (pts) with rheumatoid arthritis (RA) achieve low disease activity (LDA) after treatment with adalimumab (ADA) plus methotrexate (MTX) and can maintain LDA after ADA withdrawal[1]. However, others experience a flare in disease activity. The factors associated with loss or maintenance of response are not understood.

**Objectives:** To identify pt disease characteristics and early clinical responses, which predict maintenance of LDA upon ADA withdrawal in individual RA pts.

**Methods:** Data from the OPTIMA trial were used in this *post hoc* analysis. In period 1 (P1), pts were treated for 26 weeks (wks) with ADA+MTX or placebo (PBO) +MTX. Pts on ADA+MTX who achieved DAS28-CRP <3.2 at wks 22 and 26 (responders) were randomized to ADA withdrawal, or ADA+MTX continuation up to Wk 78. Responders to PBO+MTX in P1 continued on PBO+MTX up to Wk 78 (PBO continuation). Data from the ADA withdrawal arm were used to predict LDA at Wk 78 by DAS28-CRP (≤3.2) or SDAI (≤11). Potential factors including baseline (BL) disease characteristics and Wk 26 responses, including DAS28-CRP, SDAI, ACR score components, modified total sharp score (mTSS) and joint space narrowing score (JSN), were screened by the LASSO method[2], which performs variable selection by penalizing unduly complicated models, with/without incorporating the speed of DAS28-CRP or SDAI response as an individual predictor. Logistic regression on the LASSO-selected factors yielded coefficients used to derive individual scoring equations and prediction scores for Wk 78 outcomes (fig footnote). Prediction score cutoffs were established by the regression tree method[3]. The results were validated in data from the PBO continuation arm.

**Results:** For the prediction of DAS28-CRP LDA at Wk 78, BL physician global assessment (PhGA) and health-assessment questionnaire-disability index (HAQ-DI), and Wk 26 DAS28-CRP, HAQ-DI, JSN and CRP were selected by LASSO, and used to calculate the prediction score. Including speed of response did not affect the predictors chosen. Out of 9 pts predicted not to have DAS28-CRP LDA at Wk 78, 0 had LDA (NPV=100%) (fig 1). Out of 66 pts predicted to have DAS28-CRP LDA at Wk 78, 63 predictions were correct (PPV=96.5%). Results were comparable for most cutoff categories in the validation arm (PPV=82%); however, no pts were predicted to have a non-response at Wk 78. For the prediction of SDAI LDA at Wk 78, the NPV was 86% (1/7 predictions incorrect); PPV was 95% (39/41 predictions correct); in the validation arm, the PPV was 82%.

**Conclusions:** DAS28-CRP LDA at 78 wks could be individually predicted for up to 63% pts in OPTIMA who withdrew ADA/continued PBO+MTX with 96.5% accuracy, based on demographics and clinical outcomes at 6 months. This instrument could help identify pts who may be able to maintain LDA upon ADA withdrawal.

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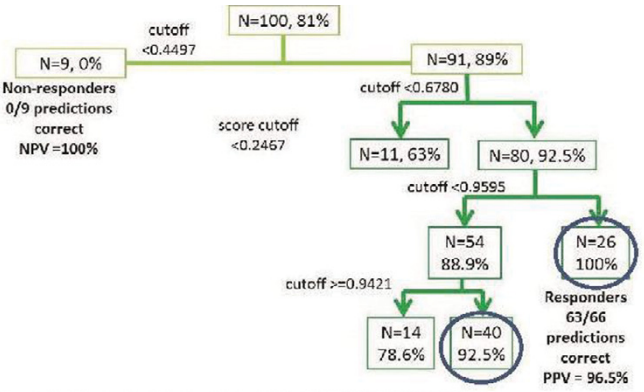


**Figure 1: Regression tree to predict Week 78 DAS28-CRP LDA.** The percentages of patients with an LDA response at Week 78 are indicated in the boxes. The encircled boxes indicate the patients predicted to have LDA at Week 78.

**Individual scoring equation for reaching Week 78 DAS28_LDA**: Logit = 6.717 – 0.212*HAQ – 0.039 * PhGA – 0.004 *DAS28_WK26 – 1.393*HAQ_WK26 - 0.027*JSN - 0.292*CRP_WK26

**For reaching Week 78 SDAI LDA**: Logit = 4.668 – 0.028 * PhGA – 0.161*CRP_WK26 – 1.411*RoW_indicator; RoW = rest of the world, including Argentina, Australia, New Zealand, South Africa

**Individual prediction score:** $\frac{\exp(logit)}{1+\exp(logit)}$.

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## SAT0048 THE PATTERN OF ACPA REACTIVITIES IN ANTI-CCP POSITIVE INDIVIDUALS WITH NON-SPECIFIC MUSCULOSKELETAL SYMPTOMS AT RISK OF DEVELOPING RA

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**Background:** There is today a paucity of prospective studies to describe the natural longitudinal history of anti-ccp positive individuals developing RA or not developing RA. Further no study to investigate the detailed ACPA reactivities in such a setting is currently available.

**Methods:** Individuals at risk of developing RA were included in a cohort at Karolinska University Hospital, Stockholm. Examinations of peripheral joints was repeated at one year follow-up visit or at any time the patients experienced worsening of their symptoms. Peripheral blood samples were available at inclusion (n=70). Serum was run on a microarray based on the ImmuoCAP ISAC system testing for ACPA reactivities toward 13 different citrullinated peptides (fillagrin, fibrinogen, alpha-enolase, vimentin, histone) (1).

**Results:** Individuals referred from primary care with musculoskeletal complaints and positive anti-ccp test were systematically investigated as part of routine care at our rheumatology clinic. Individuals lacking self-reported history of suspect arthritis, clinical arthritis according to rheumatologist and signs of synovitis on ultrasound examination were included in a clinical Risk-RA program with life-style coaching and personalized information on the risk of developing RA. Seventy individuals, with a mean age of 48 years (SD 15) and 86% females, were included in the program. Twenty (29%) individuals developed arthritis during a medium follow up time of 7 months (range 1–25 months).

Number of ACPA reactivities at baseline was significant higher among those developing (in mean 6 reactivities) as compared to those not developing arthritis (in mean 4 reactivities). A increased proportion of individuals were showing reactivity towards citrullinated (cit) vimentin (vim) 60–75, fibrinogen (fib) 573 and enolase (eno) (CEP-1) among those developing arthritis (80% for anti-cit-vim 45% for anti-cit-fib and 60% for anti-cit eno) as compared to those not developing arthritis (41% for anti-cit-vim, 30% for anti-cit-fib and 52% for anti-cit-eno). Increased level of anti-cit-vim and anti-cit-eno antibodies was also observed at inclusion for those individuals developing arthritis as compared to those not developing arthritis.

**Conclusions:** We describe here the pattern of ACPA reactivities in anti-CCP positive individuals with non-specific musculoskeletal symptoms at risk of developing RA and without clinical and ultrasonograph signs of synovitis and report that 30% of these patients will develop arthritis during a short follow-up. Number, frequency and titers of specific ACPA reactivities appear to be enriched already at inclusion among those patients that developed arthritis during follow-up.

**References:**

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