OP0249 MULTI-BIOMARKER DISEASE ACTIVITY AND AUTOANTIBODY STATUS LEAD TO COST EFFECTIVE TAPERING ALGORITHMS IN RHEUMATOID ARTHRITIS PATIENTS IN SUSTAINED REMISSION

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Background: Achieving remission is the ultimate treatment goal in patients with rheumatoid arthritis (RA). With the development and wider use of highly effective disease modifying anti-rheumatic drugs (DMARD) about half of RA patients reach the disease remission state (1), raising the question about tapering or stopping anti-rheumatic treatment and appropriate predictors (2).
Objectives: To analyse the effect of a risk-stratified DMARD tapering algorithm based on multiple-biomarker disease activity (MBDA) score and anti-citrullinated protein (ACPA) status for successful DMARD tapering and treatment cost reduction in RA patients in sustained remission enrolled in the prospective randomized controlled RETRO study (3,4).
Methods: MBDA scores and ACPA status were determined in the baseline samples of 146 patients in sustained remission. Patients either continued DMARDs (arm1), tapered dose by 50% (arm 2) or stopped DMARDs after tapering (arm 3) for one year according to the RETRO study protocol. Direct treatment costs (including testing costs at baseline) were evaluated every three months. MBDA and ACPA status were used as predictors creating a risk-stratified tapering algorithm based on relapse rates.
Results: RA patients with a low MBDA score (<30) and negative ACPA showed lowest relapse risk (19%). With either single positivity for ACPA or moderate/high MBDA scores (≥30) relapse risk increased and was high in double-positive patients (61%). In MBDA negative (<30) and MBDA single-positive (≥30) groups, DMARD tapering appears feasible. Considering only patients that did not flare, costs for synthetic and biologic DMARDs in the MBDA-negative and single-positive groups (n=41) would have been 123.751,29€ for full-dose treatment over one year. Tapering and stopping DMARDs in this low-risk relapse groups allowed a reduction of 92.821,50€ (-75%) of DMARD costs. Average reduction of DMARD costs per patient were 2.350,08€ in the double negative (MBDA-/ACPA-) and single negative (MBDA- /ACPA+) group and 1.761,43€ in the MBDA single positive (MBDA+ /ACPA-) group.

Conclusions: Combining MBDA score and ACPA status allows risk stratification for successful DMARD tapering and cost-effective use of biologic DMARD. Given that previous data of the RETRO have shown that patients relapsing after tapering their DMARDs respond well to their reintroduction, a stratified tapering and stopping of DMARDs is not only a cost economic but also clinically feasible strategy.
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OP0250 CAN RANKL SERUM LEVELS PREDICT FUTURE PROGRESSION TO RHEUMATOID ARTHRITIS IN ACPA NEGATIVE PATIENTS?

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Background: Making the earliest diagnosis of rheumatoid arthritis (RA) is crucial to initiate treatment and prevent further disease progression and joint damage. Despite recent advances with the discovery and integration of anti–cyclic citrullinated protein antibody (ACPA) in classification criteria, there is still an unmet need for new diagnostic biomarkers, notably for ACPA-negative disease. Power Doppler ultrasound has been shown to identify poor prognosis disease in ACPA negative patients.
Objectives: The receptor-activator-nuclear-factor-κB axis (RANK/RANKL) is known to regulate bone homeostasis. The aim of this pilot study is to establish whether serum RANKL levels in people with early inflammatory arthritis are associated with RA diagnosis at follow-up and to evaluate the added value of RANKL with ultrasound for early RA diagnosis.
Methods: Serum from 298 subjects (95/204 Male/Female) was collected at the baseline participant visit to the Leeds Early Arthritis clinic. Demographic (age, gender symptom duration) and clinical data (swollen and tender joint counts (SJC, TJC), CRP, DAS28, rheumatoid factor (RF) and ACPA, shared epitope (SE)) were collected.
A commercial ELISA (BioVENDOR) was used to measure RANKL. Ultrasound of 26 joints (bilateral elbows, wrists, MCP 2–3, PIP 2–3, knees, ankles and MTP 1–5) was performed at baseline recording summative scores for power Doppler (PD), grey scale hypertrophy (GS) and erosions (ERO).
Results: At 1 year follow-up, 151 patients had a confirmed diagnosis of RA (EULAR 2010 criteria) and 147 were classified as non-RA (undifferentiated arthritis, other inflammatory diagnoses or non-persistent inflammation). All routinely used biomarkers were associated with RA diagnosis (ACPA, RF, SE, TJC, SJC, CRP, DAS28, $p<0.0001$), as were imaging biomarkers (PD, GS, ERO, $p<0.001$). RANKL levels were significantly higher in RA (RA 1002.4±1053.2pmol/L, non-RA 339.2±451.5pmol/L, $p<0.0001$). A regression analysis suggested that four parameters were sufficient to account for all associations with RA: RANKL, age, SJC, and PD with 75.3% accurate prediction. An AUROC analysis suggested a cut-off for each parameter and a score was calculated, adding 1 point for each of the factors (RANKL>700, age>62, TPD>3, SJC>4). This score predicted RA with an AUROC of 0.782 ((0.23–0.840), $p<0.0001$). The same analysis repeated for ACPA negative patients only (n=193) showed similar results, providing accurate diagnosis of RA (77.6% correct by regression) and with an AUROC of 0.774 ((0.690–0.858), $p<0.0001$).
Conclusions: A score incorporating RANKL, age, SJC and PD showed good predictive value for non-RA when low and for RA when high. Furthermore, the analysis redone in ACPA-negative patients performed particularly well for predicting RA with a good AUROC value.
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OP0251 INCIDENCE OF KNEE AND HIP REPLACEMENTS IN RHEUMATOID ARTHRITIS PATIENTS FOLLOWING INTRODUCTION OF BIOLOGICAL DMARDS: AN INTERRUPTED TIME SERIES ANALYSIS USING NATIONWIDE HEALTH CARE REGISTERS

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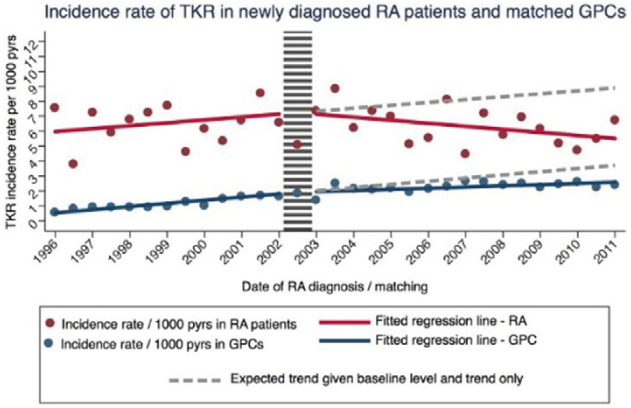
Background: Previous data have been conflicting regarding a possible impact of treatment with biological DMARDs (bDMARDs) on the need for total knee replacement (TKR) and total hip replacement (THR) in patients with rheumatoid arthritis (RA)[1].
Objectives: To investigate impact of national guidelines recommending bDMARD treatment for RA on the secular trends of TKR and THR among incident RA patients compared with matched general population controls (GPC) in Denmark.
Methods: Nationwide register-based interrupted time-series analysis using the National Patient Register and Civil Registration System.
RA: incident patients diagnosed at a rheumatology department from 1996–2011.
GPC: 10 individuals matched to each RA patient on age, sex and municipality.
Outcome: First TKR and THR, respectively.

Intervention: introduction of bDMARDs and associated publication of bDMARD recommendations in Denmark in 2002.
Statistical analyses: 5-year age- and sex-standardised incidence rates of THR and TKR calculated for incident RA patients diagnosed biannually in 1996–2011, and GPCs. Secular trends in the pre-bDMARD guideline era (1996–2002) were compared with those in the bDMARD period (2003–2016) using segmented linear regression and a 1-year lag period (2002–03). Absolute changes in TKR and THR at the midpoint (February 2007) between guideline implementation and end of study period were estimated.
Results: In total, during 1996 to 2011, 30 868 incident RA patients were identified (mean age at diagnosis 58.3 years, 70% women) and compared with 301 527 GPCs. See Table for results.

Table 1. Changes in 5-year incidence rate of total hip (THR) or total knee replacement (TKR) in incident rheumatoid arthritis (RA) patients following introduction of biological DMARDs compared with secular trends in age, sex and municipality-matched general population controls (GPC)

Cohort		n THR/TKR	Baseline incidence rate/1000 person years	Δ per year* pre-2002	Δ in level 2003	Δ per year post-2003
TKR	RA	865	5.87	+0.19	–	-0.20
	GPC	2438	0.42	+0.21	–	+0.08
THR	RA	935	8.72	-0.38	+2.23	-0.38
	GPC	4744	2.89	+0.11	–	+0.02

Stepwise backward elimination to produce most parsimonious model: p-entry <0.05 and p-exit >0.2. *Δ per year based on biannual data.



Conclusions: Prior to 2002, the incidence of TKR increased among RA patients, but started to decrease after introduction of bDMARDs and their associated guidelines in 2003 (absolute change -1.8 TKRs/1000 person years in Feb. 2007). In contrast, the incidence of TKR increased among GPCs throughout the entire study period. The incidence of THR increased in GPCs for the entire duration of the study period, whereas there was a downward going trend among RA patients, but with a surprising level increase in 2003. The overall patterns of our findings are in line with those recently reported from England and Wales[1].
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OP0252 RHEUMATOID ARTHRITIS PATIENTS WITH CONTINUED LOW DISEASE ACTIVITY HAVE SIMILAR OUTCOMES OVER 10 YEARS, REGARDLESS OF INITIAL THERAPY

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Background: Low disease activity and remission in rheumatoid arthritis (RA) patients is achieved earlier and in higher frequency when the initial treatment includes a combination of methotrexate (MTX) with corticosteroids or a biologic disease modifying anti-rheumatic drug than MTX alone. However, it is unknown whether in patients with early and persistently good response the initial treatment still has an impact on long term outcomes.
Objectives: To compare 10 years disease outcomes of RA patients with persistent low disease activity on MTX monotherapy or on initial combination therapy with infliximab or prednisone and sulfasalazine.
Methods: RA patients with 10 years follow-up from the BeSt study were analyzed. RA patients fulfilling the American College of Rheumatology 1987 criteria with <2 years symptom duration were "treated to target" aiming at disease activity score (DAS) ≤2.4, assessed with 3-monthly intervals. Patients in arms 1 and 2 started MTX monotherapy, patients in arm 3 started MTX, sulfasalazine and prednisone and patients in arm 4 started MTX and infliximab. All had DAS≤2.4 from t=6 months until t=10 years and therefore stayed on initial treatment, with patients in arms 3 and 4 tapering to monotherapy within 10 months. Patients in arms 1 and 2 were compared with patients in arms 3 and 4. Between-group differences over time were compared using (generalized) linear mixed model analyses, for the outcomes DAS, Health Assessment Questionnaire (HAQ), erythrocyte sedimentation rate (ESR), visual analogue scale (VAS) patient global health (range 0–100), percentage patients in remission and drug free remission and percentage patients with Sharp/van der Heijde score progression ≥5.
Results: At t=10 years 28/247 (11%) patients in arms 1 and 2 had sustained DAS≤2.4 compared to 68/261 (26%) patients in arms 3 and 4. Patients in arms 1 and 2 were less often ACPA positive (46% versus 54%, p=0.477), had shorter symptom duration at baseline [median (range) 14 (1–191) versus 18 (4–263) weeks, p=0.004] and less radiologic damage progression after 10 years [0 (0–16) versus 2.5 (0–26), p=0.014] than patients in arms 3 and 4. No between-group differences were found over time, except for the percentage of patients in drug free remission. Significant group-time interactions were found for DAS, ESR and VAS patient's global health, but not HAQ, percentage remission and percentage drug free remission, with slightly worse results over time for arms 3 and 4 compared to arms 1 and 2 (table 1).

Table 2: (Generalized) linear mixed model analyses to assess differences over time between MTX monotherapy responders (n=28) and combination therapy responders (n=68).

	Linear Mixed Model Analyses	β	95% CI
HAQ	Treatment group*	0.076	-0.066; 0.22
	Time	-0.0034	-0.0044; -0.0025
DAS	Treatment group*	0.031	-0.24; 0.18
	Time	-0.029	-0.037; -0.021
	Treatment group*Time	0.0056	0.0012; 0.010
ESR	Treatment group*	-3.30	-7.54; 0.93
	Time	-0.19	-0.31; -0.072
	Treatment group*Time	0.11	0.041; 0.17
VAS patient global health	Treatment group*	-4.07	-9.50; 1.37
	Time	-0.42	-0.57; -0.27
	Treatment group*Time	0.090	0.0048; 0.17
	Generalized linear mixed model analyses	**OR**	**95% CI**
SvdH score progression =5	Treatment group*	0.83	0.17; 4.01
	Time	0.94	0.83; 1.07
Remission	Treatment group*	0.58	0.32; 1.08
	Time	1.04	1.03; 1.04
Drug free remission	Treatment group*	0.14	0.033; 0.61
	Time	1.06	1.03; 1.08

*Difference between treatment groups, MTX monotherapy responders as reference group , SE = standard error, 95% CI = 95% confidence interval

Conclusions: More patients achieved continuous low disease activity on prednisone or infliximab combination therapy tapered to MTX monotherapy than on MTX monotherapy, but there appear no additional benefits of combination treatment strategies for patients who have sustained DAS≤2.4. Regardless of initial induction therapy, those who remain in low disease activity have similar long term outcomes, with only the proportion of patients in drug free remission being higher in the MTX monotherapy group. These results strongly suggest that rapid achievement of remission/LDA itself, rather than how you achieve it, is crucial for determining long-term outcome in RA.
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OP0253 PASSIVE SMOKING IN CHILDHOOD AND HISTORY OF CHRONIC DIARRHEA INCREASES THE RISK OF DEVELOPING RHEUMATOID ARTHRITIS (RA)

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Objectives: To analyse the impact of active and passive smoking and intestinal transit disorders on the risk of incident RA
Methods: This study is based on the French E3N cohort ("Etude Epidémiologique auprès de femmes de l'Education Nationale"), which included 98,995 women volunteers born between 1925 and 1950 and prospectively followed since 1990. Eleven self-administered questionnaires were sent to the participants between 1990 and 2014 to collect medical, demographic, environmental and hormonal data and dietary habits. The diagnosis of RA was collected on 2 successive questionnaires. Cases were considered certain if having declared RA and had taken a RA specific medication (methotrexate, leflunomide or biologic) since 2004 (period from which drug reimbursement data was available). Only incident and certain cases were included. Women were excluded if they had an inflammatory bowel disease and/or no information on their smoking status. Passive smoking was assessed by the following question: "When you were children, did you stay in a smoky room?". Patients were considered exposed if the answer was "yes, a few hours, or yes, several hours a day". The usual intestinal transit, reported by women prior to RA diagnosis (on average 10 years), were classified as normal