FRI0040

DEVELOPMENT AND VALIDATION OF CLINICAL PREDICTORS FOR INADEQUATE RESPONSE TO TREAT-TO-TARGET METHOTREXATE THERAPY IN NEWLY DIAGNOSED RA PATIENTS

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Background: In new-onset rheumatoid arthritis (RA), therapy should be aimed at achieving sustained remission according to current guidelines, in which methotrexate (MTX) is recommended to be included in the initial treatment strategy. However, a large proportion (~30%) eventually need additional treatment to control inflammation making it necessary to find predictors which helps clinicians in choosing the optimal initial therapy to further improve the long-term outcome of early RA patients.

Objectives: To identify and validate clinical baseline predictors associated with inadequate response (IR) to MTX therapy in disease modifying anti-rheumatic drug (DMARD)-naïve early RA patients.

Methods: For identifying clinical predictors, data was used from the U-Act-Early trial of newly diagnosed RA patients treated-to-target with a MTX strategy (n=108, development sample). MTX (oral) was started at 10 mg/week and increased in monthly steps up to 30 mg/week or maximum tolerable dose until remission. If no remission, hydroxychloroquine (HCQ) was added and, if the target, remission, thereafter still was not achieved, HCQ was replaced by tocilizumab. Patients in the tREACH trial who initiated MTX (25 mg/week) in combination with a prednisone tapering scheme were used as validation sample (n=83). In tREACH, if disease activity score (DAS) was ≥ 2.4 after three months, etanercept was added. When three months thereafter the target still was not achieved, patients switched to another tumour necrosis factor alpha inhibitor. In both studies, the definition of IR to MTX, (designated here "MTX+" therapy), was met if patients needed a biological DMARD within the first year. Clinical predictors were identified using logistic regression with backward selection ($p \leq 0.10$).

Results: In the development sample, the following predictors for IR to "MTX+" therapy were identified: DAS assessing 28 joints (DAS28), adjusted odds ratio (OR_{adj}) 2.1, 95% CI 1.4–3.1; $p < 0.001$; current smoking, OR_{adj} 3.0, 95% CI 1.1–8.0; $p = 0.027$; and alcohol consumption, OR_{adj} 0.3, 95% CI 0.1–0.9; $p = 0.021$. A risk matrix, categorised by these predictors, shows nearly a twelve and a half fold risk difference in predicted probabilities (figure 1). The area under the receiver operating characteristic curve (AUROC) of the model is 0.75 (95% CI 0.66–0.84); no statistically significant difference ($p = 0.96$) was found between the observed and predicted probabilities (i.e. calibration). When using a negative predictive value (NPV), i.e. predicted chance of not failing "MTX+" therapy, of $> 80\%$ as cut off in the development sample, the positive predictive value (PPV) was 65% (sensitivity: 0.89, specificity: 0.52). The AUROC of the model in the validation sample was 0.67 (95% CI 0.55–0.79) with no significant difference ($p = 0.28$) between observed and predicted probabilities, indicating good calibration. In the validation sample, a cut-off of NPV $> 80\%$, the PPV was 54% (sensitivity: 0.88, specificity: 0.38).

Alcohol consumption, yes: ≥ 1 unit per week. DAS28 = disease activity assessing 28 joints; LDA = low disease activity (DAS28 $2.6 \leq 3.2$); MDA = moderate disease activity (DAS28 $3.2 < 5.1$); HAD = high disease activity (DAS28 ≥ 5.1); NS = not specified, insufficient data to calculate predicted probability; IR = inadequate response.

Abstract FRI0040 – Figure 1. Risk matrix of predicted probability (%) of IR to "MTX+" therapy.

Conclusions: Higher DAS28, current smoking and no alcohol consumption were associated with an increased risk of IR to "MTX+" therapy in newly diagnosed RA patients.

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FRI0041

ASSOCIATIONS BETWEEN TYMS POLYMORPHISMS AND RESPONSIVENESS TO OR TOXICITY OF METHOTREXATE IN RHEUMATOID ARTHRITIS

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Background: Thymidylate synthase (TYMS) is a key protein in the *de novo* synthesis of pyrimidines, and is essential for DNA replication and cell proliferation. MTX is polyglutamylated to form MTX polyglutamates after entering cells, and directly inhibits TYMS. TYMS is an important target for MTX, and over-expression of the TYMS gene is associated with resistance to TYMS-targeted drugs.

Objectives: The aim of this study was to investigate whether the thymidylate synthase (TYMS) 2R/3R and 6 bp I/D polymorphisms can predict the response to or toxicity of methotrexate (MTX) in patients with rheumatoid arthritis (RA).

Methods: We conducted a meta-analysis of studies on the association between the TYMS 2R/3R and 6 bp I/D polymorphisms and non-responsiveness to or toxicity of MTX in RA patients.

Results: A total of 11 studies involving 1613 patients were considered. Meta-analysis showed no association between the TYMS 2R/3R 3R allele and non-responsiveness to MTX therapy (OR=1.087 CI=0.682–1.731, $p=0.726$). The meta-analysis indicated that there was no association between the TYMS 6 bp I/D D allele and non-responsiveness to MTX therapy (OR=0.688, 95% CI=0.281–1.683, $p=0.413$). Meta-analysis revealed no association between the overall toxicity of MTX treatment in RA and the TYMS 2R/3R 3R allele. However, meta-analysis revealed that MTX toxicity was associated with the TYMS 2R/3R polymorphism in RA patients when a co-dominant model (3 R2R vs. 3 R3R +2R2R) was used, indicating that heterozygotes (3 R2R) for the polymorphism had a higher risk of developing MTX toxicity than homozygotes (3 R3R+2R2R). Stratification by ethnicity indicated an association between the TYMS 2R/3R 3R allele and non-responsiveness to MTX in Caucasians, but not in non-Caucasians. In contrast, meta-analysis revealed no association between the overall toxicity of MTX and the TYMS 6 bp I/D D allele.

Conclusions: This meta-analysis demonstrates that the TYMS 2R/3R and 6 bp I/D polymorphisms may not be associated with non-responsiveness to MTX therapy, but that the TYMS 2R/3R polymorphism may be associated with MTX toxicity in RA, particularly in Caucasians.

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FRI0042

TENDER JOINTS HAVE LOW AGREEMENT WITH PATIENT'S EVALUATION OF SPONTANEOUS JOINT PAIN, JOINT SWELLING AND ULTRASOUND VERIFIED SYNOVITIS IN PATIENTS WITH ESTABLISHED RHEUMATOID ARTHRITIS

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Background: Tender joint count is included in the clinical composite scores (CDAI, SDAI, DAS28) which serves as a proxy for inflammatory activity. However, there may be several causes of joint tenderness, including both nociception and central sensitisation. Ultrasonography (US) is sensitive for evaluation of joint inflammation (synovitis (grey scale, GS) and vascularisation (power Doppler, PD)).

Objectives: In patients with rheumatoid arthritis (RA) to explore the agreement at a joint level between tenderness, spontaneous patient reported joint pain, swelling and US synovitis.

Methods: 174 patients with established RA (mean (SD) age 52¹³ years, disease duration 10⁸ years, 82% women, 79% anti-CCP positive were assessed when they initiated bDMARD treatment and after 1, 2, 3, 6 and 12 months. An experienced study nurse assessed presence/absence of joint tenderness and swelling (wrist, MCP1–5, PIP2–3, elbow, knee, ankle and MTP1–5 bilaterally). The same 32 joints were assessed by use of a manikin for Patient Reported Spontaneous Joint Pain (PRSJP) the last day as well as US (GS and PD, both scored 0–3) by an experienced sonographer (HBH). Agreement at joint level was explored between categorical variables using Cohens kappa (US scores transformed to presence (PD score 1–3/GS score 2–3) versus absence (PD score 0/GS score 0–1), and in addition agreement between presence of tenderness/swelling and the different US scores were explored.

Results: A total of 4091 (baseline) and 22 885 (all visits) joints were assessed. Tender joints had moderate agreement with PRSJP and swollen joints, and lower with US synovitis. Swollen joints had high agreement with US synovitis (table 1), and US synovitis was found in 75% of swollen joints. There were no differences in agreement between results at baseline and all visits, or if subgroup analyses were performed of only finger joints. A clear relationship was found between increasing GS/PD scores and percentages of joints being swollen, but this association was not found for tender joints (table 2).

Abstract FRI0042 – Table 1. Kappa values for agreement between categorical variables at baseline (4091 joints)/all visits (22885 joints)

	PRSJP	Swollen joint	GS US	PD US
Tender joint	0.34/0.40	0.32/0.32	0.21/0.21	0.20/0.20
PRSJP		0.25/0.26	0.23/0.24	0.25/0.23
Swollen joint			0.57/0.56	0.56/0.54

Abstract FRI0042 – Table 2. At joint level; percentages of agreement between joints being tender and/or swollen and US synovitis (all visits, number of joints in parenthesis)

	GS=0 (n=13874)/PD=0 (n=18656)	GS=1 (n=4077)/ PD=1 (n=1888)	GS=2 (n=3079)/ PD=2 (n=1791)	GS=3 (n=1855)/ PD=3 (n=550)
Swollen joints	3.8%/7.9%	16.3%/45.7%	47.1%/70.1%	77.7%/86.7%
Swollen, but not tender joints	2.1%/4.4%	8.8%/28.2%	26.7%/42.0%	49.4%/51.8%
Tender joints	9.7%/12.7%	20.4%/27.5%	29.7%/33.1%	32.7%/39.3%
Tender, but not swollen joints	8.0%/9.1%	12.8%/10.0%	9.3%/4.8%	4.4%/3.8%

Conclusions: Tender joints had weak agreement with presence of US synovitis, while swollen joints had strong agreement. PRSJP had moderate/weak agreement with all the other assessments. Presence of swelling was highly associated with the degree of US synovitis, while this association was not found for tenderness. Our results raise questions regarding the prominent role of tender joint count in RA clinical composite scores for disease activity.

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FRI0043 TRENDS IN ALL-CAUSE AND CARDIOVASCULAR MORTALITY IN PATIENTS WITH RHEUMATOID ARTHRITIS. A 10- TO 20-YEAR FOLLOW-UP STUDY IN 3 CONSECUTIVE INCIDENCE COHORTS

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Background: The mortality rate in patients with rheumatoid arthritis (RA) has been estimated to be 1.5–1.6 compared to the general public. Moreover, RA patients are still not benefitting fully from the declining mortality rate that the general population has enjoyed and cardiovascular disease (CVD) continues to be a major concern.

Objectives: To examine the all-cause and CVD mortality in 3 consecutive cohorts of patients with incident RA, compared to population controls

Methods: The Oslo RA register (ORAR) was established in 1994. The inclusion criteria were a diagnosis of RA according to the 1987 ACR criteria and residency in Oslo. The register was updated annually until 2009, and validated for completeness.¹ In January 2012, 3328 patients were registered in ORAR. We grouped patients into 3 successive incidence cohorts; 1996(1994–1998), 2001 (1999–

2003) and 2006(2004–2008). For each patient we identified 5 historical population controls matched according to age at disease incidence, gender and postal code of residence. Patients and controls were linked to the Norwegian Cause of Death Registry. Counts were compared using chi² tests. The hazard ratio (HR) for survival was calculated using stratified cox-regression models adjusted for highest achieved level of education.

Results: 422, 477 and 459 patients in the 1996, 2001 and 2006 cohorts were matched to 2110, 2385 and 2295 controls respectively. 20, 15 and 10 years follow-up for 1996, 2001 and 2006 cohorts were available in 201, 292 and 311 patients respectively. Results are presented in the table 1.

	1996		2001		2006	
	ORAR	Controls	ORAR	Controls	ORAR	Controls
Age years mean (SE)	55.9 (0.8)	55.9 (0.4)	54.1 (0.7)	54.1 (0.3)	54.7 (0.7)	54.7 (0.3)
Female gender n (%)	308 (73.0)	1540 (73.0)	358 (75.1)	1790 (75.1)	328 (71.5)	1640 (71.5)
Deaths at 5 years n(%)	37 (8.8)	180 (8.5)	30 (6.3)	130 (5.5)	25 (5.5)	104 (4.5)
Deaths at 10 years n (%)	95 (22.5)	371 (17.6)*	78 (16.4)	297 (12.5)*	38 (12.2)	257 (11.2)
Deaths at 15 years n (%)	147 (34.8)	586 (27.8)*	82 (28.1)	482 (20.2)*		
Deaths at 20 years n(%)	88 (43.8)	801 (38.9)				
CVD deaths 5 years n(%)	20 (4.7)	57 (2.7)*	8 (1.7)	30 (1.3)	6 (1.3)	26 (1.1)
CVD deaths 10 years n (%)	39 (9.2)	128 (6.1)	28 (5.9)	74 (3.1)*	9 (2.8)	59 (2.6)
CVD deaths 15 years n (%)	57 (13.5)	210 (10.0)*	27 (9.2)	138 (5.8)		
CVD deaths 20 years n (%)	43 (21.4)	290 (13.7)*				
HR 5 year all-cause mortality (95% CI)	1.01 (0.71–1.44)		1.01 (0.67–1.51)		1.17 (0.75–1.81)	
HR 10 year all-cause mortality (95% CI)	1.27 (1.01–1.61)*		1.18 (0.91–1.52)		0.98 (0.69–1.40)	
HR 15 year all-cause mortality (95% CI)	1.39 (1.15–1.69)*		1.41 (1.10–1.83)*			
HR 20 year all-cause mortality (95% CI)	1.49 (1.16–1.90)*					
HR 5 year CVD mortality (95% CI)	1.68 (1.00–2.82)		1.13 (0.51–2.51)		1.20 (0.49–2.95)	
HR 10 year CVD mortality (95% CI)	1.49 (1.03–2.16)*		1.69 (1.07–2.69)*		0.97 (0.47–2.02)	
HR 15 year CVD mortality (95% CI)	1.55 (1.13–2.12)*		1.67 (1.05–2.65)*			
HR 20 year CVD mortality (95% CI)	2.27 (1.56–3.31)**					

*p<0.05.

Conclusions: RA patients with disease incidence in the period 1994–2003 had increased all-cause and CVD related mortality after 10–15 years of disease duration, compared to the population of Oslo. The increased mortality was not observed in the 2004–2008 cohort. Improved survival in recent years may be related to more effective therapies and earlier diagnosis, but further analyses are warranted.

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FRI0044 EXCEEDING PREDEFINED THRESHOLDS FOR MRI BONE OEDEMA AND EROSION AND HAQ-DI CAN PREDICT RELAPSE AFTER WITHDRAWAL OF ALL TREATMENT IN MTX-NAÏVE PATIENTS WITH RA IN REMISSION AFTER 12 MONTHS OF ABATACEPT THERAPY IN THE AVERT TRIAL

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Background: To assist in clinical decision making it is important to understand the factors, and their thresholds, that might predict relapse following treatment