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 $3.2 < 5.1$); HDA = 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.

REFERENCES:

- [1] Bohanec Grabar P, Logar D, Lestan B, et al. Genetic determinants of methotrexate toxicity in rheumatoid arthritis patients: a study of polymorphisms affecting methotrexate transport and folate metabolism. *European Journal of Clinical Pharmacology* 2008;64(11):1057–1068.
- [2] Kremer JM. Toward a better understanding of methotrexate. *Arthritis Rheum* 2004;50(5):1370–1382.

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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)).