Methods: 55 persons were included, divided into 20 RA patients, 25 FDR of RA patients (without evidence of arthritis) and 10 healthy matched controls. Clinical evaluation, with emphasis on joint symptoms and signs was done for all, in addition to measurement of ESR, CRP, RF, anti-CCP, serum OPN and serum OPG.

Results: Mean ESR was significantly higher in RA (64.15±34.29) than in FDR (39.72±17.52), Mean CRP was significantly higher in RA (143.89±56.49) than in both FDR (62.23±65.73, p=0.009) and controls (6.20±12.43, p=0.003). Mean serum OPN in RA was higher in RF and CCP positive (4.43 and 4.13±3.48 respectively) than RF and CCP negative (2.65±0.35 and 3.58±2.58 respectively) but without reaching statistical difference. Mean serum OPG in RA was higher in RF and CCP positive (153.13±38.64 and 161.78±394.67 respectively) than RF and CCP negative (60.50±85.56 and 42.47±68.09 respectively) but without reaching statistical difference. 8/25 (32%) FDR had arthralgia while 17/25 (68%) FDR were asymptomatic. FDR with arthralgia had significantly higher ESR (27.8±11.22) and CRP (10.3±6.21) than asymptomatic FDR (9.8±4.13, p=0.003) and (3.93±3.58, p=0.003) respectively. OPG was higher in FDR than in controls and higher in those with arthralgia (51.55±114.68) than those without (84.4±9.67) but without reaching statistical difference (p=0.314). Similarly, serum OPG was higher in FDR with arthralgia (2.09±1.19) than asymptomatic (1.70±0.55) but also without significant difference (p=0.620).

Furthermore, mean RF and anti-CCP were higher in FDR vs controls (1.122 (p<0.0001) and overall IDI was 0.279 (p<0.0001). For hepatotoxicity, genetic prediction model using 7 SNPs showed AUC was 0.783 with sensitivity of 70.0% and specificity of 80.0%, while combined clinical and genetic model indicated AUC was 0.906 with sensitivity of 85.1% and specificity of 87.8%. Overall category-free NRI was 1.122 (p=0.0001) and overall IDI was 0.279 (p=0.0001).

Conclusions: OPN and OPG are markers of altered bone metabolism in RA. Their elevation in FDR than controls denotes a state of altered bone metabolism. Moreover, FDR with arthralgia experience higher levels of OPN, OPG, ESR, RF, CRP, RA, and anti-CCP than asymptomatic FDR. These findings reflect an ongoing disturbed bone metabolism and inflammation in FDR which could precede the clinical disease phase. Thus, OPN and OPG could serve as markers of altered preclinical bone metabolism in rheumatoid FDR. Results need to be confirmed on larger numbers of FDR.

Disclosure of Interest: None declared


SAT0083

THE GENETIC AND CLINICAL PREDICTION MODELS FOR EFFICACY AND HEPATOTOXICITY OF METHOTREXATE IN PATIENTS WITH RHEUMATOID ARTHRITIS


Background: The efficacy and toxicity of methotrexate (MTX) depend on individual patients with rheumatoid arthritis (RA) and are difficult to predict before treatment although MTX is the anchor drug and achieving the treatment target earlier is desirable to prevent progression of structural and functional damage. Our previous studies revealed high predictive accuracy of single nucleotide polymorphisms (SNPs) to predict the efficacy and toxicity of MTX, suggesting the influence of genetic variations in enzymes associated with MTX metabolism and folate metabolic pathway1,2. However, higher accuracy and replicability is demanded for clinical application.

Objectives: To develop combined genetic and clinical models to predict the efficacy and hepatotoxicity of MTX.

Methods: Patients with RA under the treatment of MTX according to Japanese guideline for the management of RA with MTX were enrolled. To predict the efficacy and hepatotoxicity, 1971 polymorphisms of 246 enzymes/transporters potentially relevant to pharmacokinetics and pharmacodynamics of MTX were measured by the DME microarray (Affymetrix Inc.) and direct-sequencing method and clinical variables at baseline were collected. As for efficacy, the EULAR-CRP response criteria was chosen to classify patients with RA as responders (good response) and non-responders (moderate or no response). Hepatotoxicity was defined as either serum AST or ALT levels higher than 1.5 times the upper limit of the normal range. Among SNPs and clinical variables with significant association with outcomes using univariate analyses, stepwise model selection was conducted by Akaike information criterion in logistic regression model and receiver operating characteristic (ROC) analyses were performed. Bootstrapping (n=100,000) was used to assess the robustness of the results.

Results: A total of 166 patients with RA was included. The median age was 61.5 years with 81.3% of women. For efficacy, genetic prediction model using 7 SNPs showed area under the curve of ROC (AUC) was 0.822 with sensitivity of 74.3% and specificity of 76.8%, while combined clinical and genetic model indicated AUC was 0.844 with sensitivity of 81.5% and specificity of 76.9%. By incorporating clinical variables into the genetic model, overall category-free net reclassification improvement (IDI) was 0.700 (p<0.0001) and overall integrated discrimination improvement (IDI) was 0.089 (p=0.0005). For hepatotoxicity, genetic prediction model using 7 SNPs showed AUC was 0.783 with sensitivity of 70.0% and specificity of 80.0%, while combined clinical and genetic model indicated AUC was 0.906 with sensitivity of 85.1% and specificity of 87.8%. Overall category-free NRI was 1.122 (p=0.0001) and overall IDI was 0.279 (p=0.0001).

Conclusions: Genetic and clinical models showed higher predictive accuracy for both efficacy and hepatotoxicity of MTX. These models should be validated with a larger scale of prospective study.

REFERENCES:

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SAT0084

ANTI-CARBAMYLATED PROTEIN ANTIBODIES AS POTENTIAL BIOMARKERS OF DISEASE ACTIVITY IN EARLY ARTHRITIS PATIENTS

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Background: It has become increasingly clear that appropriate initial management of rheumatoid arthritis (RA) increases the chances of success and improves long-term prognosis. Therefore, rheumatologists need prognostic biomarkers to select patients requiring aggressive management. It is possible that anti-carbamylated protein antibodies (anti-CarPA) may serve as such biomarkers because they are associated with erosions and their progression, and with mortality in some studies. Recently, the possibility that they are also associated with disease activity in early arthritis (EA) has been examined by several studies with discordant results.

Objectives: We aimed to explore the relationship between variation in disease activity and anti-CarPA in EA patients.

Methods: EA patients from two prospective clinics, Hospital Universitario La Paz (n=492) and Hospital Universitario La Princesa (n=501), were included. DAS28 was available at baseline and at months 6 (M6), 12 (M12) and 24 (M24) of follow-up. Anti-CarPA were determined in baseline serum samples by ELISA using in vitro carbyamylated fetal calf serum. Student t test and main effects general linear regression were used for analysis.

Results: The 27.4% of EA patients that were positive for anti-CarPA showed higher DAS28 at baseline than the negative patients (4.93 vs 4.31, p=1.8x10^-8). The difference persisted at all visits during follow-up (3.60 vs 3.19 at M6; 3.47 vs 3.09 at M12; and 3.31 vs 2.79 at M24; all with p<0.001). These differences were independent of patient sex and age, smoking, time since symptoms onset, the specific EA clinic and the year of onset. In addition, they persisted after accounting for the presence of RF or ACPA at baseline (p<1.3x10^-3 and p=5.7x10^-3 respectively) and at later visits (p<0.05 for all analyses). Analysis of the relation