POS0466

RHEUMATOID ARTHRITIS PER SE IS NOT RISK FACTOR FOR CLINICAL FRACTURES: NINE-YEAR FINDINGS OF THE TOMORROW STUDY

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Background: Patients with rheumatoid arthritis (RA) who have sarcopenia and stiff or painful joints might be at increased risk of falls and fractures.

Objectives: The present study aimed to prospectively identify the incidence of clinical fractures and associated risk factors in patients with RA in a cohort study named the TOMORROW (UMIN00003876) that started in 2010.

Methods: We evaluated anthropometric parameters, bone mineral density (BMD), disease activity, RA medication at baseline and observed the incidence of clinical fractures during nine years in 202 patients with RA (mean age, 58.6 y; medication with biological agents, 54.9%) and 202 age- and sex-matched non-RA volunteers (mean age, 57.4 y). We compared the incidence of clinical fractures between patients with RA and controls for nine years, and analyzed the risk factors for fractures using Cox proportional hazard model.

Results: The incidence of clinical fractures in RA patients was significantly higher compared to controls (27.5 vs 18.3%, $p=0.04$). However, Cox proportional hazard model, adjusted by age, sex, smoking and body mass index, revealed that low BMD at thoracic vertebrae ($< 0.7 \text{ g/cm}^2$) significantly associated to the incidence of clinical fractures (hazard ratio [HR], 1.86, $p=0.02$), but not RA morbidity (HR 1.47, $p=0.10$) (Table 1). Among patients with RA, low BMD at the thoracic vertebrae ($< 0.7 \text{ g/cm}^2$) was the most prominent risk factor for clinical fractures (HR, 2.66, $p=0.02$) (Table 1). Although the use of glucocorticoid (GC) at baseline (HR, 1.68, $p=0.09$) was not a significant risk factor for fractures, a mean GC dose ($\geq 2 \text{ mg/day}$) at entry increased risk for clinical fractures in the patients (HR, 1.91, $p=0.04$) (Table 1).

Table 1. Cox proportional hazard model (adjusted for fracture risk factors including age, sex, smoking, and body mass) of risk factors for clinical fractures.

		hazard ratio	95% CI	p
All participants	History of fractures	0.24	0.77-1.98	0.38
N=404	Morbidity of RA	1.47	0.92-2.34	0.10
	Low BMD at thoracic vertebrae ($< 0.7 \text{ g/cm}^2$)	1.86	1.09-3.17	0.02
RA patients	History of fractures	1.27	0.70-2.29	0.43
N=202	GC medication	1.68	0.92-3.06	0.09
	A mean GC dose $\geq 2 \text{ mg/day}$ at entry	1.91	1.05-3.49	0.04
	Low BMD at thoracic vertebrae ($< 0.7 \text{ g/cm}^2$)	2.66	1.20-5.89	0.02

CI, confidence interval; RA, rheumatoid arthritis; GC, glucocorticoid; BMD, bone mineral density.

Conclusion: RA per se was not a risk factor for clinical fractures in this cohort. Low BMD at the thoracic vertebrae and the use of GC with even low dose at entry were apparently significant risk factors for the incidence of clinical fractures among patients with RA.

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STUDY OF METHOTREXATE METABOLITES CONCENTRATIONS IN RED BLOOD CELLS AND MONONUCLEAR CELLS IN RHEUMATOID ARTHRITIS

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Background: Studying the dynamics of the methotrexate metabolites concentration in cells will help to predict the therapeutic effect and assess patient compliance. We suggest that studying the dynamics of changes in the concentration of methotrexate metabolites in mononuclear cells (MO) may be a more accurate method than measuring in red blood cells (RBC).

Objectives: To study the dynamics of changes in the concentration of MTX and its metabolites in RBC and MO in methotrexate-naïve patients with RA.

Methods: 33 patients (26 women, 7 men) aged 53.2 ± 11.7 years with a diagnosis of rheumatoid arthritis, according to the ACR / EULAR 2010 criteria, were included. All patients had GFR $>60 \text{ ml/min}$. Patients were monitored after 4, 12, 24 and 36 weeks from the start of MTX. Mean Cell Volume (MCV) of RBC was measured by standard methods. Samples of RBC and MO were collected separately to determine the concentrations of MTX (basic monoglutamate form), total concentration of MTPG2, MTPG3 and MTPG4 (MTPG2-4), 7-hydroxymethotrexate (7-OH-MTX) by tandem mass spectrometry.

RESULTS:

A pairwise comparison of MTX, MTPG2-4 and 7-OH-MTX concentrations, according to the Wilcoxon method did not reveal statistically significant differences at weeks 4, 12 and 24. The concentration of the studied substances did not correlate with the value of the body mass index, taking statins, glucocorticoids, a cumulative dose of MTX, and the frequency of adverse reactions. At the week 4, of therapy, the level of MTPG4 in MO was inversely correlated with the duration of the disease (correlation coefficient - 0.58, $p 0.05$) The concentration of MTX and its metabolites in MO was lower in smokers (MTX 11.2 [2.6;21.9], 7-OH-MTX 2.1 [0.5; 10.4], MTPG2 0.5 [0.1;1.3]) than in non-smokers (MTX 46.5 [25.3;97.5], 7-OH-MTX 28.2 [7.1; 64.7], MTPG2 8.2 [4.1;32.9]), $p = 0.02$, 0.01 and 0.003, respectively. At week 24 of therapy, a negative correlation was found between age and MTPG4 level (correlation coefficient 0.51, $p <0.05$).

Table 1. Total concentration of MTPG2, MTPG3 and MTPG4 (MTPG2-4), nmol/l

		Me	[25;75]	Min	Max
Week 4	RBC	42.8	19.0;155.0	3	987.7
	MO	6.2	5.3;11.9	1.6	147.2
Week 12	RBC	48.1	17.1;89.0	0.1	519.9
	MO	10.9	3.9;31.0	0.9	147.6
Week 24	RBC	39.4	17.2;70.6	2.7	191.8
	MO	8.3	2.7;14.0	0.4	72.4

Conclusion: The inadequate response to MT therapy in smokers, described in many previous studies, may be associated with a low concentration of the MTX metabolites in mononuclear cells.

The level of MTPG4 in mononuclear cells increases more slowly in patients with a longer duration of the disease.

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POS0468

PREDICTION OF RHEUMATOID ARTHRITIS DISEASE ACTIVITY BY AN ADAPTIVE DEEP NEURAL NETWORK: BETTER RESULTS IN SEROPOSITIVE PATIENTS WITH LONGER DISEASE DURATION

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Background: Deep neural networks learn from former experiences on a large scale and can be used to predict future disease activity as potential clinical decision support. AdaptiveNet is a novel adaptive recurrent neural network optimized to deal with missing clinical data. In rheumatoid arthritis (RA) it is unknown how disease characteristics influence the predictability by deep learning in terms of classification (e.g. active disease yes/no) or regression (numeric values such as DAS28).

Objectives: To investigate in which clinical RA subtypes AdaptiveNet achieves the best results for the prediction of individual disease activity

Methods: Demographic and disease characteristics from over 9500 patients and 65.000 visits from the Swiss Quality Management (SCQM) database were used to train and evaluate the network. Patient characteristics, clinical and patient reported outcomes, laboratory values and medication were used as input features. DAS28-BSR served as a target to predict active RA and future numeric individual disease activity by classification and regression. Feature importance

was determined by a Random Forest to define the relative importance of variables for disease prediction.

Results: AdaptiveNet predicted active disease defined as DAS28-BSR >2.6 at the next visit with an overall accuracy of 75.6% (SD $\pm$ 0.7%) and a sensitivity and specificity of 84.2% (SD $\pm$ 1.6%) and 61.5% (SD $\pm$ 3.6%), respectively. The performance of the prediction for correct disease status was significantly higher in patients with a disease duration >3 years and positive rheumatoid factor. Regression allowed forecasting individual DAS28-BSR values with a Mean Squared Error (MSE) of 0.9 (SD $\pm$ 0.05). Compared to Linear Regression, Random Forests and Support Vector Machines, AdaptiveNet showed an increased performance of 7% in MSE. MSE was significantly lower in patients with disease duration >3 years and with positive anti-CCP antibodies. Feature importance identified number of painful joints, longer disease duration and age as most relevant factors for prediction of remission, whereas medication played a smaller role.

Conclusion: Predictability of disease activity in RA by this deep neural network was stronger in patients with a longer disease history and a positive auto-antibody status, potentially due to a more stable disease course. Generally, AdaptiveNet had a superior capacity to predict numeric RA disease activity compared to classical machine learning architectures, however all investigated models had limitations in low specificity.

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POS0469

FALL RISK ASSESSMENT IN RHEUMATOID ARTHRITIS PATIENTS

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Background: Rheumatoid arthritis patients may have an increased risk of falls due to changes caused by the disease such as muscle weakness, joint impairment, reduced mobility and postural instability.

Objectives: The aim of this study was to analyze the occurrence of falls in RA patients and its risk factors.

Methods: Between January 2020 and July 2020, 51 patients with RA were included in the study. fall history, and the number of falls within the past 12 months were questioned. All participants were assessed with Timed Up and Go Test (TUGT), One-Leg Stand Test (OLST), Walking and Talking Test (WTT), Sternal Push Test (SPT), Tinetti Test (TT), Four Test Balance Scale (FTBS), The Short Falls Efficacy Scale-International (FES-I), Pain Severity and Patient Global Assessment (PGA) by Visual Analog Scale (VAS), disability by the Health Assessment Questionnaire (HAQ), and disease activity by Disease Activity Score in 28 joints (DAS28) were evaluated in for each patient. The Kolmogorov-Smirnov, Mann-Whitney and chi-square tests were performed with a significance level of $P \leq 0.05$.

Results: 22 patients had at least one or more falls. The average age was 54.9 ± 11.5 years with a female predominance (sex ratio = 0.13). Comparing the two groups of patients: those with a history of falls and those without, patients with previous falls were mainly married women ($p=0.57$), with a low intellectual level ($p=0.63$). The body mass index in this group was higher ($p=0.01$) with respectively a higher number of painful and swollen joints ($p=0.16$, $p=0.07$); the mean HAQ was higher ($p=0.03$), and the mean VAS was more important ($p=0.05$). 12/22 patients had co-morbidities and were poly-medicated. 20/22 had joint foot deformities (hallux valgus was the most common deformity). 21/22 were on low dosage corticosteroid therapy. The mean TUGT was 18.5 seconds (>14 seconds). The OLST was less than 5 seconds in 12/22, the sternal push test was positive in 9/22, WTT was positive in 6/22 and the mean tinetti test was 22.4 ± 5.4 suggesting a high risk of falls. The average Short FES-I was 14.6 ± 4.4 reflecting a high fear of falls in this group of patients.

Conclusion: Knowledge about risk factors can help to identify high-risk patients in order to decrease their risk of falling, thus preventing fall-related injuries.

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POS0470

GLUCOCORTICOID DISCONTINUATION IN EARLY RHEUMATOID AND UNDIFFERENTIATED ARTHRITIS PATIENTS. A SUB-ANALYSIS OF THE BeSt AND IMPROVED STUDIES

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Background: Discontinuation of glucocorticoids (GC) as bridging therapy in rheumatoid arthritis (RA) treatment is recommended as rapidly as clinically feasible. Little is known about the rate of, and possible characteristics associated with successful GC discontinuation.

Objectives: To evaluate the success rate of GC discontinuation, and to study which factors are associated with successful GC discontinuation.

Methods: Data from two treat-to-target studies; BeSt (target DAS ≤ 2.4 , LDA), and IMPROVED (target DAS <1.6 , remission) were evaluated for all patients initially treated with a tapered high-dose of oral GC with conventional DMARD(s). GCs were discontinued when DAS ≤ 2.4 was maintained for 28 weeks in BeSt, and as soon as DAS was <1.6 in IMPROVED. GC discontinuation could be attempted twice: first attempt called 'primary', second attempt after GC restart called 'secondary'. Discontinuation was considered successful if the treatment target was maintained at the next visit. Univariable, and exploratory forward and backward multivariable logistic regression analyses were performed to identify potential characteristics associated with successful discontinuation (p -value <0.2 included in final model).

Results: From the 131 patients initiating combination therapy with prednisone in the BeSt study, 93 attempted discontinuation. Primary discontinuation was successful in 60% (56/93) and secondary discontinuation in 54% (19/35). A lower DAS at the visit prior to GC discontinuation and ACPA negativity were associated with successful discontinuation (table 1). Of the 610 patients in the IMPROVED, 400 attempted discontinuation. Primary discontinuation was successful in 61% (242/400), and secondary in 51% (71/139). A lower DAS both at baseline and at the visit prior to GC discontinuation were associated with successful discontinuation (table 1).

Conclusion: Primary GCs discontinuation was successful in approximately 60% and secondary in 50% of patients, independent of the treatment target and associated threshold for GC discontinuation. Most baseline characteristics were not predictive of successful GC discontinuation, but ACPA negativity (only in BeSt), baseline DAS (only in IMPROVED) and in both studies DAS prior to GC discontinuation were predictive for successful discontinuation. Based on this data it seems that 'standard' baseline characteristics are insufficient to 'personalize' the duration of temporary GC bridging but the DAS at the moment of GC discontinuation might give guidance.

Table 1. Results logistic regression analyses

	Univariable		Multivariable ^a	
	OR (95% CI)	p-value	OR (95% CI)	p-value
BeSt				
Age, year	1.00 (0.98; 1.03)	0.98		
Gender, female	0.51 (0.24; 1.09)	0.08		
Symptom duration BL, weeks	1.00 (0.99; 1.01)	0.61		
DAS at BL	0.92 (0.61; 1.40)	0.70		
DAS prior to discontinuation	0.13 (0.05; 0.33)	<0.01	0.11 (0.04; 0.30)	<0.01
RF, positive	1.28 (0.62; 2.69)	0.50	2.24 (0.81; 6.17)	0.12
ACPA, positive	0.70 (0.34; 1.43)	0.32	0.32 (0.12; 0.86)	0.02
Erosions, present at BL	0.65 (0.28; 1.49)	0.31		
Univariable				
Multivariable ^a				
IMPROVED				
Age, year	1.00 (0.99; 1.02)	0.64		
Gender, female	0.62 (0.43; 0.89)	0.01	0.75 (0.51; 1.11)	0.15
Symptom duration BL, weeks	1.00 (0.99; 1.00)	0.43	0.99 (0.99; 1.00)	0.08
DAS at BL	0.80 (0.65; 0.98)	0.03	0.78 (0.62; 0.98)	0.03
DAS prior to discontinuation	0.24 (0.15; 0.38)	<0.01	0.24 (0.14; 0.40)	<0.01
RF, positive	0.82 (0.57; 1.17)	0.27		
ACPA, positive	0.95 (0.66; 1.35)	0.76		
Erosions, present at BL	0.80 (0.49; 1.29)	0.35		
Univariable				
Multivariable ^a				

ACPA: anti-citrullinated protein antibodies; BL: baseline; DAS: disease activity score; RF: rheumatoid factor. ^a The final multivariable logistic regression model was based on stepwise forward and backward selection of predictors, both resulting in the same final model.

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