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AB0271 FACTORS ASSOCIATED WITH HOSPITAL ADMISSIONS MORTALITY IN RHEUMATOID ARTHRITIS PATIENTS IN SPAIN. (TREND-AR STUDY)

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Background: There have been significant changes in the management of rheumatoid arthritis (RA) during the past 20 years. The potential impact of these changes on hospital admissions mortality is unknown.

Objectives: To analyse the factors associated with hospital admissions mortality in rheumatoid arthritis patients in Spain from 1999 to 2015.

Methods: This is a retrospective population study. We have analyzed a national administrative database that includes a Minimum Basic Data Set (MBDS) of hospital admissions of RA patients during the period 1999 to 2015. We studied all the cases of hospital admissions mortality. Patients were identified by concatenation of clinical record number and birth date. The analyzed factors were identified by the presence in primary and secondary diagnosis of the ICD9 codes, during the first hospital admission. Hazard Ratio (adjusted by sex and age) were calculated using Cox regression analyses.

Results: There were a total of 338.343 hospital admissions in RA patients during the study period, accounting for a total of 186.491 patients (127.203 women (68,21%) and 59.288 men (31,79%). The mean number of hospital admissions was 1,81(SD 1,7), with a minimum of 1 and a maximum of 43. The median time of follow-up was 11,85 months (DE 27,4). There were a total of 18.641 exits (5,5%). The HR (adjusted by sex and age) of the factors associated with hospital admissions mortality are shown in the next table:

Risk factor	Adjusted by sex and age Cox reg analyses		
	HR	IC	p
Gender (Male/Female)	1,242	1,20-1,28	<0,001
Age	1,066	1,064-1,068	<0,001
Charlson Index	1,276	1,268-1,284	<0,001
Stay	1,004	1,003-1,005	<0,001
Cardiovascular disease	1,318	1,274-1,362	<0,001
Dementia	1,852	1,696-2,021	<0,001
Diabetes Mellitus	1,093	1,05-1,137	<0,001
Neoplasm	2,432	2,313-2,556	<0,001
Hepatopathy severe-moderate	3,189	2,752-3,695	<0,001
COPD	1,113	1,071-1,156	<0,001
Pressure ulcers	1,115	1,006-1,235	0,036
Renal Disease	1,758	1,683-1,837	<0,001
Infectious disease during stay	1,593	1,545-1,642	<0,001
S. Felty	1,531	1,18-1,985	<0,001
Amyloidosis	2,957	2,627-3,327	<0,001
Hip fracture	0,731	0,664-0,804	<0,001
Tuberculosis	1,066	1,064-1,068	<0,001

Conclusion: In Spain, during the period of 1999-2015, the factors associated with hospital admission mortality (first admission) are: age, male sex, higher Charlson Index and longer hospital stay. The associated clinical variables are chronic hepatopathy, amyloidosis and neoplasm.

Disclosure of Interests:

None declared

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AB0272 EVALUATION OF CXCL13, sICAM-1, MMP-3 AND S100A8/A9 AS SERUM BIOMARKERS IN PATIENTS WITH RHEUMATOID ARTHRITIS TREATED WITH SUBCUTANEOUS TOLICIZUMAB

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Background: Serum levels of C-X-C motif chemokine ligand 13 (CXCL13) and soluble intercellular adhesion molecule-1 (sICAM-1) have been associated with response to tocilizumab (TCZ) in patients with rheumatoid arthritis (RA); levels of matrix metalloproteinase-3 (MMP-3) and S100A8/A9 have also been associated with RA disease activity and joint damage.

Objectives: To evaluate the association of CXCL13, sICAM-1, MMP-3 and S100A8/A9 levels with disease activity and response to TCZ in patients with RA who achieved low disease activity with 24 weeks of TCZ + methotrexate (MTX) treatment and were subsequently randomized to TCZ monotherapy (mono) or TCZ + MTX in the COMP-ACT trial (NCT01855789).

Methods: US patients with RA who had an inadequate response to MTX received initial combination therapy of MTX plus TCZ 162 mg subcutaneous for 24 weeks. Patients who achieved Disease Activity Score in 28 joints calculated with erythrocyte sedimentation rate (DAS28-ESR) ≤ 3.2 at Week 24 were randomized 1:1 (double-blind) to receive either TCZ mono or continue TCZ + MTX until Week 52. Randomized patients were included in the present study based on baseline, Week 24 and Week 40 sample availability; serum levels of CXCL13, sICAM-1, MMP-3 and S100A8/A9 were measured by immunoassay. Correlations between CXCL13, sICAM-1, MMP-3 and S100A8/A9 levels and DAS28-ESR at baseline, Week 24 and Week 40 were determined according to Spearman correlation coefficient. Changes in CXCL13, sICAM-1, MMP-3 and S100A8/A9 levels from baseline to Week 24 (open-label period) were determined using Wilcoxon test. Mean changes in CXCL13, sICAM-1, MMP-3 and S100A8/A9 levels from Week 24 to Week 40 (randomized period) were compared between treatment arms using analysis of covariance.

Results: Of 296 randomized patients, 249 were included (TCZ mono, n = 126; TCZ + MTX, n = 123). Biomarker levels were well balanced across treatment arms at baseline and Week 24 (randomization). At baseline, there were weak to mild correlations between DAS28-ESR and biomarker levels (CXCL13 [r = 0.13, P = 0.0411], sICAM-1 [r = 0.20, P = 0.0015], MMP-3 [r = 0.19, P = 0.0021], S100A8/A9 [r = 0.25, P = 0.0001]). Significant reductions in mean biomarker levels were observed from baseline to Week 24 (open-label period) among the total randomized patients (P < 0.0001). CXCL13, sICAM-1, MMP-3 and S100A8/A9 levels were relatively stable between Week 24 and Week 40 (randomized period), with no significant differences between TCZ mono and TCZ + MTX (Table).

Table 1. Adverse Events During the 12-Month Post-Index Period, Stratified by OGC Daily Dose

	Dose Q1 ≥ 1.00 to ≤ 13.75 mg N = 184	Dose Q2 > 13.75 to ≤ 25.00 mg N = 184	Dose Q3 > 25.00 to ≤ 40.00 mg N = 198	Dose Q4 > 40 mg N = 161
Patients without type 2 diabetes and without HbA1c ≥ 7.5 in the pre-index period, n	120	136	130	110
With type 2 diabetes diagnosis or HbA1c ≥ 7.5 in the post-index period, n (%)	9 (7.5)	16 (11.8)	16 (12.3)	27 (24.5)
Maximum HbA1c value across HbA1c lab results during post-index, mean (SD)	7.75 (2.46)	8.30 (2.86)	8.25 (2.42)	8.61 (3.09)
Patients with diabetes diagnosis in the pre-index period but without HbA1c ≥ 7.5 in the pre-index period, n	31	18	40	15
With worsening diabetes with HbA1c ≥ 7.5 in the post-index period, n (%)	10 (32.3)	6 (33.3)	20 (50.0)	4 (26.7)
Patients without blood glucose level ≥ 200mg/dL in the pre-index period, n	173	169	179	147
With blood glucose level ≥ 200mg/dL in the post-index period, n (%)	13 (7.5)	15 (8.9)	24 (13.4)	22 (15.0)
Adverse events in the post-index period, n (%)				
Serious infection requiring hospitalization for infection and/or IV antibiotics	31 (16.8)	39 (21.2)	44 (22.2)	40 (24.8)
Serious infection requiring IV antibiotics	29 (15.8)	33 (17.9)	42 (21.2)	35 (21.7)
Serious infection requiring hospitalization for infection	6 (3.3)	12 (6.5)	12 (6.1)	8 (5.0)
Cataracts	22 (12.0)	27 (14.7)	34 (17.2)	35 (21.7)
Gastrointestinal bleeding or ulcer	11 (6.0)	11 (6.0)	13 (6.6)	19 (11.8)
Patients with BMI in pre- and post-index, n	171	162	181	141
Increase in BMI by 5, n (%)	7 (4.1)	5 (3.1)	9 (5.0)	9 (6.4)

BMI, body mass index; HbA1c, hemoglobin A1c; IV, intravenous; Q, quartile.

Conclusion: In agreement with previous studies, the association between baseline disease activity and CXCL13, sICAM-1, MMP-3 and S100A8/A9 levels was weak to mild; TCZ + MTX treatment from baseline to Week 24 (open-label period) resulted in significant reductions in all biomarkers. Changes in levels of CXCL13, sICAM-1, MMP-3 and S100A8/A9 from Week 24 to 40 (randomized period) were similar between treatment groups, consistent with the finding of non-inferiority of TCZ mono compared with TCZ + MTX in patients with RA who achieve low disease activity with TCZ + MTX.

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Sornasse Employee of: Genentech, Inc., Michael J. Townsend Shareholder of: Stockholder of Genentech/Roche, Employee of: Genentech/Roche, Jinglan Pei Employee of: Genentech, Margaret Michalska Employee of: Genentech, Inc.

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AB0273

THE ANALYSIS OF THE CLINICAL COURSES OF THE ACPA POSITIVE PATIENTS WITHOUT SYNOVITIS: WHETHER TO FOLLOW UP THEM

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Background: ACPA (anti-citrullinated peptide antibody) is a major risk factor for the onset of RA (rheumatoid arthritis)^[1]. As ACPA becomes a common test in non-rheumatologists, ACPA positive patients not diagnosed with RA are increasing. However, it is unclear whether follow-up of ACPA-positive patients without synovitis leads to early treatment and consequently to the improvement of prognosis.

Objectives: To reveal whether to follow up the ACPA positive patients without synovitis.

Methods: In the four years from January 2015 to December 2018, we extracted the ACPA positive patients introduced from other hospitals, among which patients not diagnosed as RA at the first visit were selected. Then, their clinical courses and ACPA titers were retrospectively analyzed. The 2010 ACR-EULAR classification criteria was used for the diagnosis of RA^[2]. For the significance test, a χ^2 test and a t test with $\alpha = 0.05$ were used.

Results: Thirty six patients met the conditions, and then 10 patients, previously treated as RA, and 8 drop-out patients were excluded. In 18 patients remaining, 10 patients developed RA (follow-up days: avg. 404, max. 983) and the other 8 were non-RA, predisease patients (follow-up days: avg. 424, max. 926). All 10 RA patients initially started the treatment with MTX (methotrexate). Five of them reached remission with only MTX. Of the other five, three needed other csDMARDs because of an inadequate amount of MTX due to adverse events, and two had insufficient observation period. The ACPA titer was significantly higher in the RA patients than the predisease patients (468 versus 26.3 U/ml ($P=0.0075$)). Tenderness of DAS 28 subject joints at the first visit was a significant predictor of RA onset when trying to extract from clinical findings. (10 of 10 in RA patients vs. 2 of 8 in predisease patients ($P=0.0044$)).

Conclusion: In our research, the predictors of RA onset are not only high ACPA titer but also tenderness of DAS28 subject joints at the first visit. The early treatment with MTX could contribute to improved prognosis, so it would be useful to follow up the ACPA positive patients without synovitis. The frequency of hospital visits and the modality to detect synovitis are the subject of our analysis from now on.

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AB0274

THE PREDICTIVE VALUE OF RHEUMATOID FACTOR, ANTI-CITRULLINATED PROTEIN ANTIBODIES, ANTI-CARBAMYLATED PROTEIN: ANTIBODIES AND ANTI-PEPTIDYL ARGININE DEIMINASE TYPE-3 ANTIBODIES, ALONE OR IN COMBINATION, ON RADIOGRAPHIC DAMAGE IN RHEUMATOID ARTHRITIS

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Background: Autoantibodies such as anti-citrullinated protein antibodies (ACPA), anti-carbamylated protein antibodies (CarP) and anti-peptidyl arginine deiminase 4 (PAD4) antibodies have been associated with disease severity and radiographic progression in rheumatoid arthritis (RA). However, very little is

known about the anti-PAD 3 (PAD3) antibodies and of the added value of combining multiple autoantibodies to predict radiographic damage.

Objectives: To investigate the capability of rheumatoid factor (RF), ACPA, anti-CarP and anti-PAD3 antibodies to predict radiographic damage in RA, both individually and in combination.

Methods: We performed a nested cohort study within the « Swiss Clinical Quality Management » (SCQM) RA registry. Biobank samples were tested for RF [QUANTA Lite (QL), IgM and IgA], ACPA IgG [QL CCP3 and QUANTA Flash (QF) CCP3], anti-CarP IgG [using carbamylated fetal calf serum as antigen by prototype ELISA, research use only (RUO)] and anti-PAD3 IgG [QF PAD3, RUO] (all methods Inova Diagnostics). Outcome: radiographic damage assessed with a validated scoring method, the Ratingen (Rau) score. We examined the association of each autoantibody both separately and combined, with radiographic damage at baseline and over time with linear mixed-effects models. Multivariable analyses were corrected for age, sex, smoking status, disease duration, disease activity (DAS28), number of prior biologics and calendar year of biosampling.

Figure: Radiographic damage at baseline and progression over time based on a) the presence of anti-PAD3 antibodies and b) the number of autoantibodies present (RF IgM, QL CCP3 IgG, anti-CarP and anti-PAD3). Number of patients per biomarker subgroup – 0: 177, 1: 161, 2: 335 and 3-4: 176.

Figure 1

Results: A total of 851 RA patients were included with a median of 4 Ratingen scores per patient. Autoantibodies were positive in the following proportion of patients: RF IgM 66.3%, RF IgA 56.9%, QL CCP3 63.8%, QF CCP3 63.3%, anti-PAD3 10.7% and anti-CarP 22.4%. Significantly higher baseline Ratingen scores were associated with the presence of RF (IgM and IgA) and anti-CCP3 (QL and QF) and greater progression over time with RF IgM and QL CCP3 IgG ($p=0.01$ and $p=0.04$ respectively). Patients' positive for anti-PAD3 demonstrated higher mean baseline Ratingen scores compared with anti-PAD3 negative patients (14.9 vs. 8.8 respectively) which was significant in both univariable (Figure) and multivariable analyses ($p=0.0002$ and $p=0.02$ respectively). In the QL CCP3 negative subgroup ($n=308$), baseline Ratingen scores were significantly higher in anti-PAD3 positive patients ($p=0.01$). There were no significant differences with regards to anti-CarP, either in the whole population or in the seronegative cohorts. The presence of multiple autoantibodies was associated with higher baseline Ratingen scores, particularly the combination of RF IgM, RF IgA, QL CCP3, and anti-PAD3, with a baseline Ratingen score of 16.1 ($p<0.00001$) compared to those with no autoantibodies. The presence of at least 3 of the following autoantibodies: RF IgM, QL CCP3, anti-CarP and anti-PAD3, was associated with significantly greater radiographic progression over 10 years (Figure) than if these autoantibodies were absent ($p=0.03$).

Conclusion: The presence of anti-PAD3 antibodies was associated with significantly higher scores of radiographic damage at baseline, in both the overall population and in the subgroup of ACPA-negative patients. Combinations of autoantibodies (including anti-CarP and anti-PAD3) predicted both higher baseline radiographic damage and greater radiographic progression over time.

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