baseline (median DAS28 3V 5.48 [4.70 – 6.19]) and 90% (n=226) of them were concomitantly using corticosteroids and/or other disease-modifying anti-rheumatic drugs (129 with methotrexate (MTX), 96 with leflunomide and 35 with sulfasalazine). The most frequently reported comorbidities were cardiovascular disorders (37.5%), osteoporosis (7.6%) and depression (6.8%). The median RDCI score was 1.0 [0.0 – 2.0] and the majority of patients (63.6%) carried at least one comorbidity. When comparing baseline demographic and clinical characteristics of the 4 subgroups, stratified according to RDCI score (RDCI=0, 1, 2, or ≥ 3), we found statistically significant differences in age, age at diagnosis, sex and the prescribed anti-TNF agent ($p < 0.05$). There was a progressive increase in the mean age as the RDCI score increased between the subgroups.

RDCI strongly correlates with the number of comorbidities (NC) ($r = 0.764$, $p < 0.01$). NC was weakly correlated with patient and physician global assessment of disease activity (pVAS and phVAS) ($r = 0.183$, $p < 0.01$ and $r = 0.196$, $p = 0.019$, respectively), DAS28 3V ($r = 0.192$, $p = 0.046$) and HAQ-DI ($r = 0.301$, $p < 0.01$) at 6 months. Moreover, RDCI poorly correlated with CRP ($r = 0.192$, $p = 0.01$), pVAS ($r = 0.183$, $p = 0.02$) and HAQ-DI ($r = 0.202$, $p < 0.01$). Weaker correlations were also found at 12 months: NC with pVAS ($r = 0.196$, $p = 0.02$), DAS28 3V ($r = 0.216$, $p = 0.01$) and HAQ-DI ($r = 0.187$, $p = 0.04$); RDCI with phVAS ($r = 0.196$, $p = 0.04$).

The 12-month DAS28 remission rate was 37.8% (n=95); 6.7% (n=17) achieved EULAR good response and 54.4% (n=137) a moderate EULAR response. RDCI was not an independent predictor of DAS remission (OR 0.794, 95% CI 0.561-1.125, $p = 0.194$) nor it was of EULAR good/moderate response (OR 0.720, 95% CI 0.430-1.206, $p = 0.212$).

Conclusion: Although our data point to a weak association between morbidities, assessed by the RDCI, and response to a first bDMARD, it is important to consider this simple and useful tool in future prospective and broader studies, since information bias regarding comorbidities may have been responsible for our results.

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FRI0063

LEVEL OF N-TERMINAL FRAGMENT OF BRAIN NATRIURETIC PEPTIDE PROGENITOR AND ATHEROSCLEROTIC DAMAGE OF BRACHIOCEPHALIC ARTERIES IN PATIENTS WITH EARLY AND LONG-STANDING ACTIVE RHEUMATOID ARTHRITIS

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Background: The high prognostic significance of the N-terminal fragment of the B-type natriuretic peptide (NT-proBNP) concentration in the development of cardiovascular diseases (CVD) was identified for rheumatoid arthritis (RA) patients (pts) and general population.

Objectives: To investigate the significance of NT-proBNP levels in pts with early untreated and long-standing RA with high disease activity; to identify potential relationship of NT-proBNP levels with atherosclerotic lesion of the brachiocephalic arteries (BCA), traditional risk factors and inflammatory markers.

Methods: A total of 227 RA pts (76% females, 24% males, 55 [46;61] years old, moderate to high activity (DAS28-5,3[4,6;6,3], SDAI-27(22;35), positive for ACCP (73%)/RF (87%)) were enrolled in the study: 136 pts with early RA (disease duration ≤ 12 months) and 91 pts with long-standing RA (> 12 months). All early RA pts were not treated with glucocorticoids and disease-modifying anti-rheumatic drugs (DMARDs). Long-standing RA pts already developed the lack of efficacy/resistance and/or intolerance of DMARDs. Lack of efficacy of 3 or more DMARDs was established in 46% of pts, intolerance to previous DMARDs therapy - in 54% pts. 73% were receiving methotrexate, 21% - leflunomide, 7% - sulfasalazine, 46% glucocorticoids. Pts with early and long-standing RA were comparable in terms of age, sex, body mass index and RA activity rates (DAS28, SDAI, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels). High incidence of traditional risk factors was found in early and long-standing RA pts: the incidence rate of arterial hypertension (58%vs68%), overweight (58%vs61%), smoking (27%vs17%), DM type 2 (4%vs7%) were not significantly different. Pts with congestive heart failure were not include in the study. The control group consisted of 20 healthy donors, matched to pts by age and sex. Serum levels of NT-proBNP (pg/mL) were measured using electrochemiluminescence test Elecsys proBNP II (Roche Diagnostics, Switzerland). NT-proBNP levels > 125.0 pg/mL were considered as elevated. The

BCA intima-media thickness (IMT) was assessed by duplex ultrasound scanning. Atherosclerotic lesion of BCA was documented in the presence of plaque (IMT ≥ 1.2 mm).

Results: The NT-proBNP levels were significantly higher in RA pts than in the control group (median 92,1 (48,2-164,7) pg/mL vs 55,3 (36,6-67,3) pg/mL, $p < 0.05$). Pts with early RA had higher NT-proBNP levels (118,9 (60,2-201,3) pg/ml) than pts with long-standing RA (73,4 (43,0-114,3) pg/ml, $p < 0.001$). Elevated NT-proBNP concentrations were found in 71 (52%) early RA pts vs 21 (23%) pts with long-standing RA ($p < 0.01$). Atherosclerotic lesion of the BCA was detected in 73 (54%) pts with early RA and in 37 (41%) pts with long-standing RA ($p > 0.05$). The NT-proBNP levels correlated with age ($r = 0.51$, $p < 0.001$), CRP (0,23, $p = 0.001$) and IMT of BCA ($r = 0.46$, $p = 0.03$) in RA pts. Aforementioned correlations were significantly remained for both groups of RA pts. Association between IMT of BCA and CRP concentrations was not found.

Conclusion: NT-pro-BNP levels are higher in pts with active RA than in control subjects. Early untreated RA pts had a higher NT-proBNP levels than pts with disease duration > 12 months and resistance or intolerance of DMARDs. The increased concentration NT-pro-BNP (> 125 pg/ml) were found in half of pts with early untreated RA and every fourth pts with long-standing active RA. NT-proBNP concentration correlated with CRP level in pts with active RA. Correlation between NT-pro-BNP concentrations and IMT of BCA may be indicative of possible impact of this biomarker on atherosclerotic damage of BCA in pts with early and long-standing active RA.

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FRI0064

SAFETY OF LOW DOSE METHOTREXATE (MTX) AND TUBERCULOSIS (TB)

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Background: Increased awareness of the importance of MTX in rheumatic disease is leading to more MTX use in patients from TB-endemic areas. Current management guidelines for rheumatic disease address TB in the context of biologics but not MTX use.

Objectives: To systematically review the published literature on TB rates with MTX ≤ 30 mg per week.

Methods: We searched CINAHL, Embase, Global, MEDLINE and World of Science databases (Jan 1990 to May 2018) for terms including 'methotrexate' and 'tuberculosis'. We also searched citations from review articles. Titles, abstracts or full manuscripts of the 4707 reports identified were screened independently by 2 reviewers to identify studies reporting TB in patients taking MTX. Study quality was assessed using the McGill Mixed Methods Appraisal Tool (MMAT). Data was extracted on TB incidence (new TB diagnosis vs reactivation of latent TB), and outcomes (pulmonary, dissemination, death) and safety of isoniazid, INH. Descriptive summaries are presented on studies providing outcomes in patients taking MTX ≤ 30 mg per week.

Results: After removing duplicates and studies not meeting criteria or providing sufficient information, 31 studies were included (8 cohort, 7 case-control, 1 clinical trial, 15 case reports/case series). Only 27% of articles reported data from low to moderate human development index countries. Studies were of moderate quality. Seven case control studies were heterogeneous but most demonstrated a modest increased risk of TB with MTX (Table). Five cohort studies reported TB incidence rates in rheumatic disease (treated with MTX +/- biologics) ranging from 102-367.9/100,000 patient-years. These rates were generally higher than comparator general population rates. Two cohort studies of MTX in RA (without biologic) reported cumulative TB incidence in Maldives (12 TB cases in 44 RA patients, 27%) and in China (9/114, 7.9%). Other cohort studies generated rates of overt infection (143/100,000 patient years in Spain, higher if co-prescribed with corticosteroids and other immunosuppressants in South Africa), and latent TB rates detection (16/922 RA screened, 1.7%, in Canada). When reported, rates of extra-pulmonary TB were higher than comparator general population rates. One clinical trial (China), 2 cohorts (Japan, USA) and 2 case-series (Belgium, USA) evaluated safety of INH and MTX. Isoniazid-related hepatotoxicity and neutropenia were generally more common when taken with MTX, but were usually reversible.

Conclusion: Despite a paucity of high-quality data, this review confirms that TB screening and clinical surveillance are needed in patients from TB-endemic areas who are prescribed MTX, particularly with co-administration of corticosteroids or other immunosuppressants. Isoniazid, if monitored, appears safe and prevents TB reactivation.

References:

Table. Case control studies

Region (Year)	Diagnosis	TB with MTX	TB without MTX	Odds Ratio
Mexico (1999)	Mixed (4 RA)	1/6	5/75	2.76
Japan (2004)	RA	3/47	17/154	0.56
Canada (2009)	RA	29/483	21/1046	3.12
Brazil (2010)	Lupus	2/3	1/57	112
Taiwan (2012)	Psoriasis	33/144	464/2341	1.2
Taiwan (2015)	JIA	4/357	4/1026	2.90
South Africa (2017)	RA	0/134	0/18	NA

JIA=juvenile idiopathic arthritis

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FRI0065

CLINICAL FEATURES OF METHOTREXATE ASSOCIATED LYMPHOPROLIFERATIVE DISORDER IN RHEUMATOID ARTHRITIS PATIENTS AND INFLUENCE OF CD8 POSITIVE LYMPHOCYTE INFILTRATION

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Background: Lymphoproliferative disorders (LPD) that develop in rheumatoid arthritis (RA) patients treated with MTX (MTX-LPD) is one of the important complications for RA patients. We have previously epidemiologically demonstrated an association between MTX and the development of LPD in RA patients¹⁾. MTX-LPD has varied pathologies including various clinical symptom and histological finding. Therefore, we need more information about MTX-LPD. In addition, it is one of the characteristics for MTX-LPD that spontaneous regression (SR) after MTX discontinuation. However, the mechanism of SR is not clarified.

Objectives: We collect the information such as clinical symptom and histological finding of MTX-LPD with RA patients, and clarify the clinical features of MTX-LPD. In addition, we investigated the difference between SR cases and cases that treated with chemotherapy after MTX discontinuation (CTx cases).

Methods: We enrolled 90 MTX-LPD patients from Kagawa Prefecture, Japan between June 2005 and December 2019. Patients were diagnosed according to American College of Rheumatology (ACR) 1987 classification criteria or ACR/European League Against Rheumatism (EULAR) 2010 classification criteria, and treated with disease modifying antirheumatic drugs (DMARDs) including MTX. We collected as follow information; age, gender, duration of RA, laboratory data (lymphocyte counts and sIL-2R) and treatment of MTX-LPD. In addition, we divided 16 MTX-LPD cases diagnosed histologically into two groups (SR:CTx group; n=10:6), and analyzed the histological findings (CD4, CD8, CD163 and CD47) using the staining in immunohistochemistry (IHC) between the two groups. Each positive cell analyzed using virtual viewer soft ImageScope.

Results: Characteristics of 90 MTX-LPD patients are as follow; mean age 66.5±11.2 years, 63 female, duration of RA 18.5±19.4 years. 65 patients (72.2%) were spontaneously improved by discontinuing MTX. 58 patients (64.4%) were proven MTX-LPD histologically. In these patients, diffuse large B-cell lymphoma (DLBCL) was the most frequent histological type of MTX-LPD (56.9%). Infiltration of CD8 positive lymphocyte in the lesion was significant less in the SR cases than in the CTx cases (Figure 1). However, CD4, CD163 and CD47 positive cells had no significant difference between two groups.

Conclusion: We revealed clinical features of MTX-LPD with RA patients. In addition, CD8 positive lymphocytes are involved in tumor immunity. In this study, we suggested that the extent of CD8 positive lymphocyte infiltration may predict SR of MTX-LPD. Further study is necessary on revealing the mechanism of SR in MTX-LPD.

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Figure 1. CD8 positive lymphocytes in the specimen of lesion using the staining in immunohistochemistry (IHC) between SR and CTx group.

FRI0066

SUBCLINICAL CORONARY CALCIFICATION ASSOCIATED WITH LONG-TERM CARDIOVASCULAR OUTCOMES IN RHEUMATOID ARTHRITIS

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Background: Large, multicenter studies established the strong prognostic value of coronary artery calcium (CAC) scoring in asymptomatic individuals. Increasing CAC score is an independent predictor of worsening cardiovascular disease event risk in general patients. The prognostic significance of higher CAC score strata in the long-term cardiovascular risk in rheumatoid arthritis (RA) is unknown.

Objectives: To evaluate the long-term cardiovascular event risk across CAC strata in a prospective, single center cohort of established RA patients without symptoms or prior diagnosis of cardiovascular disease.

Methods: One hundred-fifty patients underwent computed tomography angiography for coronary atherosclerosis evaluation. CAC score was measured according to Agatston. CVD events were prospectively recorded, including cardiac death, myocardial infarction, unstable angina, revascularization, stroke, claudication, and heart failure hospitalization over 6.0±2.4 years of follow-up. Unadjusted, robust Cox proportional hazards regression models evaluated CVD event risk across higher CAC strata (CAC=1-99, CAC=100-399 and CAC≥400) compared to CAC=0. Additional multivariable robust Cox regression models with time-varying covariates evaluated the impact of log transformed CAC or different CAC thresholds (CAC>0 vs. CAC=0, CAC≥100 vs. CAC<100 and CAC≥400 vs. CAC<400)

Figure 1. Increasing CAC scores associated with higher cardiovascular event risk in RA