Methods: This analysis used data from the Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate (BRAGGSS), a one-year UK prospective cohort study of patients with RA commencing a biological drug. Prior to biologics commencement, demographic and clinical data were collected. Serum samples were sampled for MTX biochemical adherence at baseline (pre-treatment of biologics), then 3 and 6 months post-first dose. MTX concentration was measured by HPLC-SRM-MS. Time to processing variable was also noted by calculating the difference between the time the sample was processed and the time the blood was sampled. Adherence was calculated based on a cut-off limit taken from a validated MTX adherence assay. A chi-square test was used to investigate the association between adherence and biologic response. Linear regression investigated the relationship between MTX level and time to processing.

Results: 582 patients were included; 75% female, mean (S.D.) age 58 (12) years. Table 1 summarises the baseline characteristics for all patients. There was no significant relationship between adherence at pre-treatment with EULAR response at 6 month (p=0.17). However, those who were biochemically adherent to MTX at 6 months had a statistically significantly better response to biologic therapy (p=0.04). It is also found that despite being a responder to the biologic, 37% were non-adherent to MTX. However, there was no significant relationship between MTX level and time to processing thus it is unlikely to be due to the stability of MTX in blood over time.

Conclusion: Patients who were adherent to MTX, assessed biochemically, at 6 months after starting biologic therapy had better response to treatment, which may further strengthens the evidence to support the importance of concomitant use of MTX with biologics.

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Table 1. Baseline characteristics of 582 patients.

	Adherent (63%)			Non-Adherent (37%)		
Female gender (%)	71%			76%		
Age (years)	58 (20-83)			57 (18-84)		
Biologics (%)	**Drug name:**	**n**	**%**	**Drug name:**	**n**	**%**
	Etanercept (and biosimilars)	72	19.55	Etanercept (and biosimilars)	35	16.35
	Adalimumab (and biosimilars)	163	44.36	Infliximab (and biosimilars)	1	0.47
	Rituximab (and biosimilars)	21	5.73	Adalimumab (and biosimilars)	65	30.37
	Abatacept	77	20.98	Rituximab	24	11.21
	Golimumab	4	1.09	Other biologic	2	0.94
	Tocilizumab	7	1.91	Abatacept	54	25.23
	Certolizumab	7	1.91	Golimumab	1	0.47
	Tofacit(Xeljanz)	3	0.82	Tocilizumab	15	7.01
	Baricitinib (Olumiant)	13	3.54	Certolizumab	4	1.87
				Tofacit(Xeljanz)	1	0.47
				Baricitinib (Olumiant)	13	6.07
	TOTAL	**367**	**100**	**Total**	**215**	**100**

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POS0314

CAN METHOTREXATE INFLUENCE SEXUAL DYSFUNCTION IN MALE PATIENTS: ANALYSIS OF THE IIEF5 QUESTIONNAIRE AND HORMONAL STATUS

Keywords: Safety, Rheumatoid arthritis, Disease-modifying Drugs (DMARDs)

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Background: Methotrexate (MTX) is the anchor drug of Rheumatoid Arthritis (RA) treatment. It is a safe and handy drug, but it has several well-known side effects mainly not severe such as nausea, fatigue, alopecia, or an increase in transaminases. In the last years, sexual dysfunction has been reported as a rare adverse effect of MTX therapy.

Objectives: To explore this, the aim of this study is to evaluate the impact of MTX on erectile function in male patients through the IIEF5 questionnaire and hormonal dosage.

Methods: Male patients affected by inflammatory arthritis (Rheumatoid Arthritis or Psoriatic Arthritis [PsA]) according to the 2010 EULAR/ACR diagnostic criteria for RA and the 2006 CASPAR criteria for PsA and treated with chronic MTX were enrolled. Age-matched patients affected by chronic arthritis not treated with MTX were enrolled as control. Each patient underwent blood collection for a complete serum sexual hormone evaluation. IIEF5 questionnaire which consists of 5 items with a maximum score of 25 was administered to the patients.

Results: 109 patients were included, 77 in the MTX group (Group A) and 32 in the control group (Group B). The clinical and demographic features of both groups are reported in Table 1. Among the MTX group, 61 have a RA diagnosis, while the remaining 18 were affected by PsA. The median disease duration of RA and PsA patients was respectively 108 months (IQR 138) and 66 months (IQR 114). The median MTX dose was 10 mg (IQR 7.5) with a median MTX duration therapy of 8 years (IQR 17). The total IIEF5 score was lower in patients treated with MTX compared to the control group without reaching a statistically significant result (19 [IQR 11] *versus* 20 [IQR 7.7]; p=0.15, Graph 1A). However, when comparing the IIEF5 score between MTX exposed versus non-exposed patients stratifying by years of treatment, the total IIEF5 score of patients treated with MTX ≥ 5 years was statistically significantly lower when compared to those non MTX- exposed patients (17 [IQR 15] *versus* 20 [IQR 7.7]; p=0.04) and compared to those treated for < 5 years (17 [IQR 15] *versus* 20 [IQR 7]; p=0.01) (Graph 1B).

Table 1.

		Group A	Group B	p
Age	**Median (IQR)**	54 (28)	53.5 (20.5)	0.50
BMI		25.4 (3.85)	25.6 (5.8)	0.78
Arterial Hypertension	**(N%)**	23 (29.1)	23 (71.8)	**<0.0001**
Hypercholesterolemia		18 (33)	11(34.3)	0.20
Type 2 diabetes		3 (3.8)	6 (18.7)	**0.008**
Hyperplasia Prostatic		2 (2.5)	0 (0.0)	0.99
Depression/Psychotropic Therapy		8 (10.1)	5 (15.6)	0.51
Marriage		53 (67)	23 (71.8)	0.65
Alcohol (N° units/ day)		1 (2.5)	1 (2.0)	0.71
Children (N°)		1 (2)	2 (2)	0.73
Total Testosterone Median	**Median (IQR)**	16,3 (8.2)	14,8	**0.04**
SHBG		53,9 (29,15)	47.6	0.07
LH		5,6 (4,15)	5.35	0.59
FSH		5,2 (5,30)	6.65	0.98
E2		24 (13,25)	20	**0.01**
PRL		7 (3,55)	8.05	0.52
DHEA		4,7 (4,1)	3.85	0.64
GH		94 (19)	98	0.34

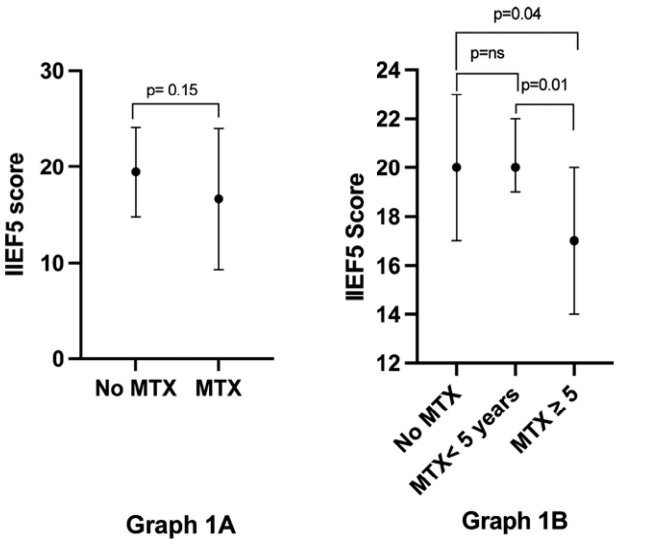

Figure 1. A) Comparison of IIEF5 score in MTX exposed versus non-exposed patients. B) patients stratified by age (< 5 years and ≥ years).

In the univariate analysis, a negative correlation between the total IIEF5 score and MTX exposure (years) has been identified (r= - 0.20 CI [-0.38 - -0.04]; p= 0.039). Age was the variable whit the strongest negative association with the IIEF5 score (r= - 0,42 CI [-0.57 to - 0.25]; p< 0.0001). MTX exposure was still associated with a lower IIEF5 score when adjusted for age (β Estimate= -2,63; CI [-5,13 to -0,13]; p=0,0391). Among the other variables, LH (r=-0,24; CI [-0,42 to -0,04]; p=0,01), FSH (r=-0,21; CI [-0,39 to -0,006]; p=0,04) and E2 (r=-0,21; CI [-0,40 to -0,009]; p=0,03) negatively correlated whit IIEF5 score while DHEA, was the only with a weak positive association (r=0,22; CI [0,02 to 0,40]; p=0,03). Patients affected by arterial hypertension and hypercholesterolemia showed lower scores compared to non-affected patients (p=0.04; p=0.03; p=0.045). In the multivariate analysis, age was the only factor associated with a decrement of IIEF5-score (β -0,21 [-0,32 to -0,094]; p=0,0005).

Conclusion: Long-term MTX exposure was associated with sexual dysfunction reported by a lower IIEF5 score in male patients adjusted for age. The preliminary results need to be confirmed in larger prospective studies.

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Disclosure of Interests: None Declared.

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POS0315 ACUTE CARDIOVASCULAR EVENTS RISK IN RHEUMATOID ARTHRITIS PATIENTS TREATED WITH TOFACITINIB OR TNF INHIBITORS, A NATIONWIDE COHORT STUDY: RELATION STUDY

Keywords: Rheumatoid arthritis, Targeted synthetic drugs, Real-world evidence

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Background: Patients with IMID, and notably patients with rheumatoid arthritis (RA), are at increased risk of major adverse cardiovascular event (MACE) compared with the general population [1,2]. It is hence paramount to assess the impact of biological or targeted DMARD (e.g., tofacitinib and TNFi) on the risk of MACE in patients already at-risk, particularly in the context of ORAL Surveillance which showed a higher risk MACE with tofacitinib, in comparison with TNFI, in RA patients [3].

Objectives: To assess the impact of tofacitinib and TNFi on the risk of MACE in patients with RA treated in real-world clinical practice.

Methods: The RELATION study is a retrospective observational cohort study using the French nationwide healthcare database (SNDS). Patients aged 18 years or older, affiliated to the national health insurance with a diagnosis of RA and initiating tofacitinib after November 1, 2017 or TNFi after January 1, 2010 (including adalimumab, etanercept, or other TNFi, without previous exposure to tofacitinib) were followed from treatment initiation to December 31, 2020. Patients with a previous history of MACE in the 4 years preceding cohort entry were excluded. All MACE excluding cardiovascular (CV) death were defined by the first hospitalization for MACE during follow-up. Comorbidities and traditional CV risk factors were identified using hospitalizations, procedures, or medication dispensing in the 4 years prior cohort entry. The unadjusted incidence rate (IR) of MACE excluding CV death was assessed in patients initiating either tofacitinib or a TNFi (with associated 95% confidence intervals (95% CI)). A 1:3 PS matching was conducted to balance the baseline characteristics of patients initiating tofacitinib and TNFi. Cox proportional hazards regression models were used to compare the risk of MACE with tofacitinib vs TNFi during the follow-up period.

Results: Between 2010 and 2020, a total of 39,578 patients with RA were included in the study. Among these, 2,811 initiated tofacitinib and 36,767 initiated a TNFi (adalimumab: 10,621, etanercept: 16,512, other TNFi: 9,634). Patients had a mean age of 53 years at cohort entry, and 72% to 81% were women. Around 61% of the cohort had at least one CV risk factor (66.3%for tofacitinib compared to 60.9% for TNFi). The two major co-medications at treatment initiation in the two groups were methotrexate (60.9%) and corticosteroids (50.8%). After PS matching, the tofacitinib cohort included 2,628 patients, and the TNFi cohort included 7,884 patients. Over a median follow-up period of 11.21 months (tofacitinib: 8.54 months, TNFi: 12.43 months), 25 incident MACE occurred in the tofacitinib group (IR: 9.86 (6.66–14.60) per 1,000 patient-year (PY)) and 159 occurred in the TNFi group (9.59 (8.21–11.20)). The risk of MACE (overall) was similar with tofacitinib vs TNFi (adjusted HR 1.06 [95% CI 0.68, 1.64]; p=0.8127). Similar results were found for ischemic heart disease (HR 0.71 [95% CI 0.35, 1.44]; p=0.3433) and cerebrovascular disease (HR 1.41 [95% CI 0.73, 2.73]; p=0.3116). For peripheral artery disease, the number of events was too low to perform these analyses.

Conclusion: In this large population-based study, tofacitinib was not associated with an increased risk of MACE in comparison with TNFi in patients with RA treated in real-world settings. Studies with longer follow-up durations may be necessary to understand the long-term implications of tofacitinib vs TNFi on the risk of MACE.

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POS0316 SURVIVIN REGULATES T CELL RESPONSES THROUGH DEPOSITION OF HISTONE H3 MARKS AND MODULATES RESPONSE TO TREATMENT WITH JAK-INHIBITORS

Keywords: Targeted synthetic drugs, Adaptive immunity, Rheumatoid arthritis

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Background: Multiple genetic polymorphisms are associated with high risk for rheumatoid arthritis (RA) [1]. The importance of epigenetic processes has been postulated, but precise molecular mechanisms behind these associations remain largely unexplored. Survivin is an important player in RA, which has been recently shown essential for IFNg signaling in CD4 T lymphocytes acting in partnership with IRF1 [2].

Objectives: We study how survivin-dependent epigenetic deposition of histone H3 tails in RA risk loci affects function of $CD4^+$ T cells and response to JAK inhibition.

Methods: Chromatin of $CD4^+$ cells (n=12) was immunoprecipitated with antibodies to histone H3K27ac, H3K4me3, and survivin, and sequenced (ChIP-seq, Illumina). Parallel ChIP-seq and RNA-seq was done in $CD4^+$ cells treated with survivin inhibitor YM155. Peaks with change >30% in deposition of H3K27ac and/or H3K4me3 upon YM155-treatment were annotated to the genomic regulatory elements (RE) via GeneHancer database. Single nucleotide polymorphism (SNP) related to RA risk were identified within those RE. $CD4^+$ T cell transcriptomics by RNA-seq was done in 24 random RA patients and in 59 RA patients treated with MTX (n=18), TNFi (n=10), JAKi (n=24) and having no DMARDs (n=7). The genes differentially expressed (DEG, nominal p<0.05) in $BIRC5^{hi}$ and JAKi-treated $CD4^+$ cells were identified by DESeq2 (R-studio, Bioconductor).

Results: Deposition of 15% (1705/11152) of H3K4me3 and 17% (1943/11530) of H3K27ac peaks changed >30% upon survivin-inhibition. Approximately 50% of these peaks overlapped with survivin peaks. The change in H3K4me3 peaks was significantly larger if the peak colocalized with survivin peak. These peaks were located within 228 RE, 28 of these RE contained 52 RA risk SNPs. Among others, changeable peaks were accumulated within ICOS/CTLA4/CD28 locus and contained 7 SNPs. Majority of genes connected to the SNP-containing RE (110/153 genes) were transcriptionally different in $BIRC5^{hi}CD4^+$T cells and participated in the regulation of immune system (GO:0002682, FDR=4.3e-4), regulation of IL2 production (GO:0032663, FDR=0.019), TNF mediated signaling (GO:0033209, FDR=5.4e-3). These SNP-RE connected genes formed three independent clusters 1) TCR receptor co-stimulators (CD40, ICOS, CTLA4, CD28, CD244, TRAF6 and TBX21, SLAMF1, TNFRSF9), 2) connected to the LCK interacting transmembrane adaptor 1 (LIME1, SLC2A4RG, ZGPAT, GMEB2, TNFRSF6B, RTEL1) and 3) heat-shock proteins (HSPD1, HSP90AB1, HDAC7, KPNB1). The clusters were functionally connected to survivin partners IRF1 and SMAD3. Notably, transcription of CD28, ICOS, and SLAMF1 functionally connected to IRF1, and CHERP, HDAC7, PRPF6 and SRSF10 functionally connected to SMAD3 were significantly changed (all, nominal p<0.05) in CD4+ cells upon survivin inhibition by YM155. Since survivin mediates IFNg-dependent processes [2], we analyzed transcription of 110 SNP-RE connected DEG in $CD4^+$ cells of JAKi-treated RA patients. We found that DEG in the IRF1 and SMAD3 clusters were inversely affected by JAKi, e.g., IRF1-related CD28, ICOS, and SLAMF1 upregulated after survivin inhibition were suppressed