THU0199 TOFACITINIB IMPROVES LEFT VENTRICULAR MASS AND CARDIAC OUTPUT IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Rheumatologists need to develop primary prevention strategies for cardiovascular disease (CVD) in rheumatoid arthritis (RA) patients. We reported tofacitinib (Tofa) improved arterial stiffness in RA patients. RA is associated with an increased *left* ventricular mass index (LVMI), a strong marker of cardiovascular mortality.There is no evidence that Tofa effects on left ventricular (LV) morphology and function.

Objectives: To study the effect of Tofa plus methotrexate (MTX) on LV morphology and function in MTX resistant active RA patients, in a cohort study design.

Methods: RA patients were eligible if they had active disease despite treatment with MTX. All patients have no steroids, and no previous history of CVD. Consecutive 28 patients with moderate to severe active RA patients (DAS28>3.2) despite MTX were received Tofa plus MTX. LV morphology and function was assessed with cardio-MRI at baseline and 24 weeks follow-up. Cardiovascular risk factors and clinical data were collected at regular visits.

Results: 24 patients completed 24 weeks. Left ventricular mass index (LVMI) was attenuated significantly by Tofa (week 0-week24, –12.4±5.4 g/m^2; p=0.0002). Cardiac output (CO) was attenuated significantly by Tofa (week 0-week24,-0.87±1.2l/min). DAS28 and CRP improved significantly by Tofa (week 0-week24; DAS28: -2.26±0.91; CRP: 14.1±8.7 mg/l) ($p<0.05$). Surprisingly, the change of disease activity (DAS 28 and CRP) is no correlation with the change of LVMI or CO in this study. Observationally, 4 cases significantly improved right ventricular mass as well as left ventricular mass (20% improved right ventricular mass index from baseline).

Conclusions: Tofa improved LVMI and CO in active RA despite MTX. TCZ improves LVMI and CO independently of its effects on disease activity. Tofa might be improved right ventricular mass. JAK-STAT pathway might be an important role of LV hypertrophy. Tofa, JAK-STAT pathway blocking, may prevent cardiovascular morbidity and mortality in RA.

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THU0200 RISK FOR DEVELOPING ADVERSE EFFECTS CAUSED BY SALAZOSULFAPYRIDINE IN RHEUMATIC DISEASES

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Background: Salazosulfapyridine is non-antimicrobial sulfonamides, which is used as a synthetic disease modified anti-rheumatic-drug (DMARD) for rheumatoid arthritis and psoriatic arthritis. Prior study suggested sulfa allergy may be more commonly seen in patients with positive anti- Ro/SS-A antibody (anti-Ro).

Objectives: To identify the risk factor for adverse effects (AEs) caused by salazosulfapyridine in patients with rheumatic diseases.

Methods: We retrospectively identified patients ≥18 years old who received salazosulfapyridine at a tertiary medical center in Japan between 2010–2015. Data were collected on the incidence of AEs, clinical features and autoantibodies.

Results: We identified 313 patients with rheumatic diseases who received salazosulfapyridine. Median age was 61 (range, 20–95); 215 of 313 (67%) were female (Table). The incidence of AEs was 15% (48/313); Median duration until developing AEs was 14 days (range, 2–50). AEs included rash (28), fever (19), elevated liver function tests (13), gastrointestinal symptoms (9), lymphadenitis (3), neutropenia and eosinophilia (1). Factors associated with AEs are female gender, positive anti-Ro or psoriatic arthritis. Multivariate logistic controlling for age, gender and anti-Ro showed that positive anti-Ro has 2.33 odds (P=0.03; 95% CI: 1.07–5.08) of having AE of salazosulfapyridine. Among patients without anti-Ro, subjects with psoriasis showed 9.95 odds (P<0.001; 95% CI: 3.51–28.2) of developing AEs than non-psoriatic patients.

Conclusions: AEs caused by salazosulfapyridine are common in patients with rheumatic diseases. Presence of anti- Ro or psoriasis may be a risk factor for AEs caused by salazosulfapyridine.

Table

	With AEs (n=48)	Without AEs (n=265)	P value
Age over 60 years — no. (%)	22 (46)	26 (56)	0.21
Female sex — no. (%)	42 (88)	173 (65)	0.002
Clinical diagnosis			
Rheumatoid arthritis — no. (%)	26 (54)	214 (81)	0.002
Sjogren's syndrome — no. (%)	15 (31)	31 (12)	0.001
Psoriatic arthritis — no. (%)	19 (40)	11 (4)	<0.001
Anti-Ro/SS-A antibody — no. (%)	14 (29)	28 (11)	0.006

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THU0201 OLDER AGE, HYPOALBUMINAEMIA AND RENAL FAILURE MIGHT BE POOR PROGNOSIS FACTORS FOR LOW DOSE METHOTREXATE-INDUCED MYELOSUPPRESSION IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Methotrexate (MTX) serves as an anchor drug in rheumatoid arthritis (RA) and the maximal dose of MTX from EULAR recommendation is 25–30 mg/w. Small cases retrospective cohort studies reported that the mortality rate of RA patients with low dose (5–25 mg/w) MTX-induced myelosuppression was about 17–25%. However, studies of low dose MTX-induced myelosuppression are rare in Chinese RA patients.

Objectives: To perform a retrospective case series analysis of the characteristics and outcomes of RA patients with low dose MTX-induced myelosuppression in China.

Methods: RA patients hospitalized at Sun Yat-Sen Memorial Hospital from January 2001 to December 2016 were recruited. Clinical data were collected and adverse effects were recorded simultaneously. Low dose MTX-induce myelosuppression was diagnosed as white blood cell $<4\times10^9$/L together with hemoglobin <130 g/L and platelet count $<130\times10^9$/L after treatment of MTX without an alternative cause for pancytopenia. Data were showed as mean ± standard deviation.

Results: (1) There were 1137 RA patients recruited and 17 patients (1.5%) of them were hospitalized for low dose MTX-induce myelosuppression. Among these 17 patients, 53% were females, age was 68±5 years, disease duration was 12±11 years.

(2) Four (23.5%) patients had dose errors, taking MTX 5–10mg daily for 24 days (range: 5–80), MTX accumulated dose was 25–200mg before myelosuppression. Mean MTX dose in the other patients (n=13, 76.5%) was 11.0±1.7 mg/w (range: 7.5 –15), course of MTX was 10±11 months (range: 0.5–48). Four (30.8%) patients manifested myelosuppression within the first month after taking MTX, and 4 (30.8%) patients had been well on a stable drug dose (7.5–12.5) for more than one year before myelosuppression, 2 patients manifested myelosuppression after adding MTX dose to 15mg/w for 2 months.

(3) Fifteen (88.2%) patients had oral mucositis, eight of them had involvement of both oral mucosa and skin. Fever was noticed in 10 (58.8%) patients. Infections were recorded in 6 (35.3%) patients, manifested as pneumonia (n=4), sepsis (n=1), urinary tract infection (n=1) and skin soft tissue abscesses (n=1). Two patients experienced abdominal pain and melena.

(4) Among the patients with neutropenia [n=17, mean neutrophil count: $(0.74\pm0.76)\times10^9$/L, range: 0–1.83], 9 (52.9%) developed severe neutropenia with neutrophil counts below 0.5×10^9/L. Five patients developed severe thrombocytopenia (platelet count $<20\times10^9$/L), and severe anemia occurred in 4 patients (hemoglobin <65g/L). Hypoalbuminemia (30.0±2.8 g/L) was noted in all patients. Glomerular filtration rate (GFR)≤30 ml/min/1.73 m^2 was noted in 4 (23.5%) patients and GFR≤50 ml/min/1.73 m^2 in 12 (70.6%) patients.

(5) Pancytopenia recovered (n=17) after discontinuation of MTX and supplementation of folic acid (10–30mg/d). Only 3 (17.6%) patients were treated with rescue intravenous leucovorin. Thirteen (76.5%) were treated with granulocyte colony stimulating factor (G-CSF) and 7 (41.2%) required blood products. Fifteen (88.2%) required antibiotic therapy. Sixteen (94.1%) patients was recovered and discharged, only one patient die from acute brainstem infarction but not from myelosuppression.

Table 1 Characteristics of 17 RA patients with low dose MTX-induce myelosuppression

Case	Age (y)	Sex	Dose (mg/w)	Dose errors	Fever	Mucositis	Neutrophil count (×10^9/L)	Platelet count (×10^9/L)	Hemoglobin (g/L)	GFR (ml/min/1.73 m^2)	Albumin (g/L)	Outcome
1	74	F	10	+	-	+	0.32	107	87	50.0	34.2	Recovered
2	65	M	10	+	+	+	0.25	2	65	49.8	27.1	Recovered
3	69	M	15	+	+	+	2.43	11	53	46.9	32.2	Recovered
4	60	M	15	+	+	+	0.12	61	77	57.4	32.4	Recovered
5	71	M	10	-	+	-	0	18	78	21.3	27.3	Recovered
6	68	F	10	-	-	+	1.64	112	84	39.1	35	Recovered
7	57	F	10	-	+	+	0.13	11	109	52.2	30.3	Recovered
8	76	M	10	-	+	+	0.62	39	88	48.3	18.9	Recovered
9	75	F	10	-	-	+	1.12	106	106	28.4	32.3	Recovered
10	63	F	10	-	+	+	0.67	37	65	33.0	32.9	Recovered
11	64	F	10	-	+	+	0	69	72	32.7	30.2	Recovered
12	70	M	10	-	-	+	0.34	93	73	55.1	28.7	Recovered
13	69	M	7.5	-	+	+	1.83	112	83	47.0	34.8	Recovered
14	62	F	15	-	-	+	0.28	124	53	23.3	31.2	Recovered
15	80	M	12.5	-	-	+	1.05	49	70	42.4	28.8	Recovered
16	74	F	12.5	-	-	-	1.75	106	74	61.8	28.6	Recovered
17	57	F	10	-	+	+	0.02	11	67	17.6	26	Died

Conclusions: Older age, hypoalbuminaemia and renal failure might be poor prognosis factors for low dose MTX-induce myelosuppression in RA.
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THU0202 UNAFFORDABLE CONVENTIONAL AND ABSENT BIOLOGIC DMARDS: INCREASING THE BURDEN OF RHEUMATOID ARTHRITIS IN FYROM

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Background: In the developing world rheumatologists and their patients are struggling to implement treat to target therapy in established Rheumatoid Arthritis (RA)which means they can hardly establish remission and low disease activity which is the mainstay of the RA treatment. The main reason is the lack of conventional synthetic and biological (c and b) DMARDs in the therapeutic armamentarium as well as their high cost which increases already difficult burden of RA.
Objectives: The aim of the study is to evaluate the RA treatment and treatment expenses in a group of patients with established RA in FYR of Macedonia including the availability of DMARDs.
Methods: We have conducted a cross-sectional study at the University Rheumatology Clinic in Skopje, including 100 patients with established RA, who fulfilled RA classification criteria from 2010. Physical examination, laboratory analyses and DAS28 were performed and all patients filled a questionnaire with 13 questions about treatment expenses and availability.
Results: There were 82 females and 18 males, with mean age of 59 and disease duration of 8.3 (SD 7,3) years and moderate disease activity DAS28 3,9+/-1,47 and 75% of seropositive RA (double positive 30%, Ant-CCP positive 30%, RF positive 15%) with mean CRP of 21,5 mg/L They spend from 10 to 100 Euros monthly (on average 27+/-17,6) for the cs DMARDs therapy. Almost 80% think that the cs DMARDs therapy is too expensive for them and 100% of them could not afford to pay or co-pay for b DMARDs. Most of the patients (49%) are using single cs DMARDs. Double and triple c DMARD therapy is used by 32% vs 17%, respectively. Even though it is highly effective, patients consider triple cs DMARD therapy expensive and with very low compliance because of the high costs and low tolerability. Only 2% of the patiens are using b DMARDS using rituximab, the only available biologic DMARD therapy in FYROM. Around 70% are taking low dose prednisolone. Almost 50% of the patients cannot take the cs DMARD therapy with a prescription and have to buy their DMARDS without any coverage from the insurance fund and the same percent have problems to find the c DMARDs with prescription because it is not available. Almost half of the patients have heard about the b DMARDs, most of them from their rheumatologist and 54% of them would like to receive it. The patient's reasons for taking b DMARDs are presented in Graph 1.
Conclusions: High expenses and low availability of c DMARDs on prescription and the urgent need for b DMARDs are adding the burden of RA in developing countries including FYROM with the increased need for full coverage for conventional DMARDs and at least partial coverage of biologic DMARDs, especially anti-TNF agents by the insurance companies. The use of biosimilars might be highly appreciated in the future.
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THU0203 CHANGES IN C-REACTIVE PROTEIN AND LIPID LEVELS IN PATIENTS WITH RHEUMATOID ARTHRITIS TREATED WITH ABT-494, A SELECTIVE JAK-1 INHIBITOR

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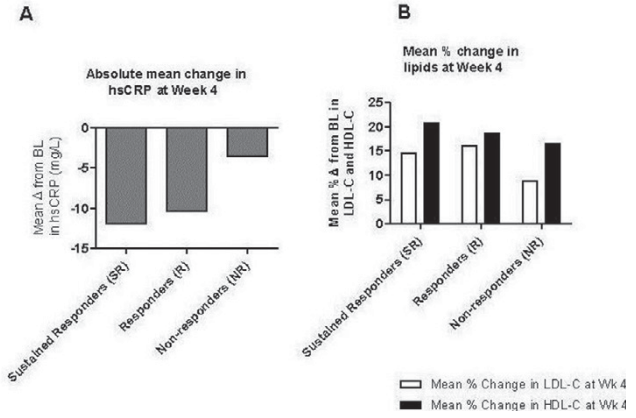
Background: In patients (pts) with rheumatoid arthritis (RA) treated with ABT-494, dose-dependent increases in levels of low and high density lipoprotein cholesterol (LDL-C and HDL-C) were observed, along with decreases in levels of C-reactive Protein (CRP). Whether these changes are due to the control of inflammation or a direct effect on CRP production in the liver is not known.
Objectives: To explore the relationship between changes in HDL-C or LDL-C and CRP with ABT-494 treatment, and to assess whether the effect on lipids is dependent on improvement of RA signs and symptoms.
Methods: Data were from two phase 2b controlled trials of ABT-494 in RA pts with inadequate response or intolerance to TNF inhibitors (TNF-IR, BALANCE-1)[1], or with inadequate response to methotrexate (MTX-IR, BALANCE-2)[2]. Pts treated with placebo or 3,6,12,18 mg ABT-494 twice daily for 12 weeks (wks) are included. Levels of high sensitivity (hs) CRP, total cholesterol (TC), LDL-C and HDL-C were measured at baseline (BL) and Wk 2,4,6, 8 and 12. Atherogenic burden at BL and Wk 12 was assessed by ratio of ApoB:ApoA1 and TC:HDL-C in 6 mg and 12 mg dose groups in both studies. Pearson's coefficients were calculated *post hoc* to assess possible correlations between HDL-C or LDL-C levels (or changes from BL) with other variables including (high sensitivity) hsCRP, at BL and Wk 12. Pts were subgrouped by response: Sustained responders (SR), pts who achieved an ACR20 response at every visit from Wk 2–12; Responders (R), pts who achieved ACR20 at least once, but not at every visit; Non-responders (NR), pts who did not achieve ACR20 at any visit.
Results: The ratios of LDL-C:HDL-C[1,2] and TC:HDL-C remained unchanged after 12 wks of treatment with ABT-494. The ratio of ApoB:ApoA1 also remained unchanged from BL to Wk 12: in BALANCE-1, 0.61 to 0.58 for the 6 mg (n=19), and 0.62 to 0.60 for 12 mg (n=11) groups, and in BALANCE-2, 0.62 to 0.64 for the 6 mg (n=18) and 0.69 to 0.66 for 12 mg (n=16) groups. An inverse relationship between LDL-C or HDL-C and hsCRP was observed throughout the treatment period. At Wk 4, among the variables tested, the strongest correlation was observed between changes from BL in hsCRP and LDL-C (-0.29, $p<0.001$) or HDL-C (-0.26, $p<0.001$). Out of 420 pts, 104 pts (25%) were ACR20 SR, 251 pts (60%) were R and 65 pts (15%) were NR. Compared to NR, SR and R had a greater absolute reduction in hsCRP (Fig. 1A). A robust percentage increase in HDL-C was observed in all 3 groups (20.8%, 18.5% and 16.4% in SR, R and NR, respectively). Compared to the SR and R (14.6% and 16%, respectively), a smaller percentage increase in LDL-C was observed in the NR (8.9%) (Fig. 1B).

Figure 1



Conclusions: Atherogenic burden did not increase in pts treated with ABT-494 for 12 wks. Compared to non-responders, pts with a clinical response experienced a larger increase in lipids and a larger decrease in hsCRP. Limited data from these phase 2 studies suggest that there might not be an increased risk of cardiovascular events. Results from the larger phase 3 trials can provide more information.
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THU0204 RELATIONSHIPS BETWEEN METHOTREXATE DOSAGES AND CLINICAL VARIABLES IN PATIENTS WITH RHEUMATOID ARTHRITIS WHO ACHIEVED REMISSION WITH METHOTREXATE MONOTHERAPY: A STUDY USING THE IORRA OBSERVATIONAL COHORT STUDY

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Background: Considerable variability exists in the way rheumatologists prescribe methotrexate (MTX) therapy in patients with rheumatoid arthritis (RA), including the dosage [ref.1]. Start higher doses or fast dose escalation are associated with higher efficacy, but also with more toxicity. In addition, factors such as renal function, body size, and age of the patient can affect the optimal dosage of MTX.
Objectives: We aimed to study the relationships between MTX dosages and clinical variables in patients with RA who achieved remission with MTX monotherapy.