Methods: The "Institute of Rheumatology, Rheumatoid Arthritis (IORRA)" is a single-center prospective observational cohort study established at our institute in 2000. Data (physicians' and patients' disease assessments, laboratory data, and many other patient information) were collected from approximately 5,000 RA patients biannually. More than 99% of RA patients treated at our institute were enrolled in this cohort, and >98% of patients answered and mailed their questionnaires back to us every time. Among the RA patients who were registered in the IORRA cohort study from 2011 through 2015, 603 patients fulfilled the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Boolean-based definition of remission in RA, at least once and used only MTX as disease-modifying antirheumatic drugs (DMARDs) including biological DMARDs for 5 years. Relationships between MTX dosages and gender, disease duration, height, body weight, body mass index, body surface area, serum creatinine (SCr), estimated glomerular filtration rate (eGFR), creatinine clearance (by Cockcroft-Gault Equation), rheumatoid factor, and anti-cyclic citrullinated peptide antibody when remission was first reached by each patient were analyzed by univariate analyses using Pearson correlation coefficient and Welch's *t* test. Subsequently, a multiple regression analysis was performed.

Results: Univariate analyses detected several candidate clinical variables associated with MTX monotherapy dosages in RA patients who achieved remission: height, body weight, body surface area, SCr, eGFR, and CCR ($p = 0.004, 0.050, 0.241, <0.001, <0.001$, and <0.001 , respectively). Subsequently, a multiple regression model developed a best-fit model with the following variables: age, height, body weight, and SCr (standardized partial regression coefficient = $-0.20, 0.10, 0.07$, and -0.22 , respectively), while its adjusted coefficient of determination was 0.114.

Conclusions: There were significant relationships between MTX monotherapy dosages and age, height, body weight, and renal function in RA patients who achieved remission. However, the low coefficient of determination indicated the model accounted for limited variability with the specified variables.

References:

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THU0205 EFFECTS OF THE JAK1-SELECTIVE INHIBITOR FILGOTINIB ON MULTIBIOMARKER DISEASE ACTIVITY SCORES IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS AND AN INADEQUATE RESPONSE TO METHOTREXATE

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Background: Filgotinib (GLPG0634, GS-6034) is an oral selective JAK1 inhibitor that has been evaluated in a 24-week phase 2B study (DARWIN 1) on the background of methotrexate (MTX) treatment in active rheumatoid arthritis (RA) patients who were MTX inadequate responders¹.

Objectives: To evaluate the effect of filgotinib compared to placebo on a multi-biomarker disease activity (MBDA) score that measures 12 disease-related biomarkers of inflammation and joint injury in RA patients taking background MTX.

Methods: Serum samples of RA patients who were on a stable dose of MTX and received either placebo (PBO) or filgotinib 100mg or 200mg once daily (QD), were tested for MBDA components (Crescendo Biosciences, CA, US) at baseline, week 4 and week 12. Median % change from baseline for MBDA score and individual components are reported for week 4 and week 12. Wilcoxon rank-sum test assessed the significance of difference between filgotinib treated groups vs. PBO.

Results: Baseline MBDA scores and component values (median; interquartile range) were similar in PBO (55; 45–64), 100mg QD (58; 42–66), and 200mg QD (59; 50–67.5) treatment groups. Filgotinib treated patients had reductions in the MBDA score from baseline at both the 100mg and 200mg QD dose levels, but not in the PBO group. At both weeks 4 and 12, these reductions in the filgotinib treated groups were significantly different from the PBO group. Most of the individual components contributed to the decrease in MBDA score, but the largest reductions were observed for serum amyloid A (SAA), C-reactive protein (CRP), and IL-6, and the biomarkers of joint-damage, matrix metalloproteinase 3 (MMP3), MMP1, vascular endothelial growth factor (VEGF), and YKL40 (human cartilage glycoprotein 39). There was an increase in leptin and no change in epidermal growth factor (EGF) concentrations.

Table 1. Median percent change from baseline of MBDA score and component concentrations

	Week 4			Week 12		
	PBO (N=62)	Filgotinib 100mg QD (N=63)	Filgotinib 200mg QD (N=68)	PBO (N=65)	Filgotinib 100mg QD (N=62)	Filgotinib par 200mg QD (N=68)
MBDA SCORE	-1	-20***	-24***	-5	-19***	-24***
CRP	15	-57***	-71***	-8	-66***	-78***
EGF	14	-18 ^{NS}	-8 ^{NS}	0	-10 ^{NS}	0 ^{NS}
IL-6	-15	-34**	-60***	-20	-41***	-63***
LEPTIN	0	8 ^{NS}	18 ^{NS}	6	14 ^{NS}	23*
MMP-1	10	-16***	-24***	-6	-18***	-26***
MMP-3	0	-24**	-33***	-9	-25***	-43***
RESISTIN	1	-12**	-22***	-1	-15*	-16***
SAA	8	-45***	-65***	7	-49***	-67***
TNF-RI	0	-11***	-26***	0	-11***	-15***
VCAM-1	5	-10***	-15***	0	-8**	-16***
VEGF	3	-16***	-25***	-2	-16***	-26***
YKL-40	2	-12*	-32***	-7	-17 ^{NS}	-33***

p-values comparing % changes between filgotinib and PBO groups NS, $p > 0.05$; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Conclusions: RA patients treated with filgotinib in combination with MTX had significant reductions in the MBDA score that was driven by key RA biomarkers encompassing both inflammation and joint injury. These findings are consistent with the filgotinib efficacy observed in RA patients over 12 weeks.

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THU0206 THE JAK1-SELECTIVE INHIBITOR FILGOTINIB REDUCES MULTIPLE MARKERS OF INFLAMMATION LINKED TO VARIOUS PATHOLOGIC CELL TYPES AND PROCESSES IN RHEUMATOID ARTHRITIS PATIENTS

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Background: JAK1, 2, 3 and TYK2 are cytoplasmic tyrosine kinases that mediate intracellular signaling of many cytokines and growth factors. Filgotinib (GLPG0634, GS-6034) is a JAK inhibitor with high selectivity for JAK1 over other JAK family members. Filgotinib has a favorable safety and efficacy profile in two Phase 2B studies in active rheumatoid arthritis (RA) patients who were methotrexate (MTX) inadequate responders.

Objectives: To assess the effect of filgotinib on a background of MTX treatment on markers of inflammation in RA patients.

Methods: Serum samples from RA patients who were on a stable dose of MTX and received either placebo (PBO), filgotinib 100mg or 200mg once daily (QD), were collected at baseline, week 4 and week 12 and analyzed for 35 soluble serum biomarkers by validated single-plex or multiplex immunoassays. Median % changes from baseline for biomarkers are reported. Wilcoxon rank-sum test assessed the significance of difference between filgotinib treated groups and PBO.

Results: Filgotinib treatment induced a dose-dependent and significant decrease

in a variety of biomarkers implicated in RA pathogenesis including inflammation (IL-1 β , IL-6, TNF α and SAA), matrix degradation and cartilage destruction (MMP1 and MMP3), immune cell trafficking (CXCL10, ICAM-1 and VCAM-1) and angiogenesis (VEGF). Cytokines involved in T_H1 (IFN- γ , IL-2, IL-12) and T_H17 (IL-1 β , IL-6, IL-21, IL-23) cell subset differentiation and activity were significantly decreased. Additionally, decrease in the B-cell chemoattractant CXCL13 and the myeloid growth factor GM-CSF supports the anti-inflammatory effects of filgotinib treatment.

Table 1. Median percent change of biomarkers at week 12 from baseline for PBO and 200mg QD dose

	PBO (N=78)	Filgotinib 200mg QD (N=75)	PBO (N=78)	Filgotinib 200mg QD (N=75)	PBO (N=78)	Filgotinib 200mg QD (N=75)		
BAFF	-2	-6 ^{NS}	IL-2	-7	-20**	MIP-1β	0	-7*
CRP	-8	-78***	IL-21	0	-28**	MMP-1	-6	-26***
CXCL-13	3	-40***	IL-23	-6	-25***	MMP-3	-9	-43***
EGF	0	0 ^{NS}	IL-4	0	0 ^{NS}	RESISTIN	-1	-16***
GM-CSF	0	-26***	IL-5	2	-14**	SAA	7	-67***
ICAM-1	0	-14***	IL-6	-20	-63***	sgp130	0	4 ^{NS}
IFN-γ	-2	-21*	IL-7	1	-17***	TNF-α	1	-15***
IL-10	-3	-17**	IL-8	-2	-12 ^{NS}	TNF-RI	0	-15***
IL-12	0	-24***	IP-10	-2	-31**	VCAM-1	0	-16***
IL-13	-1	-8**	LEPTIN	6	23*	VEGF	-2	-26***
IL-17A	2	-18*	MCP-1	4	-8 ^{NS}	YKL-40	-7	-33***
IL-1β	-2	-26***	MIP-1α	1	-8**			

p-values comparing % changes between filgotinib and PBO groups: NS, p>0.05; *p<0.05; **p<0.01; ***p<0.001.

Conclusions: Treatment with filgotinib decreased several factors that have key roles in RA for matrix degradation, cartilage destruction, angiogenesis, leukocyte adhesion and recruitment. The changes were accompanied by decreases in cytokines that promote and activate T_H1, T_H17, B-cells and myeloid cells that are important in RA. These findings provide insights into filgotinib mechanism of action and are consistent with its efficacy observed in RA patients.

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THU0207 THE EFFECT OF THE USE OF GLUCOCORTICOIDS ON HEALTH ASSESSMENT QUESTIONNAIRE IN PATIENTS WITH RHEUMATOID ARTHRITIS IN CLINICAL REMISSION -DATA FROM KANSAI CONSORTIUM FOR WELL-BEING OF RHEUMATIC DISEASE PATIENTS (ANSWER COHORT)-

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Background: In the treatment of patients with rheumatoid arthritis (RA), glucocorticoids (GCs) with csDMARDs remain an important treatment option given their capacity to increase clinical, structural and functional efficacy. On the other hand, it is reported that GCs usage even at low dosage significantly deteriorated functional capacity in patients with low disease activity state. In these previous study, disease activity and subsequent joint destruction have no small influence on functional disability.

Objectives: To investigate the effect of the use of glucocorticoids (GCs) in patients with RA who had maintained clinical remission on functional ability.

Methods: Among 2,649 patients with RA who achieved DAS-ESR<2.6 after 2013 in the multi-center cohort, 1,171 patients who had maintained DAS-ESR<2.6 were eligible. Clinical and demographic characteristics were collected at baseline. We calculated odds ratio (OR) (95% confidence interval) of the use and dose of GCs to predict the yearly progression of HAQ-DI score adjusted for age, sex, BMI, disease duration, RF titer, ACPA titer, CRP, MMP-3, DAS28-ESR, HAQ-DI, use of MTX and use of biologic DMARDs as covariates in multiple logistic regression model.

Results: Characteristics of patients at baseline were as follows (median (IQR), proportion). The age was 61 (48–68) years, female was 70.6%, disease duration was 4.5 (1.7–10.7) years, RF-positive was 64.4%, ACPA-positive was 70%,

DAS28-ESR was 2.0 (1.6–2.6), HAQ-DI score was 0.125 (0–0.5). Of the 1,171 patients, 235 (20.1%) patients had been treated with oral GCs when achieving clinical remission. CRP (0.06 (0–0.2) vs 0.03 (0–0.1), p=0.03), MMP-3 (106.1 (73.2–172.8) vs 49.5 (36.5–77.2), p<0.001), SDAI (2.9 (1.5–5.9) vs 2.6 (1.0–4.8), p=0.003), DAS28-CRP (1.6 (1.3–2.0) vs 1.5 (1.2–1.9), p=0.008), patients' global assessment (mm) (15 (5–31) vs 11 (3–25), p=0.006), physicians' global assessment (mm) (6 (3–12) vs 5 (0–10), p=0.001) and HAQ-DI (0.38 (0–0.88) vs 0.13 (0–0.38), p<0.001) were significantly higher and disease duration was significantly longer (year) (8.9 (3.2–19.6) vs 4.1 (1.6–9.3), p<0.01) in the GCs group compared to the non-GCs group. One hundred and fifty-eight (67.2%) patients had been treated with GCs during follow up, and median dose was 4.5 (2.5–5.5) mg/day. Two hundred and eighty-seven (24.5%) patients' yearly change of HAQ-DI score increased. The adjusted OR of the use of GCs at baseline was 2.06 (1.21–3.51). The adjusted OR of the daily dose of GCs <5mg was 1.61 (0.73–3.56), whereas that of GCs $\geq$ 5mg was 2.65 (1.11–6.34) in patients with keeping GCs use.

Conclusions: The use of GCs in RA patients with sustained remission was the risk factor of progression of HAQ-DI score dose-dependently.

Disclosure of Interest: None declared

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THU0208 METHOTREXATE POLYGLUTAMATES LEVELS IN ERYTHROCYTES WERE GENETICALLY AFFECTED IN RA PATIENTS WITH LOW DISEASE ACTIVITY FOR LONG PERIOD

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Background: Detection of the intracellular levels of polyglutamated MTX (MTX-PGn) can predict response of MTX or possibly its adverse effects. As efficacy and toxicity of MTX differs among individual patients, we had proposed a predictive model for MTX efficacy consisting of 9 SNPs (2015 EULAR). In the present study, we measured erythrocyte MTX-PGn in RA patients with low disease activity for long time receiving a stable dose of MTX, investigated their associations with genetic polymorphisms, and speculated MTX dose required to reach possible effective MTX-PG levels.

Objectives: To investigate if erythrocytes MTX-PGn concentration is associated with the 9 SNPs in 7 genes reportedly related to MTX-efficacy in RA patients with low disease activity.

Methods: The study was cross-sectional using 121 adult patients with RA in Shinko Hospital. All patients enrolled had received a stable dose of MTX (mean 8.9 $\pm$ 0.3 mg/week), and kept lower disease activity (DAS28-CRP <2.7, mean 1.9 $\pm$ 0.4) for at least 3 months. Concentrations of MTX-PG with 1 - 5 glutamate residues (PG1- PG5) in erythrocytes were quantitated by LC-ESI-MS/MS as described by den Boer et al. Nine SNPs in 7 genes previously found to associate with efficacy of MTX by us were genotyped by RT-PCR (Applied Biosystems, Inc.). First, association of the 9 SNPs with concentrations on MTX-PGn was analyzed by one-way layout (Wilcoxon signed-rank test). Secondly, multivariate logistic regression analyses were performed to estimate roles of MTX dose and polymorphisms in concentrations of MTX-PGn.

Results: Total PGn concentrations were 82.1 $\pm$ 31.7 nmol/L (m $\pm$ SD) and positively correlated with MTX dose (Rs =0.4104, p<0.001), but range of concentration was rather wide even if the dose was same. By one-way layout, GGH c.452C>T was associated with PG1, PG2, and total PG, SLC19A1 c.80G>A with total PG, and SLC28A3 c.267G>A with PG3. Three SNPs (FPGS c. 192T>C, EPHX1 c.357G>A, SLC28A3 c.267G>A) were related to MTX doses. Next, we investigated roles of MTX dose and 9 SNPs in maintenance of MTX-PGn concentrations as by multiple regression analyses. As PG1 levels were related to GGH c.452C>T but not to MTX dose, PG1 levels were 38.2 $\pm$ 19.6 and 54.8 $\pm$ 21.5 nmol/L in CC and CT genotypes, respectively (P=0.0291). MTX dose was strongly associated with PG3 levels as well as with those of PG4. MTX-PG3 levels were regressed as follows; MTX-PG3 (nmol/L) = -0.035 +[2.04 * MTX dose] + [2.34 * SLC19A1 c.80G>A] + [-2.01 * FPGS c.192T>C]. When upper and lower limits of them were defined, we can speculate MTX dose to reach the effective levels for individual patients. However, the ranges of effective levels were rather wide, suggesting that effectiveness of MTX may depend on not only concentrations of MTX-PG but also responsiveness to MTX-PG.

Conclusions: We measured erythrocyte MTX-PGn in RA patients with low disease activity and investigated for their associations with MTX dose and genetic polymorphisms. We could speculate MTX dose required to reach possible effective MTX-PG levels in individual patient.

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