Conclusion: Adherence to MTX can affect disease activity during follow-up in Korean patients with RA. Our results provide a rationale for patient education to maintain good drug adherence in RA patients, to control disease activity.
Disclosure of Interests: None declared

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FRI0127 SUPPRESSION OF RADIOGRAPHIC PROGRESSION AFTER GRADUAL METHOTREXATE TAPERING IN PATIENTS WITH RHEUMATOID ARTHRITIS PATIENTS MAINTAINING LOW DISEASE ACTIVITY - PROSPECTIVE MULTICENTER STUDY-

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Background: Many studies have been reported to reduce/discontinue Biologics in the treatment of rheumatoid arthritis (RA). In contrast, study for tapering methotrexate (MTX) has been limited (1,2).
Objectives: We prospectively examined whether bone destruction will progress at 48 weeks after tapering or discontinuing MTX (UMIN000028875).
Methods: The subjects were RA patients who have maintained low disease activity or lower for 24 weeks or more in DAS28-CRP after MTX administration. Patients having PDUS Grade 2 or 3 per site by bilateral hand ultrasonography (26 area) were excluded in this study owing to risk for joint destruction. The joint destruction was evaluated by the joint X-ray evaluation by modified total Sharp scoring (mTSS) at 1 year after the start of tapering MTX. Evaluation of clinical disease activities, severe adverse events, the continuation rate during MTX tapering were also evaluated. According to tapering response, prognostic factor for good response for tapering, joint destruction was determined. Predictors for successful tapering MTX and progression of bone destruction were determined. Statistical analysis was performed by t-test or Wilcoxon rank sum test using SAS .13.2 software.
Results: The subjects were 79 (16 males, 63 females). Age average 60.9 years, disease duration 4 years 4 months, MTX dose 8.43 mg / w, DAS28-CRP 1.52, DMARDs (24.3%), ACPA 192.7 U / ml (70.5%), RF 55.6 IU / ml (65.4%).MTX was tapered from an average of 8.43 mg / w before study to 5.46 mg / w one year later. In the treatment evaluation, DAS28-CRP increased from 1.52 to 1.84. 89.7% of subjects did not progress joint damage. Other disease activities significantly increased (Table 1). The one-year continuation rate was 78.2%. Since tapering effects were varied widely, we divided patients into three groups; Flared group (N=14, initial MTX dose 8.71mg/w, final MTX dose 8.42mg/w), Low response group (N=31, final MTX reduction rate< 50%, initial MTX dose 8.93mg/w, final MTX dose 6.22mg/w), High response group (N=34, final MTX reduction rate≥ 50%, initial MTX dose 8.5mg/w, final MTX dose 3.15mg/w)(Table 2).Higher RF value at baseline and higher MTX dose at 3M, 6M were predictors of whether a subject was in Low response group or High Response group. Higher RF value and mTSS at baseline and higher MTX dose at 6M were predictors whether a subject was in Flared group or High response group. Lower age was predictor of whether a subject was in Flared group or Low responder group. Finally, mean ΔmTSS /y in Flared group (0.36) was not significantly higher than in low response group (0.07) and in high response group (0.01).

Table 1

	0M	12M	P
RF	47.7 ± 70.1	59.1 ± 72.5	NS
CRP	0.15 ± 0.18	0.30 ± 0.73	NS
ESR	18.60 ± 14.28	21.47 ± 18.08	NS
DAS28-E	2.1 ± 0.65	2.46 ± 0.84	0.002*
DAS28-C	1.53 ± 0.34	1.83 ± 0.70	0.001*
CDAI	2.03 ± 1.78	3.77 ± 4.08	0.0002*
SDAI	2.20 ± 1.79	3.86 ± 3.67	<.0001*
SJC	0.55 ± 0.73	1.01 ± 1.26	0.0041*
TJC	0.10 ± 0.34	0.38 ± 1.96	0.0128*
MMP3	52.70 ± 30.14	58.75 ± 43.20	NS
HAQ-DI	0.14 ± 0.35	0.22 ± 0.42	0.0165*

* significant: Pairs test, Average(SD)

Table 2. Predictors for successful tapering MTX and progression of bone destruction

	Flared group (F)(n = 14)	Low reduced group(L) (n = 31)	High reduced group (H)(N = 34)	P value
sex (F:M)	4:10	5:26	7:27	N.S
Age(years)	54.6 (10.1)*	62.3 (10.8)*	61 (13.0)	0.05*(F vs L)
Duration(M)	56.8(32.7)	60.3 (50.9)	47.5 (37.3)	N.S
LDA (M)	30.2(28.1)	29.8 (24.8)	26.1 (23.0)	N.S
MTX dose(mg/w) baseline	8.71(2.3)	8.93 (2.2)	8.5 (2.7)	N.S
0M	6 (2.4)	6.71 (2.0)	5.88 (2.2)	N.S
3M	6.43 (2.5)	6.64 (1.9)*	5.62 (1.0)*	0.05**(L vs H)
6M	7.28 (2.2)*	6.52 (1.8)*	4.59 (1.8)*	<.0001* (F vs H) 0.0001* (L vs H)
12M	8.42 (1.9)*	6.22 (1.7)*	3.15 (1.7)*	<.0001* (F vs H,L vs H) 0.0002* (F vs L)
GSS 0M	1.71 (2.0)	2.87 (3.3)	1.68 (2.2)	N.S
PDS 0M	0.43 (1.1)	0.87 (1.6)	0.41 (1.0)	N.S
PSL(mg/dl) 0M	0.15 (0.5)	0.41 (1.3)	0.76 (1.2)	N.S
CCP(U/ml) 0M	133.1 (205.3)	210 (371.6)	179 (308.9)	N.S
RF (IU/ml) 0M	44.2 (38.5)*	75.1 (99.5)*	24.1 (27.5)*	0.003* (F vs H) 0.006* (L vs H)
DAS28-CRP 0M	1.47 (0.2)	1.6 (0.4)	1.51 (0.3)	N.S
DAS28-CRP 12M	2.76 (1.0)*	1.67 (0.5)*	1.58 (0.4)*	<.0001* (F vs LH)
mTSS 0M	16.6 (7.2)*	15.2 (14.3)	11.2 (9.1)*	0.005**(F vs H)
mTSS/y 0M	4.36 (2.3)	4.42 (4.6)	4.89 (6.8)	N.S
ΔmTSS/y	0.36 (0.63)*	0.07 (0.4)	0.01 (0.09)*	0.05*(F vs LH)

*t-test ** Willcoxon rank sum test

Conclusion: Patients with MTX-administered low disease activity and finger joint echo PDUS grade 1 satisfy almost no joint destruction even after MTX reduction. For tapering, predictors may be helpful for maintaining patient's satisfaction.
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FRI0128 FILGOTINIB PROVIDED RAPID AND SUSTAINED IMPROVEMENTS IN FUNCTIONAL STATUS, PAIN, HEALTH-RELATED QUALITY OF LIFE, AND FATIGUE IN PATIENTS WITH RHEUMATOID ARTHRITIS AND INADEQUATE RESPONSE TO METHOTREXATE: RESULTS FROM THE FINCH 1 STUDY

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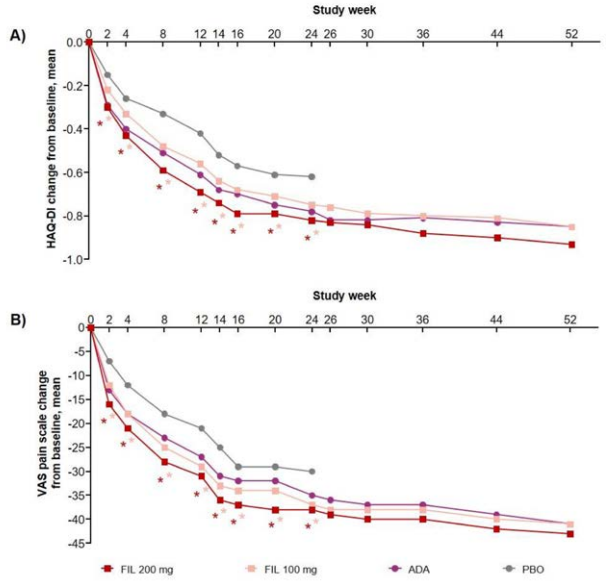
Background: In the FINCH 1 study, filgotinib (FIL)—an oral, potent, selective Janus kinase 1 inhibitor—in combination with methotrexate (MTX) provided significant improvements in the signs and symptoms of rheumatoid arthritis (RA) in patients (pts) with inadequate response to MTX.[1] While EULAR guidelines recommend a treat-to-target approach focusing on reducing inflammation to prevent joint damage, physical disability, and mortality, pts consider control of pain and fatigue, along with maintenance of physical function and health-related quality of life (HRQoL), to be important aspects for their care.[2,3]
Objectives: To evaluate the rate and magnitude of change in patient-reported outcomes (PROs) from FINCH 1.
Methods: In the FINCH 1 study (NCT02889796), pts with active RA received oral FIL 200 mg + MTX, FIL 100 mg + MTX, PBO + MTX, or subcutaneous adalimumab (ADA) 40 mg + MTX for up to 52 weeks (W); pts receiving PBO at W24 were rerandomised 1:1 to FIL 100 or 200 mg. PROs included the HAQ-DI and VAS pain scale, SF-36, and FACIT-Fatigue questionnaire. The change from baseline (CFB) at each time point was assessed up to W52 for each treatment group. The mixed-effects model for repeated measures was used to compare each FIL group with PBO for the CFB at each time point through W24. The logistic regression model was used to compare each FIL group with PBO for the proportion of pts achieving the minimum clinically important difference (MCID) of ≥0.22 reduction in CFB in HAQ-DI at each time point through W24.
Results: Of 1755 pts randomised and treated (475 FIL 200 mg + MTX; 480 FIL 100 mg + MTX; 325 ADA + MTX; and 475 PBO + MTX), 1417 (80.7%) received study drug through W52. As early as W2 through W24, pts receiving either dose of FIL experienced nominally significantly greater (p <0.001) CFB in HAQ-DI and VAS pain scale than those receiving PBO; CFB improvements were maintained through W52 (Fig 1**A, B**). At W2, compared with PBO (40.2%), a nominally significantly greater proportion of pts achieved the HAQ-DI MCID in both the FIL 200 (52.5%; p <0.001) and 100 mg (46.7%; p = 0.043) groups. This benefit vs PBO was maintained up to W24 and the proportion of pts who achieved a HAQ-DI reduction of ≥0.22 remained ≥75.8% in the FIL 200 mg group and ≥71.5% in the FIL 100 mg group from W12 through W52. FIL provided nominally significantly greater improvement in HRQoL vs PBO at W4

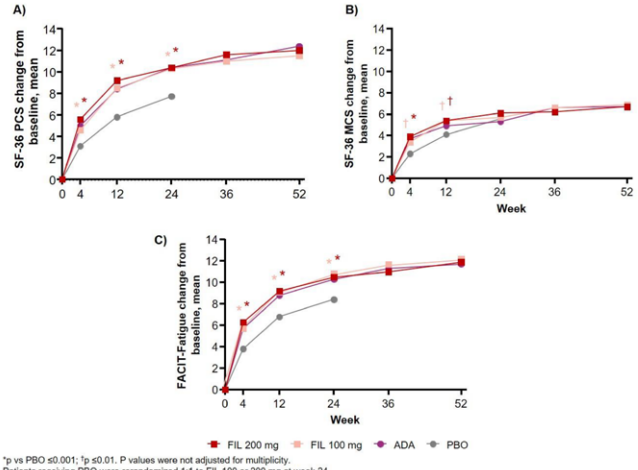
and W12 for both the CFB of the SF-36 Physical Component Summary (PCS) (p <0.001) and Mental Component Summary (MCS) (p ≤0.006); nominal significance was also seen at W24 for CFB of SF-36 PCS (Fig 2**A, B**). By W4, pts receiving either dose of FIL reported a nominally significantly greater mean CFB in FACIT-Fatigue scores vs PBO (p <0.001); significance was maintained through W24 and improvement in reported fatigue continued through W52 in the FIL groups (Fig 2**C**). In general, CFB for HAQ-DI, VAS pain scale, and FACIT-Fatigue observed for the FIL groups was higher or comparable to ADA at various time points (Fig 1, 2).

Figure 1. Change from baseline in A) HAQ-DI and B) VAS pain scale at each visit



*p vs PBO <0.001, not adjusted for multiplicity except at week 12 for HAQ-DI.
Patients receiving PBO were rerandomized 1:1 to FIL 100 or 200 mg at week 24.
ADA, adalimumab; FIL, filgotinib; HAQ-DI, Health Assessment Questionnaire Disability Index; PBO, placebo; VAS, visual analog scale.

Figure 2. Change from baseline in SF-36 A) PCS and B) MCS and C) FACIT-Fatigue



*p vs PBO ≤0.001; †p ≤0.01. P values were not adjusted for multiplicity.
Patients receiving PBO were rerandomized 1:1 to FIL 100 or 200 mg at week 24.
ADA, adalimumab; FACIT, Functional Assessment of Chronic Illness Therapy; FIL, filgotinib; MCS, mental component summary; PBO, placebo; PCS, physical component summary; SF-36; Short-Form 36.

Conclusion: Both doses of FIL provided rapid and sustained improvements in functional status, pain, HRQoL, and fatigue compared with PBO for pts with RA and inadequate response to MTX throughout the 52-week period.

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Disclosure of Interests: Alan Kivitz Shareholder of: AbbVie, Amgen, Gilead, GSK, Pfizer Inc, Sanofi, Consultant of: AbbVie, Boehringer Ingelheim,,Flexion, Genzyme, Gilead, Janssen, Novartis, Pfizer Inc, Regeneron, Sanofi, SUN Pharma Advanced Research, UCB, Paid instructor for: Celgene, Genzyme, Horizon, Merck, Novartis, Pfizer, Regeneron, Sanofi, Speakers bureau: AbbVie, Celgene, Flexion, Genzyme, Horizon, Merck, Novartis, Pfizer Inc, Regeneron, Sanofi, Yoshiya Tanaka Grant/research support from: Asahi-kasei, Astellas, Mitsubishi-Tanabe, Chugai, Takeda, Sanofi, Bristol-Myers, UCB, Daiichi-Sankyo, Eisai, Pfizer, and Ono, Consultant of: Abbvie, Astellas, Bristol-Myers Squibb, Eli Lilly, Pfizer, Speakers bureau: Daiichi-Sankyo, Astellas, Chugai, Eli Lilly, Pfizer, AbbVie, YL Biologics, Bristol-Myers, Takeda, Mitsubishi-Tanabe, Novartis, Eisai, Janssen, Sanofi, UCB, and Teijin, Susan Lee Shareholder of: Gilead Sciences Inc., Employee of: Gilead Sciences Inc., Lei Ye Shareholder of: Gilead Sciences Inc., Employee of: Gilead Sciences Inc., Hao Hu Shareholder of: Gilead Sciences Inc., Employee of: Gilead Sciences Inc., Robin Besuyen Shareholder of: Galapagos, Employee of: Galapagos, Bernard Combe Grant/research support from: Novartis, Pfizer, Roche-Chugai, Consultant of: AbbVie; Gilead Sciences, Inc.; Janssen; Eli Lilly and Company; Pfizer; Roche-Chugai; Sanofi, Speakers bureau: Bristol-Myers Squibb; Gilead Sciences, Inc.; Eli Lilly and Company; Merck Sharp & Dohme; Pfizer; Roche-Chugai; UCB

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FRI0129

DEVELOPMENT OF A PREDICTION MODEL FOR MAXIMUM METHOTREXATE (MTX) DOSE WITHOUT HEPATOTOXICITY USING AN INDEX OF ERYTHROCYTE MTX-POLYGLUTAMATE (MTXPG) LEVELS SPECULATED BY CLINICAL AND GENETIC MARKERS

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Background: MTX is transported into cells and retained long after polyglutamation. MTXPG level can predict response and possibly adverse effects of MTX. We reported erythrocyte MTXPG concentrations efficiently discriminated patients with and without hepatotoxicity[1]. We also developed genetic and clinical prediction models for efficacy and hepatotoxicity of MTX[2]. In the present study, we firstly investigated the effects of clinical and secondly genetic variables on the concentration of total MTXPG and determined oral maximum MTX dose without hepatotoxicity using these variables.

Objectives: To develop a prediction model for maximum MTX dose without hepatotoxicity.

Methods: Concentrations of erythrocyte MTX-PG (PG1 to PG4) were detected by LC-MS/MS and calculated total MTXPG as sum of them. MTX-PGn levels were measured in 265 RA patients including 40 patients with elevated AST or ALT (≥ 60 U/L; 1.5 times of upper limits) and the 6 SNPs of 6 gens related to MTXPG metabolism were identified by RT-PCR.

Results: Total concentrations of MTXPG were 141.3 ± 86.5 and 87.6 ± 47.8 nmol/L (mean±SD) in 40 RA patients with hepatotoxicity and 225 patients without, respectively (p<0.0001). By ROC analysis, the two groups were most efficiently discriminated with cutoff concentration of 100.0 nmol/L (AUC 0.731). Next, genetic and clinical model to speculate the MTXPG concentration was established by multivariate analysis using 4 clinical and 3 genetic variables which were selected from 20 clinical and 6 genetic variables by univariate analysis (p<0.1). Finally, a speculation model for MTXPG concentration by 4 clinical variables (MTX dose, BMI, RBC count, and creatinine) and one genetic variable (GGH c.452C>T) was developed (Figure). When MTXPG concentration of 100 nmol/L was applied to the model, maximum MTX dose without hepatotoxicity was calculated for each patient as **MTX dose (mg) = {100 (MTXPG) – 96 + 1.7*BMI + 28*RBC - 120*creatinine - 19.3*GGH(C/T)} / 7.7**. Real dose of oral MTX exceeded the calculated dose in 23 of 40 patients (57.5%) with hepatotoxicity, whereas it exceeded in 95 of 223 patients (42.6%) without hepatotoxicity (OR 1.82, p=0.081).

Conclusion: Maximum MTX dose without hepatotoxicity was speculated by several clinical and genetic markers without measurement of erythrocyte MTX-PG concentrations.

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