Table 1. Key endpoints at week 12.

	DAS28(CRP) ^a (mean change from BL to week 12)	ACR20/50/70 ^b (% achieving at week 12)	HAQ-DI ^b (mean change from BL to week 12)
PBO	–1.36 (1.044)	40.9/22.7/13.6	–0.39 (0.389)
GS-9876 10 mg	–0.78 (1.119)	25.0/20.0/15.0	–0.18 (0.800)
GS-9876 30 mg	–1.26 (1.276)	35.0/20.0/5.0	–0.46 (0.480)
FIL 200 mg	–2.46 (1.242); *p=0.002	81.0/47.6/38.1	–0.70 (0.649)

^aPrimary endpoint; ^bSecondary endpoint; *p (compared to PBO).

Conclusion: Clinical efficacy of GS-9876 in RA was not observed, but GS-9876 was safe and well-tolerated over a 12-week period in patients with RA on MTX. FIL showed favorable safety and clinical efficacy consistent with prior data, validating the study concept and design. Additionally, biomarker changes with GS-9876 support the continuation of studies in lupus-related diseases.

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FRI0151

THE RELATIONSHIP BETWEEN THE EFFECTIVENESS OF METHOTREXATE (MTX) IN RHEUMATOID ARTHRITIS (RA) AND MTX POLYGLUTAMATES LEVELS (MTXPGS) IN RED BLOOD CELLS BY TANDEM CHROMATOMASS SPECTROMETRY (PILOT STUDY)

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Background: Therapeutic control of the level of MTXPGs in erythrocytes may be an objective marker of its effective dose in RA treatment.

Objectives: To evaluate the relationship between the level of MTXPGs in erythrocytes and the effectiveness of the dose of MT used by RA patients.

Methods: The study included 60 random selected RA patients over the age of 18, 16 men and 44 women. The diagnosis in all cases met the criteria of ACR/EULAR 2010. All pts received MTX at a constant dose of at least 20 mg per week subcutaneously for at least the last 12 weeks. Patients were divided into 2 groups depending on the presence (group 1, n = 30) or absence (group 2, n = 30) of the therapeutic effect of MTX, according to the criteria of the EULAR response to therapy. The groups were comparable in age, sex, alcohol intake, smoking, body mass index (BMI), ACP-positivity, incidence of unwanted reactions to MTX, single dose of MTX, duration of MTX treatment course. The groups differed in duration of the disease at the beginning of the current course of continuous therapy: 5.5 [2.0, 12.0] months in group 1 and 12.0 [3.0, 60.0] months in group 2; in group 2 patients received glucocorticoids (GK) orally 17 (57%) against 9 (30%) in group 1. Blood sampling was performed no later than 36 hours after the last administration of methotrexate. From each patient 2 ml of hemolysed blood were examined using an Agilent 6410 chromatograph (Agilent Technologies) - a quantitative measurement of methotrexate polyglutamate by liquid chromatography-spectrometry.

Results: It was established that the levels of total MTXPG and MTXPG1,2,3,5 in erythrocytes did not depend on the effectiveness of MTX, the dose of which was comparable in all patients. At the same time, the level of MTXPG4 was significantly higher (p = 0.023) in patients of group 1 (26.4 ± 6.1 nmol/l) compared with patients in group 2 (22.1 ± 6.8 nmol/l). Evaluation of the ROC curve showed that MTXPG4 values below 22.5 nmol/l corresponded to the absence of the therapeutic effect of MTX. The area under the curve was 0.672, (CI 95 0.536-0.808); p = 0.022. Sensitivity - 77%, specificity - 53.3%.

Conclusion: For effective treatment of RA patients, it is necessary to administer such doses of MTX so that the achieved level of MTXPG4 in erythrocytes is not less than 22.5 nmol/l.

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FRI0152

METHOTREXATE TREATMENT PATTERNS IN ADVANCED THERAPY-NAÏVE PATIENTS WITH RHEUMATOID ARTHRITIS: CLINICAL CHARACTERISTICS AND OUTCOMES OF PATIENTS IN THE CORRONA REGISTRY

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Background: Methotrexate (MTX) is one of the most commonly used drugs in the treatment of rheumatoid arthritis (RA). Some patients may discontinue MTX therapy due to lack of efficacy or intolerance and may or may not restart MTX. There is a need to better understand the patterns of MTX use, the characteristics of these patients, and how the patterns of use are related to outcomes.

Objectives: To assess patterns of MTX use in a clinical practice setting, describe baseline demographic and clinical characteristics for groups defined by patterns of MTX use, and assess the association of patterns of MTX use with clinical outcomes and side effects during the 2 years after MTX initiation.

Methods: This observational study included patients from the US Corrona RA registry who initiated MTX from 01 October 2001 to 31 October 2018, were biologic/targeted synthetic disease-modifying antirheumatic drug (bDMARD/tsDMARD)-naïve and did not start bDMARD/tsDMARD through 2 years of follow-up. Patients were divided into 3 cohorts: those who discontinued and restarted MTX, those who discontinued without restarting MTX and those who persisted on MTX. Descriptive statistics were used to evaluate patient demographics and disease activity at MTX initiation and side effects during follow-up. Changes in clinical outcomes from baseline to 2 years were calculated for all groups. Differences in outcomes were assessed using Kruskal-Wallis one-way analysis of variance for continuous or ordinal-dependent variables and chi-square test for categorical variables.

Results: Among 785 MTX initiators, 34 (4.3%) discontinued/restarted MTX, 174 (22.2%) discontinued MTX, and 577 (73.5%) persisted on MTX within the 2-year follow-up period. Overall, mean age was 59.7 years; 72.7% were female; mean duration of RA was 4.8 years; and 52.9% were conventional synthetic DMARD-naïve. Generally, in patients who discontinued/restarted, discontinued, or persisted on MTX, those who discontinued/restarted therapy had more comorbidities at MTX initiation: hypertension (35.3%, 32.8%, or 29.3%, respectively), malignancy (14.7%, 9.2%, or 8.7%, respectively), chronic obstructive pulmonary disease (10.0%, 3.9%, 1.9%, respectively), or asthma (5.0%, 4.7%, or 2.9%, respectively). At end of follow-up, mean Clinical Disease Activity Index (CDAI) was 15.6, 10.1, and 8.8 for those who discontinued/restarted, discontinued, and persisted, respectively. Disease activity according to CDAI improved during the 2-year follow-up for all 3 groups, but less improvement was observed in those who discontinued/restarted MTX (Table). Overall, the most common side effects while on MTX therapy were elevated liver enzymes (65.4%) and fatigue (43.1%). Patients who discontinued/restarted MTX vs those who persisted had higher rates of hair loss (35.3% vs 18.9%), loss of appetite (32.4% vs 17.3%) stomach pain (26.5% vs 14.6%), mouth sores (20.6% vs 16.3%), diarrhoea (11.8% vs 9.5%), and myelosuppression (8.8% vs 2.1%).

Conclusion: More than 26% of patients who initiated MTX therapy either discontinued and did not restart or discontinued and restarted therapy during 2 years of follow-up. Patients who discontinued/restarted MTX therapy had less improvement in disease activity, experienced more side

effects, and tended to have more comorbidities at MTX initiation than those who persisted on therapy.

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Clinical Disease Characteristics and Outcomes by Pattern of MTX Use				
	Discontinued/Restarted (N=34)	Discontinued (N=174)	Persisted (N=577)	P-value
CDAI change over 2-year follow-up				
Change from baseline in CDAI, mean $\pm$ SD	3.1 $\pm$ 15.6	7.4 $\pm$ 14.9	10.4 $\pm$ 13.6	<0.01
Achieved LDA,* n (%)	10 (29.4)	58 (33.3)	213 (36.9)	0.50
Achieved MCID,* n (%)	14 (41.2)	86 (49.4)	332 (57.5)	0.04
Outcomes at end of MTX use or 2-year follow-up				
CDAI, mean $\pm$ SD	15.6 $\pm$ 14.4	10.1 $\pm$ 9.3	8.8 $\pm$ 9.5	0.001
mHAQ, mean $\pm$ SD	0.5 $\pm$ 0.7	0.4 $\pm$ 0.5	0.2 $\pm$ 0.4	<0.001
Physician Global Assessment, mean $\pm$ SD	22.0 $\pm$ 20.6	18.1 $\pm$ 16.4	14.4 $\pm$ 15.4	<0.01
Patient Global Assessment, mean $\pm$ SD	39.4 $\pm$ 32.5	31.3 $\pm$ 26.7	25.2 $\pm$ 25.0	<0.01
Pain, mean $\pm$ SD	39.1 $\pm$ 32.5	33.9 $\pm$ 27.3	27.2 $\pm$ 26.2	<0.01
Fatigue, mean $\pm$ SD	44.0 $\pm$ 35.0	32.5 $\pm$ 29.5	27.2 $\pm$ 26.8	0.06
Morning stiffness, n (%)	23 (67.7)	127 (74.3)	359 (63.5)	0.03
Morning stiffness duration (h), mean $\pm$ SD	1.5 $\pm$ 4.0	1.3 $\pm$ 3.2	0.7 $\pm$ 1.9	<0.001

CDAI, Clinical Disease Activity Index; CPP, cyclic citrullinated peptide; LDA, low disease activity; MCID, minimum clinically important difference; mHAQ, modified Health Assessment Questionnaire; SD, standard deviation.

*Achievement of LDA (CDAI $\leq$ 10) in those patients who initiated therapy in moderate (10<CDAI $\leq$ 22) or high disease activity (CDAI $\geq$ 22).

*CDAI change $\geq$ 1 for those in LDA (CDAI $\leq$ 10) at baseline, CDAI change $\geq$ 6 for those in moderate disease activity (10<CDAI $\leq$ 22) at baseline, and CDAI change $\geq$ 12 for those in high disease activity (CDAI $\geq$ 22) at baseline.

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FRI0153

OPHTHALMOLOGICAL ADVERSE EVENTS UNDER JAK INHIBITORS IN PATIENTS WITH RHEUMATOID ARTHRITIS: CASE ANALYSIS OF THE EUROPEAN PHARMACOVIGILANCE DATABASE

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Background: Ophthalmological manifestations in rheumatoid arthritis (RA) include dry syndrome, scleritis, episcleritis, uveitis and peripheral ulcerative keratitis (PUK). Recently, a new class of synthetic molecules has been developed, called JAK inhibitors (JAKinhib). We observed one case of PUK occurring two months after the introduction of baricitinib treatment with corneal perforation with secondary improvement after discontinuation of JAKinhib.

Objectives: The aim of this study is to describe and characterize the ophthalmological side effects of JAK inhibitors (JAK inhib) in patients with rheumatoid arthritis (RA) from European pharmacovigilance (PV) data.

Methods: The ophthalmological manifestations that appeared under JAK inhib were extracted from the European PV database (May 2018), EUDRAVIGILANCE following a request addressed to the National Drug Safety Agency carried out according to the following MedDRA classification "SOC eye disorders and BARICITINIB" and "SOC eye disorders and TOFACITINIB".

Results: A total of 41 patients with ophthalmic adverse events (AEs) on JAK inhib were reported. Among patients, 12 were treated with BARICITINIB and 29 with TOFACITINIB. Of these AEs, 51% were reported by the medical profession, 39% by patients and 10% by paramedical teams. The database analysis revealed 4 scleritis, 3 uveitis, 1 PUK and 1 corneal ulceration. The average time to onset of AEs was 13.2 months. The infectious causes had been eliminated.

Ocular adverse events under JAK inhibitors

	BARICITINIB n=12	TOFACITINIB n=29	Mean Delay (in days)
Ophthalmological events	AEs	AEs	
Scleritis**, n (%)	2 (17)	2 (7)	344
Corneal ulceration**, n (%)	0	1 (3)	90
PUK**, n (%)	1 (8)	0	57
Uveitis**, n (%)	0	3 (10)	838
Blurry vision*, n (%)	3 (25)	8 (28)	9
Red eyes*, n (%)	3 (25)	1 (3)	33
Dry eyes*, n (%)	2 (17)	3 (10)	NA
Photophobia*, n (%)	0	1 (3)	NA
Decreased visual acuity*, n (%)	1 (8)	1 (3)	124
Retinal detachment**, n (%)	0	1 (3)	480
Retinal haemorrhage**, n (%)	0	2 (7)	541
Cataract**, n (%)	2 (17)	5 (17)	413
Glaucoma**, n (%)	0	4 (14)	489
Age related macular degeneration**, n (%)	0	1 (3)	NA

*Adverse event reported by the patient **Adverse event reported by the medical profession
PUK: Peripheral Ulcerative Keratitis NA: Not Available

Conclusion: Ophthalmological manifestations under JAKinhib seem to be rare but not exceptional, the rheumatologist must be aware of them in order to discuss the imputability of the treatment. A discontinuation of it seems justified pending an ophthalmological opinion.

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FRI0154

SAFETY AND EFFICACY OF FILGOTINIB IN PATIENTS AGED 65 YEARS AND OLDER: RESULTS FROM A PHASE 3 STUDY IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS AND PRIOR INADEQUATE RESPONSE OR INTOLERANCE TO BIOLOGICAL DMARDS (BDMARD-IR)

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Background: Filgotinib (FIL), an oral selective Janus kinase 1 (JAK1) inhibitor, demonstrated efficacy and safety vs placebo (PBO) in bDMARD-IR patients with active RA in a global phase 3 study (FINCH2, ClinicalTrials.gov NCT02873936).¹

Objectives: We performed a prespecified subgroup analysis of the safety and efficacy of FIL in patients aged $\geq$ 65 years vs <65 years in FINCH2 to understand FIL effects in older patients.

Methods: 449 patients were randomized 1:1:1 to FIL 200 mg, FIL 100 mg, or PBO on a background of csDMARDs for 24 weeks. The primary efficacy endpoint was ACR20 response at week 12.

Results: Of 448 patients who received $\geq$ 1 dose of study drugs, 113 (25.2%) were $\geq$ 65 years of age; baseline disease characteristics were similar for both age groups. Safety and efficacy parameters by age group are in Tables 1 and 2. The most common treatment-emergent adverse events (TEAEs, by System Organ Class) category was infections and infestations; nasopharyngitis, upper respiratory tract infections, and bronchitis were the most common infections and infestations in the FIL arms in both age groups. There were no cases of opportunistic infection, active tuberculosis, malignancy, gastrointestinal perforation, or death. Efficacy outcomes were similar for both groups.

Conclusion: Overall, older age was not associated with higher incidence of safety events (serious infections, herpes zoster, MACE occurred in the group <65 yrs) and efficacy was similar in older and younger bDMARD-IR patients with active RA.

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