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Background: Filgotinib (FIL) is a Janus kinase 1 preferential inhibitor approved for the treatment of moderate to severe rheumatoid arthritis (RA) in patients (pts) with an inadequate response to disease-modifying antirheumatic drugs.[1] In a pooled analysis of Phase 3 FINCH 1–3 studies of FIL in RA, median lymphocyte levels were relatively stable over 1 year with lymphocyte decreases observed in individual FIL-treated pts. Lymphocyte levels should be monitored.[1]

Objectives: To assess the effect of FIL on lymphocyte levels and lymphopenia in the FINCH 4 long-term extension (LTE) study in RA.

Methods: Safety data of FIL 100 mg (FIL100) and 200 mg (FIL200) from LTE baseline to data cut off (01 June 2020) are reported overall and by prior FIL exposure for pts who received ≥1 FIL dose in FINCH 4 (NCT03025308; adults with RA who had completed FINCH 1/2/3). Adverse events (AEs) of lymphopenia were graded based on clinical severity; laboratory abnormalities (decreased lymphocytes) were graded per Common Terminology Criteria for Adverse Events v4.03 (CTCAE). Frequencies of both measures and exposure-adjusted incidence rates (EAIRs) of AEs are reported. Median lymphocyte levels are reported to LTE Week 48.

Results: The safety analysis set included 2729 pts (FIL200: n=1530; FIL100: n=1199). Of these, 75.4% (n=2058) had prior FIL exposure in FINCH 1/2/3. Median FIL exposure to LTE Week 48 was 600 (FIL200: 696; FIL100: 533) days. In both treatment groups, median laboratory lymphocyte levels remained relatively stable to LTE Week 48 for pts with prior FIL exposure. Pts without prior exposure had numerically higher median lymphocyte levels at LTE baseline vs pts with prior exposure (Figure 1). These decreased over time, but medians remained within normal range. The frequency and EAIR of graded decreases in laboratory lymphocyte levels were higher with FIL200 vs FIL100 (Table 1); incidence was slightly higher in pts with vs without prior FIL exposure, with the difference most apparent for Grade 2 decreases.

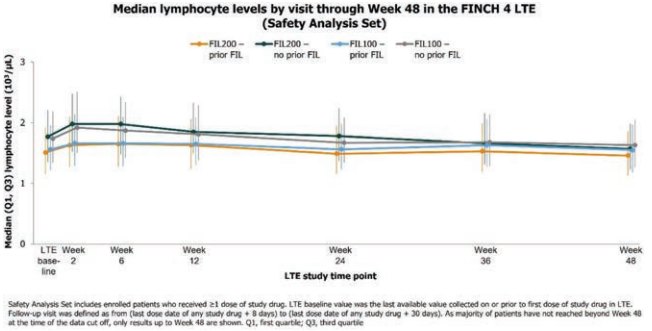

Figure 1.

Of all pts receiving FIL, 43 (1.6%) reported a lymphopenia AE; frequencies and EAIRs of lymphopenia AEs were slightly higher with FIL200 (1.9%; EAIR [95% CI]: 1.2 [0.9–1.8]) vs FIL100 (1.2%; 0.8 [0.4–1.3]). Most were Grade 1 or 2 in severity. Grade 3 lymphopenia AEs occurred in 4 (0.3%) vs 1 (<0.1%) pts receiving FIL200 vs FIL100. There were no Grade 4 AEs in either group. No serious AEs of lymphopenia or treatment discontinuations due to lymphopenia were reported. In total, 8 (0.3%) pts interrupted study treatment due to lymphopenia. Infection rates, but not serious infections, were slightly higher for pts with lymphopenia, however no relationship between lymphopenia severity and infection AE grade was seen.

Conclusion: In FINCH 4, lymphopenia AEs were infrequent but numerically greater with FIL200 vs FIL100, suggesting a dose–response relationship. While exposure at either dose may be associated with decreased lymphocytes, median lymphocyte levels were comparable in both groups and all remained within normal range at LTE Week 48, similar to observations in FINCH 1–3.

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POS0514 PREDICTION OF RESPONSE TO METHOTREXATE IN PATIENTS WITH RHEUMATOID ARTHRITIS: A MACHINE LEARNING APPROACH USING CLINICAL TRIAL DATA

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Background: Methotrexate (MTX) is the preferred initial disease-modifying drug (DMARD) for rheumatoid arthritis (RA). However, up to 50% of patients respond inadequately to MTX (1). Clinically useful predictors that effectively identify patients with RA who are likely to respond to MTX are lacking. Whether machine learning (ML) can provide robust and clinically useful prediction of response to MTX monotherapy in the first months of treatment in patients with early RA using uniformly collected baseline demographics and clinical data has not been investigated in large patient populations.

Objectives: We aimed to identify clinical predictors of response to MTX as the first DMARD among patients with RA using ML methods.

Methods: Randomized clinical trials (RCT) of patients with RA who were DMARD-naïve and randomized to placebo plus MTX were identified and accessed through the Clinical Study Data Request Consortium and Vivli Center for Global Clinical Research Data. Studies with available Disease Activity Score with 28-joint count and erythrocyte sedimentation rate (DAS28-ESR) at baseline, 12 and 24 weeks were included. Latent class modeling of MTX response was performed. Least absolute shrinkage and selection operator (LASSO) and random forest were used to identify predictors of response.

Results: A total of 775 patients from 4 RCTs were included (mean age 50 years, 80% female). Two distinct classes of patients were identified based on DAS28-ESR change over 24 weeks: "good responders" and "poor responders" to MTX

Table 1. Frequencies of treatment-emergent laboratory decreases in lymphocytes

	Prior FIL exposure		No prior FIL exposure		Overall		Total
	FIL200	FIL100	FIL200	FIL100	FIL200	FIL100	(N=2729)
	(n=1195)	(n=863)	(n=335)	(n=336)	(n=1530)	(n=1199)	
Decreased lymphocytes (any grade), n (%)	228 (19.1)	125 (14.5)	41 (12.3)	40 (12.0)	269 (17.6)	165 (13.8)	434 (16.0)
Grade 1	48 (4.0)	35 (4.1)	14 (4.2)	7 (2.1)	62 (4.1)	42 (3.5)	104 (3.8)
Grade 2	159 (13.3)	82 (9.5)	21 (6.3)	26 (7.8)	180 (11.8)	108 (9.1)	288 (10.6)
Grade 3	21 (1.8)	8 (0.9)	6 (1.8)	7 (2.1)	27 (1.8)	15 (1.3)	42 (1.5)
Grade 4	0	0	0	0	0	0	0

A treatment-emergent laboratory decrease in lymphocytes was defined as an increase of ≥1 toxicity grade from baseline at any time post-baseline up to and including the date of last study drug dose + 30 days. Severity grades were defined per CTCAE (lower limit of normal: <0.8 × 10^9/L [Grade 1]; <0.8–0.5 × 10^9/L [2]; <0.5–0.2 × 10^9/L [3]; <0.2 × 10^9/L [4]).

treatment (Figure 1). Baseline DAS28-ESR, anti-citrullinated protein antibody (ACPA) and health assessment questionnaire (HAQ) score were the top predictors of good response to MTX using LASSO (Area Under the Curve [AUC] 0.79) and Random Forest models (AUC 0.68) in the external validation set. DAS28-ESR≤7.4, ACPA positive and HAQ≤2 provided the highest likelihood of response (Table 1). Among patients with 12-week DAS28-ESR>3.2, at least 1 point improvement in DAS28-ESR baseline-to-12-week was predictive of achieving DAS28-ESR≤3.2 at 24 weeks.

Table 1. Matrix prediction model: Probability of achieving a good response to methotrexate at 24 weeks

DAS28ESR	≤7.4	80.1 (76.4, 83.8)	77.3 (70.6, 84)	Positive	**ACPA Status**
		77.1 (68.6, 85.6)	74.1 (63.3, 84.9)	Negative	
	>7.4	40.3 (32.1, 48.5)	36.5 (29.3, 43.6)	Positive	
		36.2 (23.3, 49.1)	32.5 (20.9, 44.1)	Negative	
		≤2	>2		
		HAQ			

Footnote: The number in each cell represents the percentage and 95% CI of achieving the outcome, based on the combination of predictors at baseline. DAS28-ESR: Disease Activity Score with 28-joint count with erythrocyte sedimentation rate; HAQ: Health assessment questionnaire score; ACPA: Anti-citrullinated protein antibody.

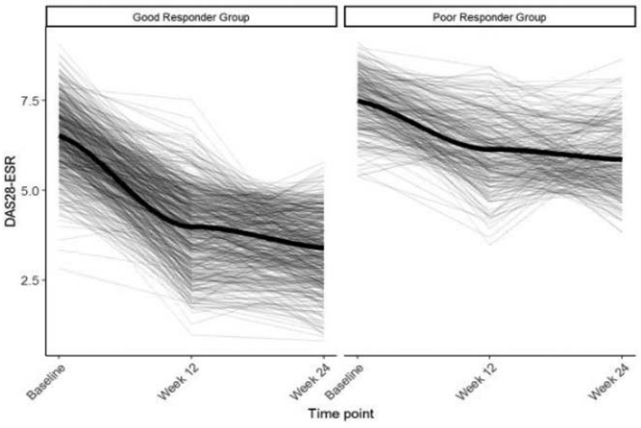

Figure 1. Two patient class trajectories identified with latent class modeling of DAS28-ESR (N=775)

Conclusion: We have developed and externally validated a prediction model for response to MTX within 24 weeks in DMARD-naïve patients with RA, providing variably weighted clinical features and defined cut-offs for clinical decision-making. Trajectory of DAS28-ESR change over 24 weeks in patients with moderate-to-high RA disease activity at baseline who are starting MTX can be predicted by baseline DAS28-ESR, ACPA status and HAQ-score. Patients with at least 1 unit decline in DAS28-ESR within the first 12 weeks of treatment who have not achieved low disease activity by week 12, may be more likely to achieve low disease activity at 24 weeks. These parameters should be considered as part of the clinical decision-making process when initiating MTX in DMARD-naïve patients with RA.

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POS0515 THE ASSOCIATION BETWEEN AUTOANTIBODIES AND RISK FOR VENOUS THROMBOEMBOLIC EVENTS AMONG PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Patients with rheumatoid arthritis (RA) have an increased risk for cardiovascular disease, including venous thromboembolic events (VTE)[1]. The reason behind the increased VTE risk is incompletely understood, but inherent features of RA, such as RA specific autoantibodies, could potentially play a role. For example, studies have linked occurrence and levels of rheumatoid factor (RF) in the general population to increased VTE risk[2]. We and others have demonstrated an association between ACPA and risk of later ischemic cardiovascular events[3]. There are also potential mechanistic links; citrullinated fibrinogen (cFib) has been associated to clot stability[4].

Objectives: We aimed to examine the association between anti-modified protein antibodies (AMPAs) and risk of VTE in RA.

Methods: We included 2809 individuals newly diagnosed with RA and included in the Swedish EIRA study 1996-2009. Through linkage to nationwide health care registers we identified past and incident events of VTE based on validated ICD code algorithms. We centrally typed baseline sera for anti-CCP2, 20 different ACPA sub-specificities, RF isotypes, carbamylated antibodies and 10 additional post-translational modifications. We followed all individuals from RA diagnosis up until their first ever VTE event, migration, death or end of study (2020-12-31) whichever occurred first. We used a Cox regression to estimate hazard ratios (HR) with 95% confidence intervals (CI). Individuals with a history of a VTE event (n=27) at RA diagnosis were excluded.

Results: We included 2782 individuals; 72% were women, median age at RA diagnosis was 54 years (inter quartile range (IQR) 18 years) and median follow-up time was 15.5 (IQR 6.8) years. During follow-up 177 incident VTE events were observed corresponding to an incidence of 5.0 per 1,000 person years.

1797 (64.6%) patients were positive for IgG anti-CCP2 and the HR for VTE (vs. being negative for anti-CCP2) was 1.33 (95%CI 1.00-1.78). The risk of VTE increased with the level of anti-CCP2, with an HR of 1.49 (95%CI 0.99-2.22) for the group with extreme levels compared to those negative for anti-CCP2 (p-value for trend 0.048). For IgA anti-CCP2 the HR was 1.35 (95% CI 0.99-1.84) when comparing those expressing IgA anti-CCP2 against those who did not. Of 20 ACPA fine-specificities studied, 18 occurred with a frequency > 10% in our sample. The median number of fine-specificities expressed was 6 (IQR 11). The risk of VTE increased with the number of ACPA fine-specificities expressed (p-value for trend 0.033). At the 0.05 significance level, two fine-specificities were each associated with VTE; cPept Z1 [HR=1.40 (95%CI 1.06-84)] and cPept-1 [HR=1.47 (95%CI 1.12-1.93)]. None of the six antibodies against cFib assessed were statistically significantly associated with VTE risk. No associations were observed for other AMPAs. Among the three RF isotypes, only IgM RF was statistically associated with VTE [HR=1.38 (95%CI 1.04-1.83)].

Conclusion: RA-related antibodies analysed in clinical practice (anti-CCP2 IgG, RF) are associated not only with risk of myocardial infarction, stroke and cardiovascular death as previously demonstrated but also with VTE. There were no clear specific signals with ACPA fine-specificities, other AMPAs, or IgA RA autoantibodies.

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