MTX (3), HCQ (1), AZA (1) MMF (1). A significant improvement of the dyspnea was observed. FVC and HRCT showed an improvement in the period between 6 and 12 months. DLCO remained stable in the majority of the patients (%). DAS28 also improved.
After a follow-up of 12 months, the only serious adverse effect was a severe Infection respiratory.

Table 1

	Baseline	3 months	6 months	12 months
MMRC, n (%)	18	15	16	16
– No change		10 (67)	10 (63)	10 (63)
– Improvement		5 (33)	6 (37)	6 (37)
– Worsening		0	0	0
CVF, n (%)	16	10	5	13
– No change		7 (70)	5 (100)	10 (77)
– Improvement		1 (10)	0	3 (23)
– Worsening		2 (20)	0	0
DLCO, n (%)	14	6	3	12
– No change		5 (83)	1 (33)	8 (66)
– Improvement		0	2 (67) 7 2 (17)	
– Worsening		1 (17)	0	2 (17)
HRCT, n (%)		7	9	7
– No change		6 (86)	7 (78)	4 (57)
– Improvement		1 (14)	1 (11)	3 (43)
– Worsening		0	1 (11)	0
JOINT, DAS28 – Mean	4.32±1.35	3,21±0.73	3,44±0.87	2.83±0.70
CRP (mg/dl)-, Mean	2.01±2.35	1.12±0.9	1.98±1.95	1.03±0.9
ESR (mm/1sth), Mean	49.0±30.64	37.79±37,73	38.63±30.63	24.50±22

Conclusions: RTX seems to be an effective and relatively safe treatment in RA patients with ILD. However, these data should be verified in prospective and randomized studies.
Disclosure of Interest: None declared
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FRI0227 SARILUMAB SIGNIFICANTLY SUPPRESSES CIRCULATING BIOMARKERS OF BONE RESORPTION AND CARDIOVASCULAR RISK COMPARED WITH ADALIMUMAB: BIOMARKER ANALYSIS FROM THE PHASE 3 MONARCH STUDY

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Background: MONARCH (NCT02332590) was a randomized, active-controlled, double-blind, double-dummy, phase 3 superiority trial comparing sarilumab monotherapy with adalimumab monotherapy. Exploratory biomarkers associated with inflammation, bone erosion, and cardiovascular (CV) risk were evaluated in this study.
Objectives: To compare the effects of sarilumab monotherapy vs adalimumab monotherapy on circulating biomarkers associated with acute-phase response (CRP, serum amyloid A [SAA]), bone resorption (RANKL and osteoprotegerin [OPG]), and CV risk (lipoprotein (a) [Lp(a)]) in patients from MONARCH.
Methods: Sera were analyzed at baseline and posttreatment through wk 24 from patients who consented to biomarker analyses and received SC sarilumab 200 mg q2w (N=153) or adalimumab 40 mg q2w (N=154). Biomarkers were assessed using validated ELISAs. Nonparametric methods were used to evaluate differences in the percent change from baseline in biomarker levels between treatments at each time point. Percent change from baseline in biomarkers at wk 24 was also compared, separately by treatment group, between ACR50 responders and nonresponders at wk 24. The Benjamini-Hochberg procedure was used to correct *P* values for multiplicity and control false discovery rate. Significance level was $P<0.05$.
Results: A significant difference in RANKL was observed at wks 2 and 24 between sarilumab and adalimumab groups ($P<0.0001$; Table). Numerically, RANKL decreased after sarilumab and increased after adalimumab treatment. Significantly greater reductions in Lp(a), SAA, and CRP were observed at wks 12 and 24 after treatment with sarilumab vs adalimumab. The difference in OPG between groups was significant at wk 2 only.

Table 1. Median Percent Change From Baseline in Serum Concentrations of Circulating Biomarkers

		Sarilumab 200 mg q2w (N=153)	Adalimumab 40 mg q2w (N=154)
CRP	Wk 12	-94.2†	-29.7
	Wk 24	-94.0†	-24.0
SAA	Wk 12	-79.9†	-32.2
	Wk 24	-83.2†	-17.4
RANKL	Wk 2	-2.5†	4.4
	Wk 24	-18.3†	10.5
OPG	Wk 2	0.9*	-4.0
	Wk 24	2.2	3.3
Lp(a)	Wk 12	-35.0†	-0.4
	Wk 24	-41.0†	-2.8

*Adjusted $P<0.01$ vs adalimumab. †Adjusted $P<0.0001$ vs adalimumab.

At wk 24, change in OPG, RANKL, and Lp(a) did not differ between ACR50 responders and nonresponders at wk 24 in either treatment group. Responders in both groups demonstrated greater reductions vs nonresponders in CRP (sarilumab, -95.8% vs -87.3%; adalimumab, -47.6% vs -6.4%; all $P<0.01$); a trend was observed for SAA (sarilumab, -92.3% vs -73.2%; adalimumab, -33.0% vs 0.0%; unadjusted $P<0.05$, not significant after adjustment).
Conclusions: Sarilumab monotherapy significantly suppressed bone-resorptive and CV risk markers to a greater degree than adalimumab monotherapy. Reductions in CRP were significantly different in ACR50 responders vs nonresponders after either treatment. Analyses to assess predictive and prognostic effects of biomarkers (including markers of myeloid and lymphoid synovial phenotypes) are ongoing.
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FRI0228 UGT1A1 GENETIC VARIANTS ARE ASSOCIATED WITH INCREASES IN BILIRUBIN LEVELS IN RHEUMATOID ARTHRITIS PATIENTS TREATED WITH SARILUMAB

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Background: Sarilumab is a human mAb that blocks IL-6 from binding to both membrane-bound and soluble IL-6Rα. Variants in the *UGT1A1* gene have been shown to be strongly associated with increased unconjugated bilirubin levels in patients treated with tocilizumab, another IL-6Rα inhibitor.[1,2] *UGT1A1* encodes the enzyme responsible for the glucuronidation of bilirubin and variation in this gene is also responsible for Gilbert's syndrome, a mild benign condition characterized by elevations in unconjugated bilirubin and jaundice. The underlying main genetic variation responsible for Gilbert's syndrome has been identified as a TA repeat located in the promoter of *UGT1A1* (UGT1A1*28 allele), which is in linkage disequilibrium with a single nucleotide polymorphism, rs6742078, previously associated with higher bilirubin levels after tocilizumab treatment.[1]
Objectives: To test for an association between rs6742078 and bilirubin levels in RA patients treated with sarilumab.
Methods: DNA was collected from patients enrolled in MOBILITY (NCT01061736), which evaluated the efficacy and safety of sarilumab + methotrexate (MTX) in RA patients with inadequate response to MTX. The pharmacogenetic analysis was conducted in 599 Caucasian patients treated with MTX + sarilumab (150 or 200 mg q2w) or placebo. Log-transformed unconjugated and total bilirubin levels were analyzed at baseline and over the treatment period (using maximum bilirubin).
Results: There was a strong association between the rs6742078 TT genotype and higher unconjugated bilirubin levels. The least squares mean (SE) for patients at baseline with the TT genotype was 0.48 (0.02) mg/dL vs 0.25 (0.009) and 0.21 (0.009) mg/dL for those with GT and GG genotypes, respectively ($p=1.02\times10^{-21}$). After sarilumab treatment, the difference between genotype groups increased over the course of the study ($p=4.3\times10^{-10}$; Figure). In the binary analysis of maximum total bilirubin in sarilumab-treated patients, the TT genotype was significantly associated with mild bilirubin elevations (OR =34.7; $p=1.2\times10^{-8}$; Table).

Table 1. Maximum Total Bilirubin in Sarilumab-Treated Patients by rs6742078 Genotype

	Maximum total bilirubin, n (%)		
Genotype, n (%)	≤1.5×ULN	>1.5×ULN	Total
GG/GT	352 (92)	4 (27)	356 (90)
TT	29 (8)	11 (73)[a]	40 (10)
	381	15	396

OR=34.7[b]; $p=1.2\times10^{-8}$. [a]Elevations remained ≤2×ULN. [b]Logistic regression with recessive genetic model, adjusting for ancestry covariates.

Conclusions: The association observed between the rs6742078 TT genotype in *UGT1A1* and unconjugated bilirubin elevations in sarilumab-treated patients is consistent with previous observations in tocilizumab-treated patients. These findings suggest that sarilumab-related increases in bilirubin levels are likely benign and caused by common genetic variation in *UGT1A1* and are not due to underlying liver injury.
References:
[1] Mori et al. Mod Rheumatol. 2012;22:515–523.
[2] Lee et al. Pharmacogenet Genomics. 2011;21:365–374.
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