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SAT0179 THE ASP358ALA VARIANT IN THE IL6R GENE IS SIGNIFICANTLY ASSOCIATED WITH DIFFERENCES IN SOLUBLE IL-6R PROTEIN LEVELS BUT NOT WITH DIFFERENCES IN SARILUMAB RESPONSE IN RHEUMATOID ARTHRITIS (RA) PATIENTS

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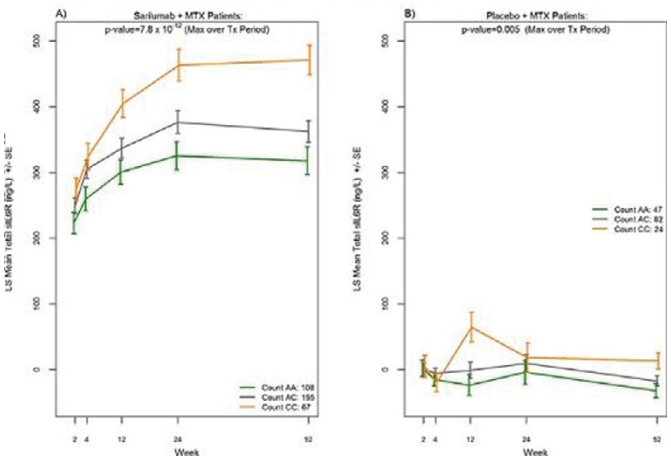
Background: Sarilumab is a human mAb that blocks IL-6 from binding to both membrane-bound and soluble IL-6Rα (sIL-6R). A missense variant in the *IL6R* gene, Asp358Ala (rs2228145), falls within a proteolytic cleavage site and individuals with an alanine at this position have increased sIL-6R in circulation.[1] In addition, this variant has been associated with several diseases including RA.[2]
Objectives: To determine the impact of the Asp358Ala variant on sIL-6R concentrations and response of RA patients to sarilumab.
Methods: DNA was collected from patients enrolled in the MOBILITY study (NCT01061736) that evaluated the efficacy and safety of sarilumab + methotrexate (MTX) in RA patients with inadequate response to MTX. The pharmacogenetic analysis was conducted on 599 Caucasian patients (396 sarilumab 150 or 200 mg q2w + MTX, 203 placebo + MTX).
Results: Concentrations of sIL-6R were strongly associated with the Asp358Ala genotypes at baseline (p=4.2 × 10^{-11}). The difference in sIL-6R concentrations between genotype groups continued to increase in sarilumab-treated patients through the end of treatment, particularly for the CC genotype (Figure; p=7.8 × 10^{-12}). There was a modest association for change in sIL-6R in placebo + MTX–treated patients (p=0.0052). Variation in Asp358Ala was not associated with sarilumab efficacy, including mTSS at week 52 and ACR scores (Table).

Table 1. Efficacy Endpoints[1] and sIL-6R Levels by Asp358Ala Genotypes in Sarilumab-Treated Patients[2]

Genotype	sIL-6R	mTSS[3]	ACR20	ACR50	ACR70	MCR[4]	SJC[5]	TJC[6]
AA (n=129)	317.7 (21.0)	1.4 (0.5)	59	40	22	13	-10.9 (0.8)	-16.5 (1.2)
AC (n=190)	362.3 (16.4)	0.7 (0.3)	65	43	22	12	-11.1 (0.6)	-18.3 (1.0)
CC (n=77)	470.8 (22.8)	0.9 (0.5)	75	48	31	17	-11.6 (1.0)	-19.1 (1.5)
p value	7.8×10^{-12}	0.89	0.06	0.67	0.57	0.71	0.25	0.20

[1]sIL-6R, mTSS, SJC, TJC show LS mean (SE). Wk 24 ACR20, ACR50, ACR70, and MCR show % achieving endpoint. [2]150 or 200 mg q2w doses combined. [3]van der Heijde modified total Sharp score at wk 52. [4]Major clinical response is defined as achieving and maintaining ACR70 for ≥24 consecutive weeks during the 52-wk period. [5]Swollen joint count. [6]Tender joint count.

Figure 1. Total sIL-6R by Asp358Ala genotype in patients treated with A) Sarilumab + MTX and B) Placebo + MTX



Conclusions: The Asp358Ala variant in the *IL6R* gene is significantly associated with differences in sIL-6R levels at baseline and after sarilumab treatment. The differences across genotypes may be due to increases in sIL-6R production. Importantly, this variant was not associated with differences in sarilumab treatment response. These data suggest that the sarilumab doses used for this clinical study saturate both the membrane and soluble forms of IL-6R and effectively block IL-6 signaling. Sarilumab provides therapeutic benefit for RA patients irrespective of their Asp358Ala genotype status.

References:
[1] Garbers et al. Biochim Biophys Acta. 2014;1842:1485–1494.
[2] Okada et al. Nature. 2014;506:376–381.

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SAT0180 EFFICACY AND SAFETY OF SARILUMAB 200 MG Q2W ADMINISTERED AS COMBINATION THERAPY OR MONOTHERAPY IN DIFFERENT PATIENT POPULATIONS WITH ACTIVE RA

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Background: Sarilumab, a human mAb blocking the IL-6Rα, was evaluated in 3 pivotal clinical trials.
Objectives: To assess efficacy and safety of sarilumab 200 mg q2w + csDMARDs or as monotherapy (MONARCH) in adults with active RA and inadequate response or intolerance to MTX (MOBILITY/MONARCH) or TNFi (TARGET).
Methods: MOBILITY (NCT01061736) was a 52-wk study; TARGET (NCT01709578) and MONARCH (NCT02332590) were 24-wk studies. Patients were randomized to placebo (Pbo) or SC sarilumab 150 or 200 mg q2w + MTX (MOBILITY) or csDMARDs (TARGET). MONARCH patients were randomized to SC monotherapy with adalimumab 40 mg q2w or sarilumab 200 mg q2w. Efficacy endpoints assessed in all 3 studies will be presented.
Results: Within studies, baseline demographic and disease characteristics were similar among treatment groups. Sarilumab 200 mg q2w improved ACR responses, HAQ-DI, DAS28-CRP, and CDAI (Table). Treatment response with sarilumab + csDMARDs was similar in MTX-IR and TNF-IR patients and with sarilumab monotherapy. Incidence of TEAEs and SAEs with sarilumab was more frequent vs Pbo (MOBILITY, TARGET) and similar to adalimumab (MONARCH). The most common TEAEs included infections, neutropenia, and injection site reactions and occurred more often with sarilumab vs Pbo (MOBILITY, TARGET). In MONARCH, rates of infection were similar with sarilumab and adalimumab,

Abstract SAT0180 – Table 1. Sarilumab Efficacy in 3 Phase 3 Studies

	MOBILITY		TARGET		MONARCH	
	Pbo + MTX (N=398)	Sarilumab 00 mg q2w + MTX (N=399)	Pbo + csDMARDs (N=181)	Sarilumab 200 mg q2w + csDMARDs (N=184)	Adalimumab 40mg q2w (N=185)	Sarilumab 200 mg q2w (N=184)
ACR20, wk 24, %	33.4	66.4*	33.7	60.9*	58.4	71.7†
ACR50, wk 24, %	16.6	45.6*	18.2	40.8*	29.7	45.7†
ACR70, wk 24, %	7.3	24.8*	7.2	16.3*	11.9	23.4†
HAQ-DI, mean change from baseline ± SD						
Wk 16/12/24	-0.3±0.6	-0.6±0.6*	-0.3±0.5	-0.5±0.6*	-0.4±0.6	-0.6±0.7†
DAS28-CRP, mean change from baseline ± SD						
Wk 24	-1.6±1.4	-3.0±1.3*	-2.0±1.2	-3.2±1.3*	-2.1±1.2	-2.9±1.3‡
CDAI, mean change from baseline ± SD						
Wk 24	-20.3±15.8	-27.9±13.2*	-23.9±12.9	-30.4±14.5*	-25.5±12.9	-29.7±12.7‡

*P<0.01 vs Pbo. †P<0.01 vs adalimumab. ‡Nominal P<0.01 vs adalimumab.