Background: Sjögren’s syndrome (SS) is a complex autoimmune disease with exocrine gland dysfunction leading to substantial morbidity. There are 10 published genetic susceptibility loci.

Objectives: Our genome-wide association study (GWAS) aimed to identify additional risk loci of genome-wide significance (GW; p<5E-08) in European-derived primary SS.

Methods: A total of 3232 cases and 17481 controls genotyped on GWAS arrays and 619 cases and 6171 controls genotyped on ImmunoChip (IC) arrays were imputed after quality control. Logistic regression was calculated adjusting for ancestry using the first 4 principal components to identify SS-associated SNPs. GWAS and IC results were meta-analyzed using weighted Z-scores. Bayesian statistics were used to assign posterior probabilities and define credible SNP sets for each locus. Bioinformatic analyses were used to predict functionality.

Results: Seven novel loci exceeded GW in the GWAS analysis: NAB1, MIR146A-3PTG1, XKR6, MAPT-CRHR1, RPTOR-CHMP6-BAIAP2, TYK2 and SYNGR1. Meta-analysis with IC data identified three more novel loci exceeding GW: CD247, PRDM1-ATG5 and TNAIP3. Several additional loci with suggestive association (p<1E-05) were also identified: ADAMTS2L, CGNL1 and HPRF1. Several identified loci have reported functional implications in immune regulation and autoimmune disease. In lupus, rs2431697 correlated with rs2293765, which was shown to alter MIR146A expression, resulting in type I interferon pathway imbalance. Similarly, TYK2 risk association reportedly drives interferon, IL10 and RET signaling pathways. PRDM1 encodes Blimp-1, a master regulator of immune cell differentiation. CD247 encodes the zeta subunit of the T cell receptor complex. XKR6 is implicated in apoptotic cell ingestion. ATG5 is also involved in apoptosis, as well as autophagy and antigen presentation. Additional bioinformatic analyses revealed immune-relevant functional implications for each risk locus. The SS-associated credible set included variants downstream of TNAIP3 in a region reported to abolish looping between an enhancer and the TNAIP3 promoter in lupus and a coding variant that has been shown to alter NF-kB activity and neutrophil extra-cellular traps. The rs2293765 in the 5' UTR of NAB1 showed evidence of enhancer/promoter activities. The rs2293765 in the SYNGR1 locus showed enhancer and transcription start site activities in B and T cells. The rs7210219 in the MAPT-CRHR1 locus showed enhancer/promoter activities in various tissues.

Conclusion: We have identified ten novel genetic susceptibility loci associated with SS pathology. Our finding increases the current number of GWAS loci in SW patients of European origin, from 10 to 20. Future work is needed to identify and characterize the functional variants in each region.

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Figure 1. Global activation of the type I IFN signature among all groups of patients. IFN means interferon; HC, healthy controls; aPL+, antiphospholipid antibodies positive; PAPS, primary antiphospholipid syndrome; SAPS, secondary antiphospholipid syndrome; SLE, systemic lupus erythematosus.
OP0049

EFFICACY OF ANIFROLUMAB IN ACTIVE SYSTEMIC
LUPUS ERYTHEMATOUS: PATIENT SUBGROUP
ANALYSIS OF BICLA RESPONSE IN 2 PHASE 3
TRIALS


Background: Treatment of patients with systemic lupus erythematosus (SLE) with the type I interferon (IFN) receptor inhibitor anifrolumab resulted in higher British Isles Lupus Assessment Group (BILAG)–based Composite Lupus Assessment (BICLA) response rates vs placebo at Week 52 in the phase 3 randomized trials, TULIP-2 (primary endpoint; 16.3% difference)1 and TULIP-1 (secondary endpoint; 16.4% difference).2 BICLA is a validated composite global disease measure that registers both partial and complete improvement within organ systems.

Objectives: TULIP-2 and TULIP-1 data were evaluated to analyze BICLA responses to anifrolumab vs placebo at Week 52 in protocol-defined subgroups of patients with active SLE.

Methods: TULIP-2 and TULIP-1 were randomized, double-blind, placebo-controlled trials that evaluated efficacy and safety of intravenous anifrolumab vs placebo administered every 4 weeks, with the primary endpoints assessed at Week 52, in patients with moderate to severe SLE despite standard-of-care treatment.1,2 BICLA responses are defined by all of the following: reduction of baseline BILAG-2004 A and B domain scores to B/C/D and C/D, respectively, and no worsening in any organ system; no worsening of the SLE Disease Activity Index 2000 (SLEDAI-2K) score; no worsening of ≥0.3 points in the Physician’s Global Assessment (range 0–3); no trial treatment discontinuation; and no use of medications restricted by the protocol.2 BICLA responses were compared between anifrolumab 300 mg and placebo groups, and robustness of BICLA responses was assessed across protocol-defined subgroups. TULIP-1 data were analyzed incorporating the amended restricted medication rules, as described.3

Results: In TULIP-2 and TULIP-1, 180 patients in each trial received anifrolumab 300 mg (182 and 184 patients received placebo, respectively). Baseline demographics, disease characteristics, and standard-of-care medications were balanced between anifrolumab and placebo groups within both TULIP trials. Patients in TULIP-2 and TULIP-1 had comparable BICLA responses (Figure). Across multiple subgroups, higher percentages of patients achieved BICLA responses at Week 52 in the anifrolumab vs placebo arms (Figure). Concordance of BICLA responses favoring anifrolumab across the protocol-defined subgroups of baseline disease severity (SLEDAI-2K <10 points [difference 15.3%, TULIP-2; 16.9%, TULIP-1] vs ≥10 points [difference 16.7%, TULIP-2; 17.1%, TULIP-1]) and baseline oral corticosteroid use (prednisone or equivalent <10 mg/d [difference 20.1%, TULIP-2; 16.2%, TULIP-1] vs ≥10 mg/d [difference 12.0%, TULIP-2; 17.7%, TULIP-1]). Numerically different BICLA effect sizes between the anifrolumab vs placebo arms were observed in both studies in relation to baseline IFN gene signature status (high [difference 17.3%, TULIP-2; 19.1%, TULIP-1] vs low [difference 11.2%, TULIP-2; 7.5%, TULIP-1]). Other subgroups including age, sex, age at onset, race, and anti-drug antibody status showed similar uniformity of response.

Conclusion: The uniformity of robust BICLA response rates across prespecified subgroups in both phase 3 trials shows consistent clinical benefit of anifrolumab irrespective of patient baseline characteristics. However, given the small patient numbers in some subgroups, these results should be interpreted with caution.

References:

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