OP0202

EFFECT OF RSLV-132 ON FATIGUE IN PATIENTS WITH PRIMARY SJÖGREN'S SYNDROME – RESULTS OF A PHASE II RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PROOF OF CONCEPT STUDY

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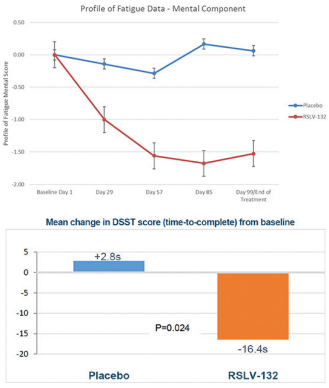
Background: Fatigue is the key symptom that leads to poor health related quality of life and loss of work productivity in patients with primary Sjogren's syndrome (pSS). RSLV-132 is a first-in-class drug comprising RNase1 fused to the Fc region of IgG1. It is designed to increase serum RNase activity to digest RNA associated immune complexes, thereby reducing Toll-like receptor (TLR) activation and subsequent production of type 1 interferon (IFN), B-cell proliferation, and autoantibody production – mechanisms that are key to pSS pathogenesis. IFN pathway dysregulation has also been implicated in fatigue.
Objectives: To explore the clinical efficacy of RSLV-132 in improving patient-reported outcomes (PRO), particularly fatigue among patients with pSS.
Methods: PSS patients with positive anti-Ro and IFN gene expression signature were randomised 3:1 to RSLV-132 10 mg/kg IV or placebo (PBO) at weeks 0,1, 2, and then fortnightly until week 12. Use of hydroxycholoroquine, other immunomodulatory therapies or prednisolone > 10mg daily were not permitted. There was no minimum entry criteria for EULAR Sjogren's syndrome disease activity (ESSDAI) or EULAR Sjogren's syndrome patient reported index (ESSPRI). The primary endpoint was changes in gene or protein expression levels in blood indicative of reduced inflammation. Secondary endpoints, among others, included safety and tolerability, and changes in PRO between baseline and week 14 including ESSPRI, FACIT, Fatigue visual analogue score (0-100), Profile of fatigue (PRO-F (0-7)) and Neuropsychological tests.
Results: Thirty patients were randomised (RSLV=22, PBO=8). Baseline clinical and demographic characteristics were comparable between groups. Two subjects randomised to active drug withdrew from the study before dosing.
Among the patients receiving RSLV-132, the mental component of PRO-F improved by 1.53 points compared to worsening of 0.06 points in the PBO group (p=0.046). Consistently, there was a significant improvement in the RSLV-132 group in their Digital Symbol Substitution Test performance with a reduction of 16.4s in completing the test compared to an increase of 2.8s in the PBO group (p=0.024). The physical component of PRO-F improved by 0.8 points in the RSLV-132 group compared to improvement of 0.06 points in the PBO group (p=0.142). Similar trends were observed for ESSPRI and FACIT-F scores.



There was no drug effect on ESSDAI but the baseline median ESSDAI scores were low for both groups (RSLV=3 (IQR (0,11), PBO=5 (IQR (0,18)).
Treatment Emergent Adverse Events were reported by all participants and similar between arms; overall RSLV-132 was safe and well-tolerated. One SAE of parotitis in the RSLV-132 arm occurred 88 days after last dose of study drug and was considered unrelated to the RSLV-132.
Analyses of the primary endpoints and other secondary endpoints are ongoing.
Conclusion: RSLV-132 is a promising therapy to improve the symptoms of fatigue in patients with pSS, with a good safety profile. Further investigation of its use in pSS is warranted.

REFERENCE:
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Molecular fingerprinting

OP0203

CHARACTERIZING THE EPIGENOMIC LANDSCAPE OF PSORIASIS PATIENTS DESTINED TO DEVELOP PSORIATIC ARTHRITIS

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Background: Approximately 30% of psoriasis patients develop psoriatic arthritis (PsA), typically within 10 years of psoriasis onset. A large proportion of individuals with PsA remain undiagnosed. Epigenetics is potentially a major mechanism through which environmental factors influence PsA risk. An understanding of how the epigenome changes during the transition to PsA could yield predictive biomarkers and facilitate PsA diagnosis. We hypothesize that epigenetic deregulation at the level of DNA methylation occurs early in PsA pathogenesis, prior to overt clinical symptoms, and epigenetic marks can be used as biomarkers for disease prediction.
Objectives: To discover predictive biomarkers of PsA and gain an understanding of the pathogenesis of PsA by characterizing the epigenomic landscape of psoriasis patients who later developed PsA (converters) and comparing it to psoriasis patients who did not develop PsA (non-converters).
Methods: We performed an epigenome-wide comparison of DNA methylation in baseline whole blood samples from psoriasis converters (n=60) and non-converters (n=60) from a longitudinal cohort. Converters and non-converters were matched for age, sex, psoriasis duration, and duration of follow-up. DNA was analyzed on Human MethylationEPIC BeadChips using the ChAMP package. Cell type heterogeneity was corrected using RefbaseEWAS. Differentially methylated probes and regions were identified using limma and DMRcate, respectively. The FEM package was used to infer differentially methylated gene modules within a protein-protein interaction network.
Results: Converter baseline samples were collected a median of 4.2 (interquartile range 1.9-6.3) years prior to the onset of PsA, while non-converters samples were collected a median of 4.3 (1.2-7.3) years prior to the most recent clinic visit. The RefbaseEWAS method estimated that converters had slightly higher proportions of CD4+ T cells and granulocytes compared to non-converters, however the differences were not statistically significant. After adjustment for cell type heterogeneity, 68 individual CpG sites were found to be differentially methylated between converters and non-converters (FDR<0.05). Differentially methylated regions (DMRs) containing at least 4 significant CpGs were identified in genes such as *FBXO27* (beta fold change [FC]=0.06, region-wise adjusted $p=4.1x10^{-4}$), a ubiquitin ligase involved in lysosomal degradation, *RCAN1* (FC=0.05, $p=5.2x10^{-3}$), a protein which inhibits calcineurin-dependent signaling pathways and is involved in bone homeostasis, and *PMAIP1* (FC=0.04, $p=6.71x10^{-3}$), which encodes the NOXA protein involved in mediating apoptosis of activated B cells. Several significant CpG sites mapped to protein-protein interaction subnetworks involved in Th17 differentiation (*IRF4* and *MAF*), TNF alpha signaling (*IKBKE*, *REL*, *MAVS*,