EFFECT OF RSLV-132 ON FATIGUE IN PATIENTS WITH PRIMARY SJÖGREN’S SYNDROME – RESULTS OF A PHASE II RANDOMISED, DOUBLE-BLIND, PLACEO-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 Sjögren’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 with Toll-like receptor (TLR) activation and sub-sequent production of type 1 interferon (IFN), B-cell proliferation, and autoimmune- body 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 hydroxychloroquine, other immunomo-duulatory therapies or prednisolone > 10mg daily were not permitted. There was no minimum entry criteria for EULAR Sjögren’s syndrome disease activity (ESSDAI) or EULAR Sjögren’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 0.1), PBO=3 (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

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 epige-nome 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 RebaseEWAS. 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 at median of 4.2 (interquantile 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 RebaseEWAS method estimated that converters had slightly higher proportion 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^-6), 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=6.7x10^-2), 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 Tn17 differentiation (IRF4 and MAP), TNF alpha signaling (JAK/REK, REL, MAVS,
EMAPALUMAB, AN INTERFERON GAMMA (IFN-γ)-BLOCKING MONOCLONAL ANTIBODY, IN PATIENTS WITH MACROPHAGE ACTIVATION SYNDROME (MAS) COMPICATING SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS (SJIA)

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Background: MAS is a severe complication of rheumatic diseases, most frequently sJIA, caused by excessive activation and expansion of T cells and macrophages. It is characterized by fever, hepatosplenomegaly, liver dysfunction, cytopenias, coagulation abnormalities and hyperferritinemia, possibly progressing to multiple organ failure and death. MAS is categorized as a secondary form of HLH. A vast body of evidence points to uncontrolled overproduction of IFN-γ as a major driver of hyperinflammation and hypercytokinemia in MAS and HLH. Emapalumab has been shown to effectively control disease activity in patients with primary HLH.

Objectives: To assess the pharmacokinetics (PK), efficacy and safety of intravenous (IV) emapalumab in patients with MAS and confirm the proposed dose regimen.

Methods: This is a pilot open-label single arm international study (NCT03311854). Patients had to have MAS (defined according to the 2016 ACR/EULAR classification criteria), on corticosteroids of confirmed or high presumption of, sIL2R equivalent response to high-dose IV glucocorticoids. Emapalumab initial dose was 6 mg/kg and treatment was continued at 3 mg/kg, twice weekly for a total of 4 weeks or less upon achievement of complete response. Serum concentrations of emapalumab, IFN-γ-induced chemokine CXCL9 and sIL2R were measured. Safety assessments included adverse events (AEs) and laboratory abnormalities. Efficacy was defined as complete response by week 8, i.e. absence of MAS clinical signs plus blood white cell and platelet counts above lower limit of normal, LDH, AST/ALT <1.5 x upper limit of normal, fibrinogen >100 mg/dl, and ferritin decreased by >80% or to <2000 ng/ml, whichever was lower. Two protocols are in place to recruit 5 patients each in Europe and North America (trial not started yet).

Results: We report on 6 patients recruited in the European protocol.

<table>
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</table>

Conclusion: Emapalumab administration with the tested dosing regimen led to rapid neutralization of IFN-γ as shown by normalization of CXCL9, associated with evidence of decreased T cell activation. In all patients, emapalumab treatment was effective in controlling MAS with a favourable safety profile.

REFERENCE:

LIVE ATTENUATED VACCINES IN PEDIATRIC RHEUMATIC DISEASES ARE SAFE: MULTICENTER, RETROSPECTIVE DATA COLLECTION

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Background: Common practice is to withhold vaccination with live-attenuated vaccines in patients with rheumatic diseases on high-dose DMARDs, glucocorticosteroids or biological agents, due to limited safety data, and the (theoretical) risk of introducing an infectious disease to the patient. Evidence for this approach is limited. We collected data from pediatric rheumatologists who vaccinate these patients, to gather information about the safety profile of live-attenuated vaccines in patients with rheumatic diseases. We document the incidence of adverse events related to vaccination.

Objectives: To collect retrospective data in patients with JIA and other diseases vaccinated with live-attenuated vaccines in patients with rheumatic diseases on high-dose DMARDs, glucocorticosteroids or biological agents.

Methods: Data from 13 pediatric rheumatology centers in 10 countries were collected.

Results: 234 patients were reported; mean age 5±2.7, 70% girls. 206 had JIA; 46% oligoarticular, 36% polyarticular, 8% systemic, 5% SPA types, 5% JIA and uveitis. 48% of JIA patients were in remission on medication. Disease activity was low in 38%, high in 2%, moderate in 7%; 11 patients had juvenile dermatomyositis, 3 systemic and 2 localized scleroderma, 4 isolated idiopathic uveitis, 1 CINCA syndrome, 1 MKD, and 1 PMF.

Conclusion: 110 patients had MMR booster while on MTX; 7 reported mild side-effects of local skin reaction and pain, none had disease flare. 76 had booster while on anti-TNF; 7 reported mild and transient adverse events of local skin reaction, fever and URTI. 39 had booster while on anti-TNF alone; 1 reported fever. 3 had