(SRI-4) response as a primary endpoint, and of (2) relative and (3) absolute changes in the SELENA-SLEDAI scores as key secondary endpoints. Trial registration: NCT02955615

Results The primary endpoint was not met in the intention-to-treat population (ILT-101: 68%, placebo: 58%; p=0.3439), due to a 100% SRI-4 response rate in the placebo group at two study sites from the same country. A post-hoc analysis on a pre-specified per-protocol population that excluded patients from these two sites (n=53) showed a statistically significant difference for the SRI-4 response rate (ILT-101: 83.3%; placebo: 51.7%; p=0.0168), and for the two key secondary endpoints, accompanied by differences in several secondary exploratory endpoints. ILT-101 was well tolerated and there was no generation of anti-drug antibodies.

Conclusions The post-hoc hierarchical analysis of the primary and key secondary endpoints in a per-protocol population, complemented by the exploratory analyses of multiple other secondary endpoints, support that low-dose IL-2 is beneficial in active SLE.

Thursday 06 October 2022 from 17:30 to 19:00

S12 cytokines and interferons

S12.1 IL-16 – A URINARY BIOMARKER FOR PROLIFERATIVE LUPUS NEPHRITIS

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10.1136/lupus-2022-elm2022.25

Background Lupus nephritis (LN) is a severe manifestation of systemic lupus erythematosus (SLE). The pathogenesis is incompletely understood and good biomarkers for non-invasive diagnostics are scarce. Interleukin (IL)-16 is an immunomodulatory cytokine with an emerging role in SLE and LN.[1–4]

Aim To investigate IL-16 as a potential biomarker for LN in a well-characterized cohort of SLE patients.

Methods We measured urinary and plasma IL-16 levels in predefined patient groups: active LN (n=84), active non-renal SLE (n=63), inactive non-renal SLE (n=73) and in matched population controls (n=48) using ELISA. The LN group included patients with proliferative (PLN, n=47), mesangioproliferative (MES, n=11), and membranous (MLN, n=26) LN. Renal expression of IL-16 was investigated by immunohistochemistry (IHC). Associations between IL-16 and clinical variables and the diagnostic value of IL-16 levels for LN were explored.

Results Urinary IL-16 levels were highest among patients with LN (p<0.0001), particularly among those with PLN (p<0.035). High plasma IL-16 levels were observed in patients with active SLE, both in active renal and non-renal groups (p<0.01). In PLN, urinary IL-16 levels correlated to renal activity index (ρ=0.39, p=0.007), and albuminuria (ρ=0.31, p=0.034). IL-16 was expressed in a high proportion of cells in renal inflammatory infiltrates. In the regression models, urinary IL-16 discriminated PLN cases from all other investigated cases in the cohort (AUC=0.797, p=0.001) and other LN patients (AUC 0.775, p=0.001), while plasma IL-16 did not. Detectable urinary IL-16 had superior specificity but lower sensitivity than elevated dsDNA, low C3 or C4 for diagnosing PLN both among the whole cohort and among LN patients.

Conclusions Our data suggest that urinary IL-16 can non-invasively discriminate patients with proliferative lupus nephritis from other SLE patients. Furthermore, the abundance of IL-16 in urine and presence in kidney tissue imply a role in the pathogenesis of lupus nephritis. Its potential as a therapeutic target in SLE should be explored.

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3. Xue, H. *et al*. The IL-16 gene polymorphisms and the risk of the systemic lupus erythematosus. *Clin Chim Acta* 2009.
4. Fava, A. *et al*. Urine Proteomics and Renal Single Cell Transcriptomics Implicate IL-16 in Lupus Nephritis. *Arthritis Rheumatol* 2021

S12.2 TYPE I INTERFERONS AND THEIR AUTOANTIBODIES IN THE CONTEXT OF SYSTEMIC LUPUS ERYTHEMATOSUS

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10.1136/lupus-2022-elm2022.26

Purpose Type I IFNs and their autoantibodies are implicated in the pathogenesis of Systemic lupus erythematosus (SLE), but their incidence and importance is still unclear. Neutralizing autoantibodies against IFNα have been previously reported in patients with autoimmune polyendocrinopathy syndrome type I (APS-1), rheumatoid arthritis, thymoma and more recently life-threatening COVID-19 patients. We hypothesized that autoantibodies towards type I IFNs, that develop in some patients with SLE, are neutralizing and may interfere with the course of the disease.

Methods Luciferase immunoprecipitation (LIPS) analysis was used to screen 474 SLE patient and 312 control serum samples for the presence of IFNα binding autoantibodies and determine their subclasses. Type I IFN neutralizing capacity was tested using a reporter cell line. Circulating levels of IFNα were measured with Single Molecule Array (Simoa).

Results 14% of SLE patients were positive for anti-IFNα and 13% were positive for anti-IFNω. The autoantibodies against IFNα were predominantly of IgG1 subclass and neutralized IFNα bioactivity in approximately one half of the positive cases. Once developed, anti-IFNα autoantibodies were present throughout the disease course. IFNα2 and -α8 were targeted first in two informative follow-up cases. The reactivity broadened to other IFNα subtypes and IFNω within several months. Serum levels of IFNα correlated negatively with anti-IFNα neutralizing titers. Patients with high levels of autoantibodies against IFNα had significantly lower levels of circulating IFNα compared to anti-IFNα negative patients. Interestingly, patients with high IFNα neutralizing capacity displayed significantly lower disease activity than patients without these autoantibodies.

Conclusions Based on our results we suggest that autoantibodies that are able to neutralize the circulating levels of all IFNα subtypes may have a beneficial effect to SLE disease course.

S12.3 TYPE I INTERFERONS INDUCE TIE2-MEDIATED ENDOTHELIAL CELL DYSFUNCTION IN SYSTEMIC LUPUS ERYTHEMATOSUS

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10.1136/lupus-2022-elm2022.27

Purpose Endothelial cell (EC) dysfunction is a hallmark of SLE and has been generally accepted to be one of the important factors contributing to the higher risk of thrombosis and atherosclerotic events observed in SLE patients. Although the presence of traditional factors (smoking, diabetes, increased age, obesity) and the presence of autoantibodies are associated with atherosclerosis and thrombotic events, they do not completely explain the higher risk of these events in SLE, suggesting the existence of other mechanism/factors.

Tie2 is a tyrosine kinase receptor essential for vascular development and blood vessel remodeling through interaction with its ligands angiopoietin-1 (Ang-1) and Ang-2. In homeostatic conditions, both Ang-1 and Ang-2 activate Tie2 signaling and induce vascular stabilization in a Tie1-dependent manner. However, inflammatory processes induce Tie1 cleavage, leading to the inhibition of Ang-1-induced Tie2 activation, and to the increase of Ang-2 now acting as a Tie2 antagonist, culminating in vascular dysfunction and EC activation 9–11. Importantly, this process has been implicated in both atherosclerosis and thrombosis.

As type I Interferons (IFN-α and IFN-β) are key cytokines in the pathogenesis of SLE, the aim of this study is to determine whether these cytokines induce Tie2 signalling-mediated endothelial cell dysfunction.

Methods Serum levels of Ang-1, Ang-2 and sTie1 in SLE patients (n=48) and healthy control (HC, n=29) were measured by ELISA. Human Umbilical Vein Endothelial Cells (HUVEC) were stimulated with IFN-α and IFN-β (both 1000 International Units –I.U.-) for 1, 2, 4, 6, 8, 12, 24, 48 and 72 hours. mRNA and protein expression of Ang-1, Ang-2, Tie1 and Tie2 were determined by quantitative PCR (qPCR) and ELISA, respectively. The phosphorylation of Tie2 determined by western blot and HUVEC viability was determined by calcein assay.

Results Type I IFNs, mainly IFN-β, significantly reduced the mRNA levels of TIE1 and TIE2. At level protein, IFN-β stimulation induced a significant increase in the secretion of the Tie1 ectodomain (sTie1). On the other hand, IFN-α and IFN-β did not modulate the mRNA expression of ANG1 or ANG2. However, both IFNs significantly reduced the protein secretion of Ang-1 after 24 h of stimulation. In the case of Ang-2, IFN-β induced Ang-2 secretion at early time points (<4h). Furthermore, IFN-α and IFN-β stimulation reduced Tie2 activation (Figure 1). At the functional level, both type I IFNs significantly reduced the viability of HUVEC (Figure 2).

Finally, and similarly to previous studies, we found reduced levels of Ang-1 and elevated levels Ang-2 in SLE patients compared to HC. Importantly, we showed for first time (to our knowledge) that sTie1 levels were also significantly elevated in SLE patients (Figure 3).

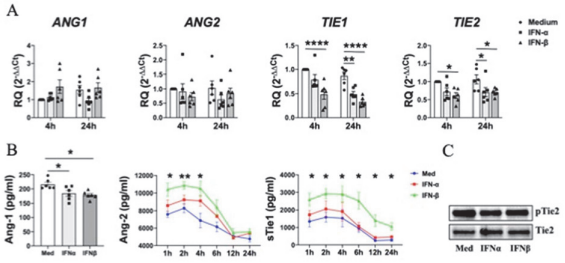

Figure 1. (A-B) Ang-1, Ang-2, Tie1 and Tie2 mRNA expression (A) and protein secretion (B) in HUVEC stimulated with IFN-α or IFN-β (1000 IU/ml) for the indicated time points. Means and SEM are shown. * p<0.05 , ** p<0.01 and **** p<0.0001. **(C)** Representative immunoblot of Tie2 phosphorilacion in HUVEC stimulated with IFN-α or IFN-β (1000 IU/ml) for 24 h.

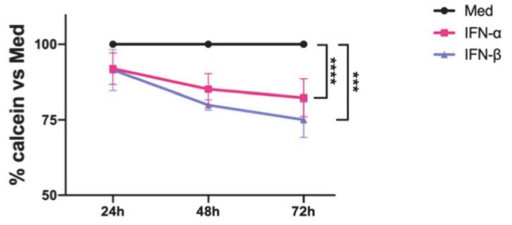

Figure 2. Cell viability in HUVEC stimulated with IFN-α or IFN-β (1000 IU/ml) for the indicated time points. Means and SEM of 6 independent experiments are shown. *** p<0.01 and **** p<0.0001.

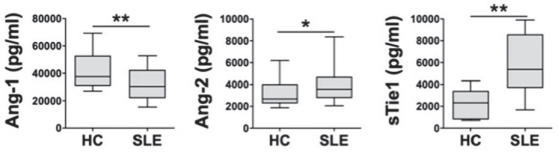

Figure 3. Ang-1, Ang-2 and sTIE1 levels in serum of HC (n=29) and SLE (n=48) patients. Data is presented as a box plot, where the boxes represent the 25th–75th percentiles, the lines within the box mark the median value, and lines outside the boxes denote the 10th and 90th percentiles. * p<0.05 and ** p<0.01.

Abstract S12.3 Figure 1

Conclusions Our results demonstrate that type I IFNs play a relevant role in the stability of endothelial cells by inhibiting Tie2 signaling, suggesting that these processes may be implicated in the cardiovascular events observed in SLE patients.

Friday 07 October 2022 from 08:30 to 09:30
S13 antiphopholipid syndrome

S13.1 DEVELOPING SYSTEMIC AUTOIMMUNE DISEASES IN HEALTHY SUBJECTS PERSISTENTLY POSITIVE FOR ANTIPHOSPHOLIPID ANTIBODIES: LONG-TERM FOLLOW-UP STUDY

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