O13 INNATE IMMUNITY TRANSCRIPTIONAL PROFILES AS POTENTIAL PREDICTIVE BIOMARKERS FOR TREATMENT RESPONSE IN SYSTEMIC LUPUS ERYTHEMATOSUS: INSIGHTS FROM A LONGITUDINAL STUDY

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Background Systemic Lupus Erythematosus (SLE) is a prototypic, systemic autoimmune disease that can affect many organs. Current treatment of SLE is largely empirical, while the existing immunosuppressive treatments fail to induce remission in over 40% of patients.

Methods Whole blood transcriptome samples were obtained from 95 patients with moderate to severe SLE at baseline, 1 month and 6 months after initiation of treatment with cytotoxic agents (cyclophosphamide, mycophenolate mofetil), mycophenolate mofetil/anti-CD40 antibody, rituximab or belimumab. Disease activity was assessed using the SLEDAI-2K. Response to treatment was defined as achievement of Low Disease Activity State (LLDAS) or remission at 6 months. Differentially expressed genes (DEGs) were identified using the DEseq2. Weighted correlation network analysis (WGCNA) was applied to detect modules of co-expressed transcripts. Abundances of cell types were assessed by CIBERSORTx.

Results 95 patients were enrolled in our study. Most of the patients were women (93.7%) with a mean [SD] age at SLE diagnosis of 42.9 [13.6] years and a mean disease duration [SD] at sampling of 5.1 [7.2] years. Cyclophosphamide was the most frequently used immunosuppressive agent (n=46), followed by belimumab (n=24) and rituximab (n=21). 43 patients responded to treatment. Transcriptional disturbances related to type I interferon signaling (p=0.04, r= 0.15) and leukocyte chemotaxis (p=0.005, r=0.21) positively correlated with response to treatment at 6 months. Enrichment of processes linked to complement activation and PI3KK/Akt pathway distinguishes active Lupus Nephritis (LN) responders from LN non-responders at baseline. Gene expression signatures indicative of cell cycle checkpoint regulation and humoral immunity emerged as potential determinants of resistant disease 6 months after treatment initiation. Marked reduction in the naïve B cell compartment uniquely characterized successful response induction, while the neutrophilic fraction exhibited a statistically significant reduction upon treatment, irrespective of the 6-month outcome.

Conclusions Baseline transcriptional signatures related to innate immunity correlated with 6-month response to treatment in SLE. Disturbances linked to cell cycle regulation decisively shaped the transcriptional landscape of 'resistant' disease.

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O14 RITUXIMAB OBJECTIVE OUTCOME MEASURES TRIAL IN SLE (ROOTS): OUTCOMES OF RANDOMISED AND RESCUE RITUXIMAB THERAPY IN A DOUBLE-BLIND RANDOMISED PLACEBO-CONTROLLED TRIAL

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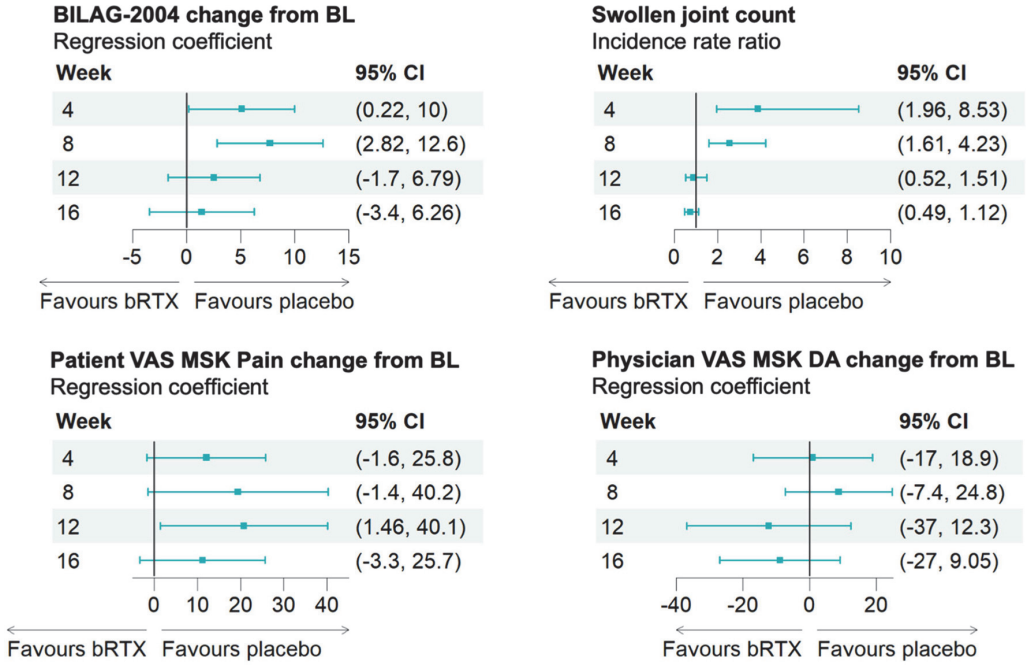
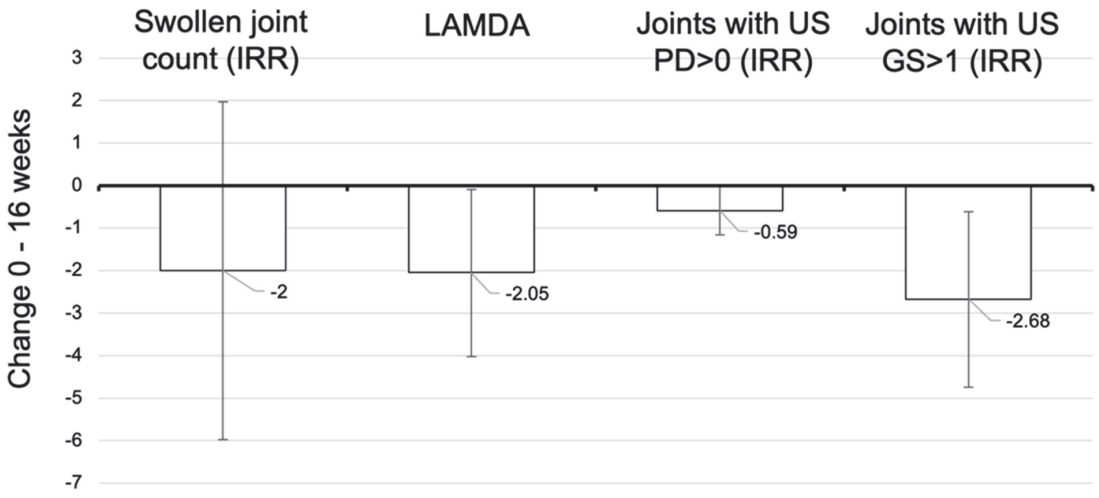
Objective (i) Assess a novel musculoskeletal SLE trial design with objective eligibility and endpoints and a low-glucocorticoid standard of care; (ii) further validate Lupus Arthritis and Musculoskeletal Disease Activity Score (LAMDA) and



Abstract O14 Figure 1 Efficacy during randomised phase (n=25)



Abstract O14 Figure 2 16-week objective outcome measures across all rituximab cycles administered (n=22)

MSK ultrasound; (ii) preliminary evidence for efficacy of Rituximab.

Methods Enrolment required clinical synovitis and/or ultrasound tenosynovitis/joint power Doppler with ≤10mg prednisolone. Patients were randomized to 1000mg Rixathon or placebo, on days 1 and 15, each preceded by 100mg methylprednisolone. BILAG-2004, SLEDAI-2K, LAMDA, tender and swollen joint counts, physician global, patient MSK pain and global VAS, PROs, BICLA, SRI-4 were evaluated monthly. US of both hands and wrists was performed at 0 and 16 weeks. The primary endpoint was feasibility. The key efficacy timepoint was 16-weeks. After 16-weeks placebo patients with active disease were eligible for rescue rituximab with repeat follow-up assessments. US and LAMDA were validated against BILAG-MSK improvement using baseline-adjusted regression.

Results Of 27 patients randomised, 12 received placebo, of whom 9 received rescue. BILAG-MSK domain at baseline was scored A in 7/27 (26%), B in 16/27 (59%) and C in 2/27 (7.4%). At 16 weeks, BILAG-MSK response was significantly associated with improvement in LAMDA (OR 0.48, 95% CI 0.18, 0.84); US joints grey-scale (OR 0.56, 95% CI 0.28, 0.85) and US tendons PD (OR 0.33, 95% CI 0.04, 1.01).

Unexpectedly, some outcome measures showed greater improvement in patients who received methylprednisolone and placebo than with methylprednisolone and rituximab. These measures then converged by 16 weeks (figure 1). However, pooling all rituximab cycles administered (as initial therapy or as rescue) showed significant improvement in LAMDA (coefficient(95% CI) -2.68 (–4.02, -0.09)), number of joints with US-PD>0 (-0.59(-1.16, -0.02)), and number of joints with GS>1 (-2.68(-4.74, -0.62) at 16 weeks (figure 2).

Conclusions SLE arthritis trials offer a homogenous trial population, low GCs, and validated objective outcome measures. Initial worsening before benefit with rituximab may be explained by increased antigenic load and removal of B cell regulatory functions before beneficial effects on plasma cells and B cell antigen presentation are manifest. Detecting such nuances may reflect the greater sensitivity of this trial design.

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O15 B CELL, T CELL, CYTOTOXIC/NK CELL, AND MITOCHONDRIAL GENE DYSREGULATION PATTERNS SEPARATE NEUROPSYCHIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS INTO TWO DISTINCT SUBGROUPS WITH DIFFERENTIAL ANTICIPATED RESPONSE TO TARGETED THERAPIES

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Objective The management of neuropsychiatric (NP) systemic lupus erythematosus (SLE) is poorly optimised and specific treatment is lacking. The aim of this study was to perform an in-depth investigation of the transcriptome of SLE patients with active central nervous system (CNS) involvement to gain insights into underlying molecular mechanisms and identify new potential drug targets for CNS lupus.

Methods We analysed differentially expressed genes in peripheral blood from patients with active CNS lupus (n=26) and active non-NP SLE (n=43) versus healthy controls (n=497) from the European PRECISESADS project (NTC02890121), as well as dysregulated gene modules. Gene modules were subjected to correlation analyses with serological markers, and regulatory network and druggability analysis.

Results Unsupervised co-expression network analysis revealed 23 dysregulated gene modules (figure 1A). Four showed differential dysregulation between two distinct subgroups of CNS lupus patients. The interferon module was upregulated in both subgroups. The 'B cell', 'T cell', 'cytotoxic/NK cell', and