THE ROLE OF D-DIMER TEST AS A SCREENING TOOL FOR VENOUS THROMBOEMBOLISM IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS AS COMPARED TO MATCHED CONTROL SUBJECTS

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Background: d-dimer test is widely used as a screening tool for venous thromboembolism (VTE). Meanwhile, d-dimer can increase in various conditions including severe infection, and inflammation. However, it has been rarely reported whether d-dimer test is useful for screening of VTE in systemic lupus erythematosus (SLE) patients.

Objectives: We evaluated the role of d-dimer test as a screening tool for VTE in patients with SLE, compared to age-, and sex-matched non-autoimmune disease subjects.

Methods: In this retrospective cohort study, a total of 283 SLE patients and 1132 age-, and sex-matched control subjects (those who had no rheumatic diseases) who underwent d-dimer test as a screening test for VTE were enrolled at Seoul National University Hospital between January 2000 and July 2017. VTE was defined to be present when a thromboembolism was proven in imaging studies which included computed tomography, lung perfusion scan or duplex ultrasonography. Predictive value of d-dimer test for VTE was compared between SLE patients and control subjects by calculating area under the curves (AUC) in receiver operating characteristics (ROC) curves of d-dimer test. Finally, the usefulness of d-dimer test was evaluated in different subsets of SLE patients by analyzing ROC curves.

Results: The mean (SD) age of the 283 SLE patients was 36.8 (13.5) years and that of 1122 control subjects was 38.2 (12.8) years. The mean (SD) plasma level of d-dimer was 2262.1 (3794.5) ng/ml in SLE patients, while it was 1087.5 (5063.1) ng/ml in the control group (p<0.001). The incidence of VTE was significantly higher in SLE patients than the controls (12.7% vs. 5.8%, p<0.001). When the cut-off value of d-dimer test was set to 500 ng/ml, the AUC for VTE was only 0.614 in SLE patients, while it was 0.891 in the control group, suggesting that d-dimer test cannot predict VTE in SLE patients as accurately as in the general population. In SLE patients, d-dimer level increases in various conditions including severe infection, and inflammation. However, it has been rarely reported whether d-dimer test is useful for screening of VTE in SLE patients as compared to matched control subjects.

Conclusions: d-dimer test cannot predict VTE in SLE patients as accurately as in the general population. In SLE patients, d-dimer’s diagnostic capability for VTE is even lower in the presence of APS Abs.

REFERENCES:


Disclosure of Interest: None declared


SLE DISEASE ACTIVITY INDEX GLUCOCORTICOID INDEX (SLEDAI-2KG) IDENTIFIES MORE RESPONDERS THAN SLEDAI-2K

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Background: Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K) is one of the most commonly used disease activity indices in clinical practice and research but this index doesn’t account for severity within each descriptor. Moreover, in clinical trials, the use of standard of care (SoC), which includes glucocorticoid (GC) often confounds trial results.

We developed and validated a novel lupus disease activity index, SLEDAI-2K GC (SLEDAI-2KG), that describes disease activity while accounting for GC dose. SLEDAI-2KG has the same descriptors as SLEDAI-2K in addition to a new descriptor “GC” with different weight scores based on the dose of GC. Furthermore, SLEDAI-2KG has a low administration burden and a simple scoring system similar to SLEDAI-2K.

Objectives: We aimed to compare the performance of SLEDAI-2K and GC in identifying responders in response to SoC.

Methods: Patients have been followed prospectively according to a standard protocol between January 2011 and January 2014, at a single lupus centre, with active disease (SLEDAI-2K≥6), on prednisone ≥10 mg/day, and with follow up visits within 5–24 months were studied. Treatment was determined based on the judgment of the treating rheumatologist. Response to SoC therapy, at first follow up visit, was assessed by SLEDAI-2K and SLEDAI-2KG. Responders were defined based on the decrease in SLEDAI-2K and GC score by ≥4. The performance of SLEDAI-2K and SLEDAI-2KG was also compared using different cut-off points; 5, 6 and 7. Descriptive analysis was used.

Results: 111 patients met the inclusion criteria of the study and were further analysed. Patients’ characteristics are represented in table 1. SLEDAI-2KG identified more responders at 6 months (94% vs. 84%) and at 12 months (92% vs. 76%) compared to SLEDAI-2K by cut off of 4. SLEDAI-2KG also identified more responders with cut off points 5, 6 and 7 (table 2).

Abstract FRI0395 – Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total (n=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (female)</td>
<td>98 (88.3%)</td>
</tr>
<tr>
<td>Age at baseline (mean±SD)</td>
<td>35.75±11.51</td>
</tr>
<tr>
<td>SLE duration at baseline (mean±SD)</td>
<td>9.02±7.74</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>13 (11.7%)</td>
</tr>
<tr>
<td>Asian</td>
<td>23 (20.7%)</td>
</tr>
<tr>
<td>Black</td>
<td>51 (45.9%)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>24 (21.6%)</td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
<tr>
<td>Months from baseline to 1st follow-up (mean±SD)</td>
<td>7.68±2.95</td>
</tr>
<tr>
<td>SLEDAI-2K at baseline (mean±SD)</td>
<td>12.39±6.03</td>
</tr>
<tr>
<td>Prednisone dose at baseline (mg/day) (mean±SD)</td>
<td>22.94±14.19</td>
</tr>
<tr>
<td>SLEDAI-2K at baseline (mean±SD)</td>
<td>17.48±6.78</td>
</tr>
<tr>
<td>SLEDAI-2K at 1st follow-up</td>
<td>8.08±6.04</td>
</tr>
<tr>
<td>Prednisone dose at 1st follow-up (mg/day) (mean±SD)</td>
<td>15.23±10.94</td>
</tr>
<tr>
<td>SLEDAI-2KG at 1st follow-up</td>
<td>12.67±6.98</td>
</tr>
</tbody>
</table>

Abstract FRI0395 – Table 2. Responders by SLEDAI-2K and SLEDAI2KG in 111 patients

<table>
<thead>
<tr>
<th>Indices</th>
<th>Percentage of responders at 6 months</th>
<th>Percentage of responders at 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥4</td>
<td>≥5</td>
</tr>
<tr>
<td>SLEDAI-2K</td>
<td>84%</td>
<td>68%</td>
</tr>
<tr>
<td>SLEDAI-2KG</td>
<td>94%</td>
<td>88%</td>
</tr>
<tr>
<td>Additional Responders</td>
<td>10%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Conclusions: The novel index, SLEDAI-2KG, is superior to SLEDAI-2K in identifying responders at 6 and 12 months accounting for steroid dose and thus adjusting for severity within each descriptor of SLEDAI-2K. SLEDAI-2KG has the ability to enhance analyses in clinical trials to differentiate between responders on minimal and moderate/large doses of GC.
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FRIDAY, 15 JUNE 2018

Systemic sclerosis, myositis and related syndromes – etiology, pathogenesis and animal models.

**FRI0396**

THE AKT KINASE AND PTEN, DRIVE MYOFIBROBLASTS DIFFERENTIATION BY ACTIVATING THE TGFβ AUTOCRINE LOOP

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**Background:** Pulmonary fibrosis is a major cause of mortality in scleroderma (SSc) and Idiopathic Pulmonary Fibrosis (IPF). Fibrosis is driven by Inappropriate myofibroblast differentiation and persistence. Understanding this process, is vital for developing an effective treatment. Angiotensin II is implicated in fibroblast activation in the heart and kidney, through interactions with growth factors (e.g. EGF and TGFβ).

**Objectives:** We examined the role of Angiotensin II in myofibroblast activation in the lung.

**Methods:** Lung fibroblasts were isolated from SSc, IPF, or control patient lungs (6 each). Fibroblasts were also cultured from PTEN null and wild-type mice. Protein expression after angiotensin II treatment (AngII) was investigated by western blotting. Myofibroblast differentiation and function was assessed through the contraction of 3D collagen gels and scratch migration assays. The signalling pathways involved were dissected using specific inhibitors: PI3-kinase/AKT (wortmannin, LY294002), TGFβ (1d11 neutralising antibody, SB431542 ALKS inhibitor) Ataxia-Telangiectasia Mutated (ATM – Ku55933), AKT (Lisosartan).

**Results:** SSc and IPF lung fibroblasts showed increased AKT phosphorylation and suppressed PTEN expression (p<0.05). Their phenotype was more myofibroblastic. AngII treatment activated AKT, suppressed PTEN and induced myofibroblast differentiation in normal lung fibroblasts. In both AngII-treated and PTEN null lung fibroblasts AKT activation required the ATM kinase. Inhibition of AKT either with PI3K or ATM inhibitor abrogated these effects. The increased expression of Myofibroblast-related genes after AngII treatment, was also blocked by inhibition of TGFβ with a neutralising antibody or an ALKS inhibitor. AKT phosphorylation on the other hand was only partially blocked by TGFβ inhibition.

**Conclusions:** Our data demonstrate for the first time that AngII signals via the ATM kinase, which together with PTEN suppression are essential for the activation of AKT by AngII. AngII promotes myofibroblast differentiation, by stimulating the fibroblast TGFβ1 autocrine loop through AKT. Our data shows that activation of AKT through ATM and PTEN, may serve as the molecular link between pulmonary hypertension and lung fibrosis in fibrotic diseases.

**Acknowledgements:** Arthritis Research UK, Royal Free Hospital Charity and Scleroderma Research UK.

**Disclosure of Interest:** None declared


**FR0397**

PECULIAR EXPRESSION OF AUTOAPPROHY BIOMARKERS IN NECROTIZING AUTOIMMUNE MYOPATHY MUSCLE

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**Background:** Immune mediated necrotizing myopathy (IMNM) is a recently recognised pathology within the spectrum of idiopathic inflammatory myopathies (IIMs). Specific autoantibodies and the response to immunosuppressants aid to make the diagnosis and suggest immune-mediated pathogenesis, although histopathological features are not specific for IMNM. Autoapathy and ubiquitin-proteasome system are two interacting systems by which dysfunctional cellular components are degraded in the cell. Their dysregulation, in sporadic inclusion

Body Myositis (sIBM), seems to be responsible for the protein aggregates. The autoapathy dysfunction in IMNM was not widely investigated.

**Objectives:** To investigate autoapathy marker expression, macrophages localization and accumulation of misfolded proteins in non-necrotic fibres of IMNM muscle in comparison with Dermatomyositis (DM), Polymyositis (PM) and sIBM.

**Methods:** Among 52 IIMs diagnosed from January 2015 to June 2017, we reviewed muscle biopsies and stored sera. Six subjects were included in the IMNM group, characterised by many necrotic muscle fibres, regenerating muscle fibres and no significant inflammation despite of numerous but scattered macrophages removing necrotic muscle fibres. Two patients had anti-signal recognition particle (SRP) autoantibodies, two patients anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGR), the others tested negative for specific autoantibodies. All IMNM patients had a positive response to immunosuppressants. Muscle sections were immunolabelled with the following antigens: ubiquitin, autoapathy markers LC3b, p62 (a receptor of autoapathy), TDP-43 (a marker of ubiquitinated proteic inclusions), SM31 and SM310 (Phosphorylated Neurofilaments), CD31 (endothelial cell marker), C5b-9 (membrane attack complex), CD4 (T-helper lymphocytes), CD8 (T-suppressor lymphocytes), CD68 (macrophages), CD20 (B-lymphocytes), CD56 (NK lymphocytes and regenerating muscle fibres), MHC I, MHC II. Quantitative results were compared among IMNM (n=6), DM (n=4), sIBM (n=4), PM (n=5) and healthy controls (n=4).

**Results:** In IMNM, inflammation was mild compared with DM, PM, sIBM, and consis-

enced in sporadic endomyositis and/or perivascular cells CD68+. Skeletal muscle fibres (SMFs) containing LC3b+puncta were significantly higher in IMNM and IMNB than in DM or PM. In all IMNM, the greater proportion of LC3b+puncta was localised in CD68+ fibres (figure 1), instead, sIBM showed a high number of LC3b+puncta in vacuolated SMFs with low expression of CD56+SMFs. As expected, p62 and SM31 aggregates were significantly higher in sIBM than in the other IIMs, even if, also in IMNM, there were moderate p62 accumulations and a little proportion of SMFs stained by SM31. Finally, in IMNM there was the highest number of ubiquitin +SMFs.

**Conclusions:** These findings suggest an involvement of cellular clearance systems in the pathophysiology of IMNM similarly to sIBM. Nevertheless, LC3b+puncta in regenerating fibres can be considered a peculiar biomarker in IMNM. Further studies of larger cohort of patients are needed to better define IMNM.

**Disclosure of Interest:** None declared


**FR0398**

SL-401, A NOVEL TARGETED THERAPY DIRECTED TO THE INTERLEUKIN-3 RECEPTOR (CD123), KILLS PLASMACYTOID DENDRITIC CELLS FROM SYSTEMIC SCLEROSIS PATIENTS

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**Background:** SL-401 is a novel biologic targeted therapy directed to the interleukin-3 receptor (CD123), kills plasmacytoid dendritic cells from systemic sclerosis patients.

Further studies of larger cohort of patients are needed to better define IMNM.

**Disclosure of Interest:** None declared


**FR0399**