nate both the production and response to type I IFN. There is also a lack of prop-
eration in SLE of cells in the type I IFN system and recently, we observed that
autoantibodies to NK cells may contribute to the activation of the type I IFN
system. These NK cells autoantibodies block the inhibitory NK cells receptors
and were found in an SLE subset with an active and severe disease phenotype.

21 Health professionals

21.3 Uncertainties and opportunities for patients with SLE

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2Department of Physiotherapy, Sunderby Hospital, Luleå, Sweden,
3Division of Rheumatology, Sunderby Hospital, Luleå, Sweden,
4Division of Neumunologic Diseases, Department of Internal Medicine 3, Medical University of Vienna, Vienna, Austria,
5Division of Occupational Therapy, Department of Health, University of Applied Sciences – FH Campus Wien, Vienna, Austria,
6Department of Health Sciences, Lund University, Lund, Sweden.

The aim of this presentation is to describe results from a study in which per-
sons with established systemic lupus erythematosus (SLE) expressed their ex-
periences concerning illness in everyday life and further to discuss implications
for healthcare professionals. Nineteen persons with SLE with varying disease
activity and low or no organ damage were interviewed in focus groups. Inter-
views were transcribed and analysed by qualitative content analysis. The study
revealed two themes. The theme of Multifaceted uncertainty involved categories
such as reliance on medication and healthcare and an unreliable body. The theme
of Focus on health and opportunities included categories such as a learning pro-
cess implying personal strength and limitations and possibilities in activities at
work.

Conclusions and implications. Persons with established SLE experienced both
uncertainty and focus on health and opportunities. This is in line with theories
concerning uncertainty in illness, in which uncertainty could be experienced as
a threat or a possibility; and further theories concerning shifting perspectives
of illness and wellness in chronic disease; and personal growth following adver-
sity and stressful events. Healthcare professionals could use theories like these
when developing patient education, communication, and support. The findings
highlight the importance of understanding patients’ experiences of uncertainty
to support focus on health and opportunities in self-management and lifestyle
changes. Patient-reported outcome measures that capture personal factors such as
uncertainty and opportunities need to be developed in SLE.

References

M. Mattsson, et al. Uncertainty and opportunities in patients with established sys-

24 Current state in lupus nephritis

24.1 Pathogenesis of LN and differences compared to other organ
manifestations in SLE

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Systemic Lupus Erythematosus (SLE) is a systemic autoimmune disease with
various clinical manifestations. The hallmark of SLE is the presence of antibod-
ies against nuclear constituents, like double-stranded (ds)DNA, histones and nu-
cleosomes. Local deposition of anti-nuclear antibodies in complex with nuclear
autoantigens induces serious inflammatory conditions that can affect several tis-
ues and organs, including the kidney.

The levels of anti-nucleosome and anti-dsDNA antibodies seem to correlate with
glomerulonephritis. Apoptotic microvesicles are present in the extracellular ma-
trix and circulation of patients with SLE, which is most likely due to an aberrant
response to type I IFN. There is also a lack of prop-
eration in SLE of cells in the type I IFN system and recently, we observed that
autoantibodies to NK cells may contribute to the activation of the type I IFN
system. These NK cells autoantibodies block the inhibitory NK cells receptors
and were found in an SLE subset with an active and severe disease phenotype.

28 New therapies and strategies in SLE

28.1 Biologicals: evidence, trials, state of the art

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A critical review of recent phase III trials will be presented (e.g., tabalumab,
epratuzumab, situlimumab) in the first part of the talk. The second part will re-
view following innovative ideas and measures are currently under consideration
by pharmaceutical companies, biotechnology startups and lupus organizations
that underwrite and support drug development:

a. Creating a new paradigm for designing clinical trials: Examples include su-
periority vs. equivalence trials, being sensitive to international clinical standards of
practice, making CROs (clinical research organizations) more user friendly for
academic academic trial sites, improving the quality of reference laboratories and revising
requirements for ANA positivity relating to participation.

b. Creating a new and improved clinical trial landscape with more efficient and
mission relevant approaches. These include prevention of disease development
among those at risk, induction trials limited to patients with early/active disease,
initiatives to maintain improvement and prevention of flares, and focusing on
organ specific studies.

c. Evaluating the possibility of performing short, cost-effective, small-scale tri-
als, repurposing agents already on the market for lupus where safety is already
documented, withdrawing effective drugs to assess efficacy as short term, highly
focused limited interventions.

Improving trial design: Examples include improved composite disease activity
measures, mining from completed studies, evaluating candidate surrogate
markers/biomarkers, optimizing trial site and patient recruitment strategies, and
educating patients investigators about participation.

Submitted Presentations

4 Role of B cell products and B cell function

OS4.4 Epratuzumab, a monoclonal antibody targeting CD22, inhibits
BCR/CD40-stimulated B cell proliferation in vitro

G. Fossati, S. Rugecki, A. Maloney, A. Shoek.
UCB Pharma, Slough, United Kingdom.

Background. Epratuzumab is a humanized monoclonal antibody that targets the
B cell-specific protein CD22 and is currently in phase 3 clinical trials in patients
with systemic lupus erythematosus (SLE). Epratuzumab inhibits BCR signalling
events, but longer-term functional consequences have not been investigated.

Methods. Peripheral blood mononuclear cells (PBMC) from healthy donors
were labelled with crystal trace violet (CTV) and cultured with soluble CD40
ligand (sCD40L) (50ng/mL) and/or anti-IgM (12μg/mL) ± epratuzumab in IgG,
F(ab’2) or Fab’ formats (all at 10μg/mL). Cells were then stained with a panel of
surface markers and analyzed by flow cytometry. To assess apoptosis, cells were
analyzed for expression of FLICA (caspase 3/7) or for cell membrane integrity
with propidium iodide and Annexin V. Results. Proliferation of B cells, assessed by both CTV and cell count, was
significantly inhibited with anti-IgM alone and with anti-
IgM+ sCD40L (>85%) and with epratuzumab in IgG in CTV assays, respec-
tively, n=8). There was no evidence that apoptosis was induced irrespective of
epratuzumab treatment.

Conclusions. Epratuzumab inhibited the proliferation of B cells in PBMC cul-
tivated through the BCR or through combinatorial BCR and CD40 acti-
vation. These data demonstrate that epratuzumab does modulate B cell function,
which may have implications for understanding the effects of epratuzumab treat-
ment on B cell function in SLE patients.
OS4.5 Pharmacodynamic changes in gene expression observed in two phase 3 trials of BAFF blockade with tabalumab in SLE

R.W. Hoffman,1 J.T. Merrill,1 M.E. Alarcón-Riquelme,2 M. Petri,3 E.R. Dow,1 E. Nantz,1 L.K. Nisenbaum,1 K.M. Schroeder,1 W. J. Komocar,1 N.B. Perumal,1 G.V. Rocha5, R.E. Higgs1
1Eli Lilly & Company, Indianapolis, IN, United States, 2Division of Rheumatology, 4-A-42, VU University, Amsterdam, Netherlands, 3Department of Medicine, 4-A, Aix-Marseille University, Marseille, France, 5Department of Medical Centre, Clayton Campus, Victoria, Australia, 6GENEO Centre for Genomics and Oncological Research: Pfizer/University of Granada/Andalusian Region Government, Granada, Spain, 7Johns Hopkins School of Medicine, Baltimore, MD, United States.

Purpose. RNA profiling was performed on 1,760 SLE patients from ILLUMINATE 1 & 2 which studied the anti-BAFF, IgG4 monoclonal antibody, tabalumab, for efficacy in SLE. This study characterized baseline and pharmacodynamic (PD)-induced changes in gene expression from these two cohorts of SLE patients.

Methods. Blood was collected at baseline, week (W) 16 and W52. RNA was analyzed using Affymetrix HTA 2.0 microarrays. Serum IgG anti-dsDNA antibodies (abs), C3, C4 and IgG, IgA & IgM were measured and B cells enumerated. Statistical analyses to identify PD-induced gene changes in cohorts receiving 120 mg tabalumab Q2W and Q4W using a mixed effects model.

Results. Significant PD changes were observed in Q2W and Q4W arms vs placebo for serum anti-dsDNA abs, C3 & C4, IgG, IgM & IgA, and B cells (p<0.001). Expression changes in 410 genes were identified in tabalumab-treated patients including plasma cell markers, B cell markers, TNF superfamily members, Fc & Fc-like receptors and complement. Baseline elevation of interferon responsive genes (IRG) was associated with elevated anti-dsDNA abs and decreased levels of C3 & C4. B cell number correlated with expression of B cell-associated gene changes in PD changes in B cell and plasma cell genes were observed in both the treatment dose and associated with changes in anti-dsDNA abs, serum Ig and complement levels.

Conclusions. Pharmacodynamic changes associated with tabalumab treatment included serum anti-dsDNA abs, C3 & C4, IgG, IgA & IgM, and B cells. Significant changes were observed in 410 genes consistent with BAFF blockade.

5 Oral presentations 1: Clinical science

OS5.1 Remission in SLE: consensus findings from a large international panel on Definitions of Remission in SLE (DORIS)

R. van Vollenhoven1, C. Aranow,2 G. Bertisi1, E. Silva Dutra de Oliveira Bonfa,1 R. Cervera1, N. Costedoat-Chalumeau,1 T. Dörner,1 F. Hossia1, K. Kerstrem1, E. Morand2, M. Mosca1, S. Navarra1, M. Petri3, M. Urowitz,1 A. Voss1, A. Vourlioudis5, M. Ward5, V. Werthe1, M. Schneider1,6 Definitions of Remission in SLE (DORIS) consensupanel.
1The Karolinska Institute, Stockholm, Sweden, 2Feinstein Institute for Medical Research, New York, NY, United States, 3University of Crete, Crete, Greece, 4Disciplina de Reumatologia Av. Dr. Arnaldo, 455 - 3 andar – Reumatologia, Sao Paulo, Brazil, 5Department of Medicine, Universitat de Barcelona, Barcelona, Spain, 6CHU Paris-GH Pitie Salpetriere-Charles Foix - Hopital Pitie-Salpetriere, Paris, France, 7Charite Universitaetsmedizin Berlin, 8Klinik m3 Rheumatologie und klinische Immunologie, Berlin, Germany, 9Rheumatology Department, Cliniques universitaires Saint-Luc, Université catholique de Louvain, Brussels, Belgium, 10Lupus Europe, London, United Kingdom, 11Monash Medical Centre, Clayton Campus, Victoria, Australia, 12Universita Degli Studi Di Pisa, Pisa, Italy, 13University of Santo Tomas Hospital, Manila, Philippines, 14Johns Hopkins University School of Medicine, Johns Hopkins Outpatient Center, Baltimore, MD, United States, 15Centre for Prognosis Studies in the Rheumatic Diseases University of Toronto, Toronto, ON, Canada, 16Department of Rheumatology & Company, VU University, Amsterdam, Netherlands, 17Department of Rheumatology Odense University Hospital, Odense, Denmark, 18Clinical Trials and Outcomes Branch NIAMS, Bethesda, MD, United States, 19Veterans Administration Hospital University and Woodland, Philadelphia, PA, United States, 20Heinrich-Heine-Universität Poliklinik für Rheumatologie, Düsseldorf, Germany.

Background. Treat-to-target recommendations identified ‘remission’ as a target in SLE but recognize that there is no generally accepted definition for remission in lupus.

Objective. To achieve consensus, in a large multi-party international panel, on potential definitions for remission in SLE.

Methods. An international expert panel of sixty rheumatologists, nephrologists, dermatologists, clinical immunologists, and patient representatives participated in preparatory exercises, a full-day face-to-face meeting, and follow-up exercises and electronic voting rounds.

Results. Eight key statements regarding remission in SLE achieved >90% agreement. There were different viewpoints on the required duration of remission. In addition, the panel expressed strong support (>90%) for the following principles which will guide the further development of remission definitions:

I. A definition of remission in SLE will be worded as follows: Remission in SLE is a durable state characterized by [a definition of: absence of symptoms, signs, abnormal labs, (serology)].

II. Remission-off-therapy requires the patient to be on no other treatment for SLE than maintenance antimalarials.

III. Remission-on-therapy allows patients to be treated with maintenance antimalarials, stable, low-dose steroids (prednisone <5 mg/d), maintenance immunosuppressives and/or stable (maintenance) biologics.

IV. Assessment of clinical symptoms and signs should be based on a validated index, e.g., clinical-SLEDAI = 0, BILAG D/E only, clinical ECLAM ≤0; supplemented with PhysGA <0.5 (D-3), and with labs included.

V. For testing construct validity of each definition the most appropriate outcomes were identified.

Conclusion. The work of this international consensus panel provides a framework for testing individual definitions of remission against longer-term outcomes.

OS5.2 Cardiovascular Events Prior to or Early After Diagnosis of SLE

M.B. Urowitz, D.D. Gladman, N.M. Anderson, D. Ibanez, Systemic Lupus International Collaborating Clinics (SILCC), University Health Network, Toronto Western Research Institute, University of Toronto, Toronto, ON, Canada.

Purpose. Previous studies have shown a history of cardiovascular events prior to diagnosis of SLE and RA, this study describes the frequency of myocardial infarction (MI) prior to the diagnosis of SLE and within the first 2 years of follow-up.

Methods. A multinational inception cohort of SLE patients from 31 centres was followed yearly according to a standardized protocol from 2000-2014. MIs were reported and attributed on a specialized vascular event form. Descriptive statistics were used.

Results. Of 31,848 patients had an MI. Of those, 23 patients had an MI occur prior to diagnosis or within the first 2 years of SLE. Of the 23 patients studied 60.3% were female, 82.6% were Caucasian, 4.3% Black, 8.7% Hispanic and 4.3% other. The mean age at SLE diagnosis was 52.5±15.0 years. Of the 23 MIs that occurred, 16 MIs occurred at a mean of 6.1±7.0 years prior to diagnosis and 7 occurred within the first 2 years.

Risk factors associated with early MI in univariate analysis: male sex, older age at diagnosis, lower SLEDAI-2K and hypertension. In multivariate analysis: age (OR=0.17 95% CI (1.04, 1.10)) and male sex (OR=3.2, 95% CI (0.13, 0.78)) remained significant.

Conclusion. MI prior to or early after SLE diagnosis may indicate earlier low grade disease activity not diagnosed or a concomitant alternative predisposition to AS and SLE.
OS5.3
Use of Antibiotics and Subsequent Risk of Systemic Lupus Erythematosus: A Matched Case-Control Study
N. Amiri, M. Eminiyan, R. Lipson, D. Thompson, S. K. Ratl, A. Avina-Zubidet1-4,
1University of British Columbia, Vancouver, BC, Canada, 2Emmes Canada, Burnaby, BC, Canada, 3Arthritis Research Canada, Richmond, BC, Canada.
Objective. To examine the association of exposure to cyclines, macrolides, and penicillins antibiotics with the development of subsequent Systemic Lupus Erythematosus (SLE).
Methods. We conducted a nested case-control study using an administrative health database in British Columbia, Canada, from 1997-2010. Cases were defined using a validated algorithm that includes a combination of ICD-9 and ICD-10 codes and SLE drug therapy. Incident cases were age-, sex-, and entry time-matched to 10 controls using density-based sampling. We evaluated cumulative exposure to any cyclines, macrolides, and penicillins prior to SLE diagnosis allowing for removal of cases with any exposure in the year prior to the index date. Adjusted odds ratios were computed using conditional logistic regression.
Results. We identified 3,639 new SLE cases corresponding to 36,032 matched controls. All three classes of antibiotics had a statistically significant association with the development of SLE in the unadjusted models (Table I). However, after adjusting for the Charlson comorbidity index, hormone use, healthcare resource use and socioeconomic status only females exposed to cyclines showed to a statistically significant association [OR = 1.6 (95% CI, 1.3-1.9)].
Conclusion. Females exposed to cyclin antibiotics had a 60% increased risk of developing SLE.

Table I. Odds Ratios of SLE in Patients with Prior Exposure to Three Classes of Antibiotics.

<table>
<thead>
<tr>
<th>Drug Exposure</th>
<th>Unadjusted Odds Ratio</th>
<th>Adjusted Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All 2.5 (2.2-3.8)</td>
<td>All 1.6 (1.3-1.9)</td>
<td></td>
</tr>
<tr>
<td>Male 2.0 (1.5-2.7)</td>
<td>Male 1.7 (0.9-3.1)</td>
<td></td>
</tr>
<tr>
<td>Female 2.6 (2.3-2.9)</td>
<td>Female 1.6 (1.3-1.9)</td>
<td></td>
</tr>
<tr>
<td>Macrolides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All 2.3 (1.2-6)</td>
<td>All 0.9 (0.7-1.1)</td>
<td></td>
</tr>
<tr>
<td>Males 2.3 (1.6 -3.3)</td>
<td>Males 1.4 (0.7-2.9)</td>
<td></td>
</tr>
<tr>
<td>Females 2.3 (2.0 -2.6)</td>
<td>Females 0.8 (0.6-1.1)</td>
<td></td>
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<tr>
<td>Penicillins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All 1.9 (1.7-2.3)</td>
<td>All 1.0 (0.8-1.2)</td>
<td></td>
</tr>
<tr>
<td>Males 1.9 (1.4 -2.5)</td>
<td>Males 0.7 (0.3-1.3)</td>
<td></td>
</tr>
<tr>
<td>Females 1.9 (1.7-2.1)</td>
<td>Females 1.0 (0.8-1.3)</td>
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OS5.4
Utility of untimed single urine protein/creatinine ratio as a substitute for the 24 hour proteinuria for the assessment of proteinuria in systemic lupus erythematosus
Objective. To determine the utility of untimed Sample of Urine Protein/Creatinine (PCR) as a screening test for proteinuria and its ability to accurately measure the level of proteinuria in lupus.
Methods. Analysis was performed on data from a single lupus cohort between May 2008-December 2014. Proteinuria was measured concurrently by 24 hour urine sample collection (24hP) and PCR. Based on 24hP, samples were divided into 4 groups: I: <0.5, II: 0.5-0.99, III: 1.0-1.99, and IV: ≥2g/day. Correlation of 24hP and PCR was measured. Agreement between 24hP and PCR was determined by Intraclass Correlation Coefficient (ICC), Concordance Correlation Coefficient (CCC) and Bland-Altman plot. The cut-offs of PCR predicting a 24hP of 0.5, 1.0 and 2.0 g/day were determined with ROC curve.
Results. Although the correlation of 24hP and PCR for all samples was high, for groups I, II, III and IV it was low-moderate. The agreement for all samples and groups I, II, III and IV was poor. The Bland-Altman confirmed that PCR overestimated the result of 24hP (in particular groups III and IV) significantly poor agreement. PCR of 800 mg/g predicted a 24 h-P of 0.5 g/day (91% sensitivity and 80% specificity); PCR of 1590 mg/g and 3540 mg/g predicted 1.0 and 2.0 g/day respectively.
Conclusions. PCR can be used as a screening test for proteinuria and the cut off value to predict a 24h-P ≥0.5 g/day is 800 mg/g. PCR is not a valid test to quantify proteinuria. The accurate level of proteinuria should be measured by 24h-P.

OS5.5
Comparison of disease characteristics and organ damage in patients with juvenile and adult-onset systemic lupus erythematosus in large cohort from Turkey
B. Artim-Esen1, O. Kasapoğlu2, K. Barut1, S. Şahin1, A. Ommu1, Y. SahinKayak1, S. Kamul2, L. Ocal3, M. Imam1,2.
1Istanbul University, Istanbul Faculty of Medicine, Department of Internal Medicine, Division of Rheum, Istanbul, Turkey, 2Istanbul University, Cerrahpaşa Faculty of Medicine, Department of Paediatrics, Division of Rheum, Istanbul, Turkey.
Background. Age at onset has been shown to effect the clinical course and outcome of the SLE. Herein, we aimed to define the differences between patients with juvenile-onset (jo-SLE) and adult-onset (ao-SLE) SLE followed up in two tertiary referral centres.
Methods. Seven hundred nineteen (76.9 %) patients with ao-SLE and 216 (23.1 %) patients with jo-SLE were examined. Demographic characteristics, clinical features, autoantibody profiles and damage data (SLICC damage index) were compared between the groups.

Results. Photosensitivity (71.6 vs 56.5%), malar rash (73.6 vs 45.6%) and oral ulcer (25.3% vs 15.4%) were significantly more frequent in jo-SLE (p<0.05).
Renal involvement was significantly more prevalent in the jo-SLE affecting 53.2 % (vs 38.9 %) (p<0.05).
Autoimmune haemolytic anaemia (AIHA) also occurred more often in the jo-SLE (33.3 vs 9.5 %, p<0.05) whereas reverse was true for pleuritis (11.6 vs 18.4 %, p<0.05). A higher frequency of anti-dsDNA (78.7 vs 66.4%) and anti-cardiolipin IgG (31.9 vs 21 %) and IgM (36.6 vs 19.3%) were observed in the jo-SLE group. However, there were significantly more patients with anti-Sm positivity in ao-SLE (19.6 vs 10.2%, p<0.05). Renal damage was significantly more frequent in the jo-SLE (43 vs 17.5 %) (p<0.05).

Conclusions. jo-SLE was associated with a higher frequency of renal involvement and damage. As renal involvement is a major predictor of prognosis and outcome, this study highlights the importance of awareness of the age of onset of SLE and supports the necessity of vigilant follow-up of this subgroup.

OS5.6
Clinical and serological differences between juvenile-onset and adult-onset systemic lupus erythematosus patients from a national registry of patients (RELESSER)
V.Torrente-Segarra1, T. C. Salmon-Monte1, J. Rúa-Figueroa2, J. Calvo-Aleñ1, F. J. López-Longo1, M. Galindo1, J. M. Pego-Reigosa3 on behalf of the RELESSER Study Group.
1Department of Rheumatology, Hospital General Hospital- Moisés Broggi, Hospitalit Estelar Llobregat, Spain, 2Department of Rheumatology, Parc de Salut Mar, IMIM, Barcelona, Barcelona, Spain, 3Department of Rheumatology, Hospital Universitario De Negrín, Las Palmas de Gran Canaria, Spain, 4Department of Rheumatology, Hospital Sierallana, Torrelavega, Spain, 5Department of Rheumatology, Hospital Gregorio Marañón, Madrid, Spain, 6Department of Rheumatology, Instituto de Investigación Hospital 12 de Octubre (12+1), Madrid, Spain, 7Department of Rheumatology, Hospital do Mexixeiro, Vigo, Spain.
Objective. To assess clinical and serological differences between patients with juvenile-onset systemic lupus erythematosus (jSLE) and adult-onset (aSLE) from a National database.
Methods. Data included in the transverse phase of the National Register of lupus of the Spanish Society of Rheumatology (RELESSER –T) were analysed, which includes retrospective data from SLE patients. Inclusion criteria: patients with SLE with >= r = 4 ACR criteria for SLE who were divided into 2 groups: disease date onset <18 years and >18. Sociodemographic, clinical, serological, activity, treatment and cumulative damage and chronicity data were collected. Associative descriptive statistical analysis was performed.
Results. We reviewed 3,426 aSLE (89.6% women) and 484 jSLE (89.8% girls), 93.1% Caucasian in both groups; age at diagnosis: 38 ±14 and 16 ±6.3 years, respectively; average delay in diagnosis 24 ±747.4 and 39 ±99.5 months, respectively; mean age at follow-up: 48 ±41.3, 31 ±5.0 years, respectively. Table I shows all significant differences (p<0.05). In aSLE 68.7% had positive anti-DNA Ab vs. 82.9% of jSLE (p<0.001).
Conclusions. jSLE have higher percentage of nephritis, hypertension (associated with nephritis), anti-DNA, C3 and C4, and the rate of renal failure, chronic renal failure, organic brain syndrome and thrombotic thrombocytopenic purpura and more SLE family background. jSLE also have higher SLEDAL, Katz, but lower Charlson scores. Secondary Sjögren (anti-Ro), fibromyalgia and osteoporosis are more common in aSLE. jSLE receive more steroid treatment, synthetic immunosuppressants, IV immunoglobulin, rituximab, sibutramine, dialysis and kidney transplantation.
This study was supported by the FIS (ISCIII) PI11/02857. It has also been partially supported by GSK, UCB, Roche and Novartis. Dr. Pego-Reigosa receives support from Biocris (grant 316206) of the 7th Framework Programme of the European Union (FP7 / REPOPT - 2012-2013.1 ).
OS5.7
Coronary-Artery Atherosclerosis in SLE patients younger than sixty years
1 Instituto Nacional de Ciencias y Nutricion S.Z., Mexico City, Mexico, 2 Instituto Nacional de Cardiología Ignacio Chávez, Mexico City, 3 Mount Sinai Hospital and University Health Network, Toronto Canada, Toronto, ON, Canada.

Premature atherosclerosis is a major cause of morbidity and mortality in patients with SLE, but little is known about the frequency, extent, risk-factors, and burden of coronary-artery disease.

Methods. We studied 223 SLE patients (95 males y 128 females) attending our outpatient clinic and 193 healthy controls, matched by age and race. Patients and controls had a standardized assessment of demographic characteristics and traditional cardiovascular risk factors. In addition, patients had an evaluation of lupus characteristics, medications, and laboratory tests including immunological, extended lipid profile, homocystein, and hsCRP. Patients and controls were screened for coronary-artery calcification(CAC) using a 64-slice Multidetector Computed Tomography and the extent of calcification was measured by means of the SABA2 score.

Results. Mean (SD) age of lupus patients and controls was 32.9 (9.4) and 33.5 (9.8) years, respectively. Coronary-calcifications were detected in 25 patients (11%) and 7 (4%) controls (OR 3.35, 95% CI 1.36-9.38, p<0.001). Median calcium score in patients was 15.9 (0.2-576.8), and 7.7 (1.1-140.2) in controls. Calcifications in lupus patients and controls were detected since age 23 and 41 years, respectively. Patients had more often hypertension (30% vs 5%, p<0.001) and higher levels of homocystein (12.3±7.9 vs 9.5±3.6, p<0.001) than controls. Logistic regression analysis showed an independent association of age, male gender and SLE diagnosis with calcifications.

Conclusions. Asymptomatic CAC is more common, extensive and presents at younger age in lupus patients than in the control group. Lupus diagnosis is an independent risk factor for coronary-artery calcification.

7 Genetics and Epigenetics
OS7.4
A genetic variation in HLA-DR region associated with hypothyroidism and high expression of HLA-DRB1 and DRB5 genes contribute to enhanced autoantibody production in systemic lupus erythematosus
1University of Texas Southwestern Medical Center, Dallas, TX, United States, 2 Mount Sinai Hospital, Toronto Canada, Toronto, ON, Canada, 3 Xiangya Hospital, Central South University, Changsha, China.

Genetic variations within the HLA region have been identified as major risk loci for SLE. However the association between HLA genetic variation and autoantibody production is not well defined. In this study, we measured IgG autoantibodies against 95 self-antigens in a cohort of 212 SLE patients and 320 controls. A SNP in HLA-DR region, rs9268832, previously identified to be associated with SLE, was genotyped on all samples. Whole genome methylation and transcription analysis were performed on a subset of samples. The HLA SNP alleles and their association with DNA methylation, gene expression and autoantibody production was determined.

The SNP rs9268832 is a C/T variation and the TT allele frequency is significantly higher in SLE than controls (p<0.01). Gene ontology analysis showed that the SLE patients carrying TT allele exhibit higher DRB1 and DRB5 genes expression compared with CC or CT allele carriers. The TT allele SLE patients that the SLE patients carrying TT allele exhibited higher DRB1 and DRB5 genes expression compared with CC or CT allele carriers. The TT allele SLE patients that the SLE patients carrying TT allele exhibited higher DRB1 and DRB5 genes expression compared with CC or CT allele carriers. The TT allele SLE patients that the SLE patients carrying TT allele exhibited higher DRB1 and DRB5 genes expression compared with CC or CT allele carriers. The TT allele SLE patients that the SLE patients carrying TT allele exhibited higher DRB1 and DRB5 genes expression compared with CC or CT allele carriers. The TT allele SLE patients that the SLE patients carrying TT allele exhibited higher DRB1 and DRB5 genes expression compared with CC or CT allele carriers.
with CC individuals. Autoantibody profiling distinguished 19 highly expressed autoantibodies associated with different clinical manifestations in SLE. Among them, the anti-DNA autoantibodies (anti-dsDNA, anti-sDNA, anti-Chromatin, anti-nucleosomes) were significantly higher in TT allele SLE patients who displayed higher expression of DRB1 and DRB5 gene expression compared with CC or CT allele SLEs. The HLA-DR risk alleles modulate HLA-DRB1 and DRB5 gene expression through hypomethylation of the CpGs in regulatory regions. The hyper expression of the antigen presenting genes could be associated with initial breach in immune tolerance to self-antigens in the risk population.

8 Oral presentations 2: Basic science

OS8.1
The oxidative burst mediates anti-inflammatory clearance of dead cells in a mouse model of Systemic lupus Erythematosus (SLE) and inflammatory arthritis
J. Huth1, D. Krienhofer1, L.E. Munoz1, R. Holmdahl1, G. Krone1, G. Schett1, M. Herrmann1, M.H. Hoffmann1
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The production of reactive oxygen species (ROS) via the oxidative burst has recently been implicated in regulation of inflammation and protection from arthritis, multiple sclerosis, and psoriasis. The aim of this project was to elucidate the impact of the oxidative burst on lupus-like autoimmunity.

The clinical course of pristane-induced lupus (PIL) was compared between WT and ROS-deficient (Ncf1***) mice by analysis of serological markers and organ involvement. Ex vivo phagocytosis assays and flow cytometry were employed to analyze uptake and degradation of cell debris. Formation of neutrophil extracellular traps (NETs) was monitored in blood and periartema. Involvement of the antioxidative response was investigated by qPCR and CHIP. Ncf1** mice developed strongly elevated levels of typical lupus-autoantibodies, e.g., anti-dsDNA, anti-histone and anti-Sm/RNP, arthritis, and glomerulonephritis resulting in earlier death. We observed a preferential uptake of dead cell material but not of inert latex beads into inflammatory monocytes and granulocytes, and a dramatically reduced ability to form NETs in Ncf1*** mice. A similar phagocytosis phenotype was observed in patients with SLE. Immunoglobulin G-coating of latex beads significantly enhanced their uptake. Genes related to the antioxidative response dependent on the transcription factor NRF2 were strongly downregulated in Ncf1*** mice.

Our results show that autoimmunity occurring in the ROS-deficient Ncf1*** mice gives rise to exacerbated Lupus. Ablation phagocytosis in ROS-deficient mice results in spontaneous occurrence autoantibodies to surface molecules of dead cells and a defective regulatory antioxidative response contribute to this phenotype.

OS8.2
Aberrant microparticle and micro-RNA profiles in the circulation of SLE patients
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Despite the well-established diagnostic value of specific circulating autoantibodies in SLE there are no laboratory markers for monitoring disease activity. Also, the understanding of mechanisms leading to the sustained autoimmunity, immune tolerance to self-antigens in the risk population.

OS8.3
Modulation of deregulated chaperone-mediated autophagy by a phosphopeptide in Lupus
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The Pi40 peptide, a 21-mer linear peptide (sequence 131-151) derived from the ssnRNAP U1-70K, holds a lot of promise for treating lupus patients. In a multi-center, randomized, placebo-controlled phase-Ib study, PI40/Lupuzor was safe and met its primary efficacy end points in lupus patients (Zimmer et al., 2013). These results confirm pre-clinical data generated in MRL/lpr lupus-prone mice. The mechanism of action of PI40 was further studied in this mouse model. Previou sstudies showed that PI40 reduces autophagic flux in MRL/lpr B cells (Page et al., 2011). We now identify that chaperone-mediated autophagy (CMA) is hyperactivated in MRL/lpr B cells and is down-regulated after treatment with PI40 peptide. The mechanism through which PI40 inhibits CMA is largely related to its ability to alter the integrity of the HSPA/HSP90 heterocomplex of lysosomal chaperones. PI40 enters MRL/lpr B-lymphocytes via a clathrin-dependent endo-lysosomal pathway and accumulates at the lysosomal lumen where it could interact with lysosomal HSPA and hamper its chaperone function in CMA. This correlates with the observation that PI40 decreases the overexpression of LAM- P2A (a rate limiting factor in CMA) in MRL/lpr B cells in vivo. Loss of HSPA chaperoning function and destabilization of LAMP2A induced by PI40 may thus interfere with the endogenous (auto)antigen processing and loading to major histocompatibility complex class II molecules, leading to a lower activation of autoreactive T cells and consequently to an improvement of the autoimmune condition observed in lupus individuals. These results shed light on mechanisms by which PI40 can modulate lupus disease.

OS8.4
Interferon regulatory factor-5 promotes disease in the MRL/lpr mouse model of lupus
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Interferon regulatory factor 5 (IRF5) polymorphisms are strongly associated with an increased risk of developing systemic lupus erythematosus. In mouse lupus models, IRF5-deficiency reduced disease severity, consistent with an important role for IRF5 in disease pathogenesis. IRF5 is highly expressed in B cells where it is involved in isotype switching to IgG2a and TLR-mediated activation. However, whether IRF5 contributes to lupus pathogenesis by promoting B cell differentiation or plasma cell survival in not fully understood. We generated IRF5-deficient (IRF5/-/-) MRL/lpr mouse lupus model, and found that IRF5/-/- MRL/lpr mice develop much less severe disease than their IRF5-sufficient (IRF5+/+) littermates. Despite markedly lower serum levels of anti-nuclear autoantibodies and reduced total splenocyte and CD4+ T cell numbers, IRF5/-/- MRL/lpr mice have similar numbers of all splenic B cell subsets compared to IRF5+/+ MRL/lpr mice, suggesting that IRF5 is not involved in B cell development up to the mature B cell stage. However, IRF5/-/- MRL/lpr mice have greatly reduced numbers of splenic plasmablasts and bone marrow plasma cells. Serum levels of B lymphocyte stimulator (BLYS) were markedly elevated in the MRL/lpr mouse model but no effect of IRF5 on serum BLYS levels was seen. Overall our data demonstrate that IRF5 contributes to disease pathogenesis in the MRL/lpr lupus model and that this is due, at least in part, to the role of IRF5 in plasma cell formation. Our data also suggest that combined therapy targeting both IRF5 and BLYS might be a particularly effective therapeutic approach in lupus.
OS8.5

Detection of auto-antibodies directed to doublestranded DNA in SLE: comparison of different assays during quiescent and active disease

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Introduction. Auto-antibodies directed to doublestranded DNA (anti-dsDNA) are specific for systemic lupus erythematosus (SLE) and used in diagnosis and follow-up. Multiple assays are used without clear evidence which assay performs best.

Methods. Seven different assays were compared during lupus nephritis (n=58). The two assays with the highest accuracy to detect nephritis were selected and further tested in 152 SLE patients with quiescent disease, 40 SLE patients with active disease and 214 disease controls. Furthermore, longitudinal samples of SLE patients with and without exacerbations were examined to determine the positive predictive value of an increase for an exacerbation.

Results. Of seven assays, Farr (Siemens) and EliA (ThermoFisher Scientific) had the highest diagnostic accuracy in active nephritis (both 95%). Furthermore, sensitivity in active SLE was equal using Farr or EliA (95% vs 93%). In quiescent disease, specificity of EliA was higher (55% vs 91%). In longitudinally analyses, a 25% increase of anti-dsDNA preceded an exacerbation in 75% vs 69% (Farr vs EliA). In SLE patients without exacerbations a rise was seen in 7% vs 13%. Rises in anti-dsDNA occurred more often prior to nephritis (n=17) compared to non-nephritic flares (n=17), which was not different between both assays (Farr: 82% and 66%, EliA: 93% and 43%).

Conclusions. Farr and EliA have the highest diagnostic accuracy in detecting nephritis. However, EliA had higher specificity in quiescent disease. Both assays performed equally in predicting exacerbations. Most importantly, EliA has several advantages compared to Farr, including no use of radioactive materials and less time consumable.

OS8.6

TWEAK Receptor-Fc Suppresses Germinal Center Formation and Pathogenic B Cells in a Lupus Mouse Model via Inhibition of the TWEAK/Fn14 Pathway

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Systemic lupus erythematosus (SLE) is an autoimmune-mediated chronic inflammatory disease. Half of patients with SLE suffer from lupus nephritis, which is major cause of death in SLE. TNF-like weak inducer of apoptosis (TWEAK) is a fibroblast growth factor-inducible 14 (Fgf14) interactions mediate inflammatory responses that are linked to the pathogenesis of lupus nephritis. Blocking of the TWEAK/Fn14 pathway by TWEAK receptor-Fc was performed in a SLE mouse model and the likely therapeutic mechanisms were investigated.

To investigate the impact of TWEAK on B-cell differentiation in SLE, levels of AID, Blimp-1, and IRF4 messenger RNA were measured in CD19+ B cells extracted from spleen of sanroque mice and cultured with TWEAK. To identify the therapeutic effects of TWEAK receptor-Fc on SLE, sanroque mice were treated with TWEAK receptor-Fc or a control-Fc for 3 weeks. IgG, IgG1, and IgG2a levels were measured in the sera of each group. Spleens from each group were stained with antibodies against CD4, B220, GL-7, CD138, and PD-1. Kidneys were stained with H&E and PAS. Administration of TWEAK increased the mRNA levels of AID, Blimp-1, and IRF4. Treatment with TWEAK receptor-Fc suppressed levels of IgG, IgG1 and IgG2a in sera and reduced numbers of B, plasma-, and follicular helper T-cells (Th) in spleens of sanroque mice. In addition, renal protective effects of TWEAK receptor-Fc were shown.

TWEAK receptor-Fc had beneficial effects in a SLE mouse model by repressing B cells, plasma cells, Th, and renal damage. This suggested that the TWEAK receptor-Fc represents a potential therapeutic agent for SLE.