# 7th Annual Meeting of the Lupus Academy Meeting Report

**Rio de Janeiro, Brazil**

**6–8th September 2018**

## Introduction

The Lupus Academy is a long-term initiative committed to improving patient outcomes in systemic lupus erythematosus and allied diseases. By providing a highly interactive educational forum, the Lupus Academy is dedicated to sharing best clinical practice through the dissemination and discussion of cutting edge scientific and clinical research.

During the past 7 years the Lupus Academy has built a solid reputation for providing high quality educational meetings, which stimulate discussion, provide clinical practice insight and support improved patient outcomes.

The 7th Annual Meeting of the Lupus Academy was held in Brazil in September 2018, with the aim of reviewing and discussing insights in global research and clinical practice in lupus and associated diseases. This two day meeting brought together >300 clinicians and scientists, with a specialist interest in lupus, from around the world. The meeting was CME accredited and was designated for a maximum of 12 AMA PRA category 1 Credits™.

The scientific programme, developed by a Steering Committee of 12 international experts, provided a highly interactive forum through which information and experiences about the management of lupus was exchanged.

This report highlights key content from the main meeting sessions, excluding interactive workshops.

## Meeting Objectives

**To facilitate improvement in clinical practice and patient outcomes by enabling clinicians to:**

- Understand the current views on phenotyping systemic lupus erythematosus for improved clinical outcomes.

- Discuss current classification criteria for the effective management of systemic lupus erythematosus.

- Develop their clinical practice in line with recent developments in the classification, treatment and transplant outcomes for patients with lupus nephritis.

- Improve their clinical practice by better and more effectively identifying SLE cases, including patients with infection and flare, family planning and pregnancy, juvenile and adolescent lupus, haematologic lupus, lupus and cancer, and lupus and overlap syndromes.

- Understand the treat-to-target principle in terms of clinical and patient outcomes in lupus, considering current treatment targets, including remission and quality of life outcomes.

- Improve their management of lupus by using biomarkers to predict flares and present damage, including atherosclerosis, bone disease, infection and malignancy.

- Understand the clinical phenotypes and the management of CNS lupus and how imaging can be used to improve their clinical management of this manifestation.

# Keynote Lectures: Phenotyping and Pathogenic Mechanisms in Lupus

## Which lupus is it? Phenotyping lupus in 2018: Murray Urowitz (Canada)

Professor Urowitz reviewed the value of better phenotyping patients to facilitate decisions in the management of lupus disease course and outcomes. Four approaches were presented, including phenotyping according to (1) organ involvement, (2) disease outcomes, (3) biomarkers and (4) common comorbidities.

Professor Urowitz began his presentation by highlighting lupus as a multifaceted disease that cannot be simply defined by the term lupus; there is a need to explain what 'lupus' is--phenotyping lupus is important. Inclusion criteria for clinical trials require a SLEDAI-2K score of ≥6, yet this is score can be generated by many different manifestations of lupus (e.g. arthritis, skin renal etc.), each of which may respond differently to a single therapeutic intervention. Moreover, the complexity of the organ system needs to be considered when assessing response to treatment (e.g. renal Classes I-IV).

Professor Urowitz's presentation focused on four ways in which phenotyping lupus is important for both observational practice (i.e. long-term outcomes) and clinical studies (i.e. inclusion criteria), these included (1) organ involvement, (2) disease outcomes, (3) biomarkers and (4) common comorbidities.

1. Organ Involvement

ACR criteria require a malar or discoid rash, but SLICC criteria have several clinical criteria including acute cutaneous lupus, chronic cutaneous lupus, mucosal manifestations and alopecia. Professor Urowitz highlighted the differences between different types of lupus rashes (ie. acute, subacute, discoid, vasculitis etc) and how they respond to treatments. Despite these rashes having different SLEDAI scores, they are often grouped under the term 'skin lupus'. There is a need to differentiate these lupus subtypes in terms of SLEDAI in clinical trials, if treatment efficacy is to be accurately assessed.

There are at least six classification criteria for lupus kidney disease. Like skin lupus, each of the six classification criteria will respond differently to treatment as rates of proliferation and other factors differ. Despite these manifestations coming from different disease states they get the same value.

CNS lupus is highly complicated as clinical presentations vary so much, with generalised manifestations such as headache, psychosis and cognitive dysfunction requiring very different management to localised manifestations like stroke, visual disturbance and cranial nerve disturbance, which may have a very different pathogenesis. Again, it is important to separate these manifestations when including patients in clinical trials. Professor Urowitz reiterated that all trials use the classification criteria as inclusion criteria for study to ensure uniformity of patient populations among centers, but it is important to use criteria that are enriched for the different manifestations, skin and joint being the most common manifestations.

2. Disease Course

Lupus is typically described as relapsing-remitting, persistently active or monophasic disease. Most clinical trials include patients with active disease, with the objective of making the disease inactive. However, it is important to understand the patient's history, for example if they have had relapsing-remitting disease or not and how many times they have relapsed. Likewise, patients with persistently active disease will respond differently depending on how long their disease has been

active for (eg. SLEDAI 6). Moreover, patients with monophasic disease taking part in prevention of flare study will respond differently, depending how long their disease activity has been monophasic.

3. Biomarkers

Biomarkers can be split into two groups (1) serologic (clinically useful) and (2) experimental biomarkers. There are many important serologic markers, yet these are not all present in every patient (Table), for example pathogenic autoantibodies, such as anti-dsDNA antibodies, are only present in 75% of patients with lupus nephritis, leaving 25% of the lupus nephritis population being excluded from study if this biomarker was used to measure disease activity in a clinical trial setting. Similarly, anti-SM antibodies are only found in <30% of patients with kidney disease (1) Therefore, it is important to be careful, when using serological markers to classify disease, to ensure that patients are not excluded.

**Table: Pathogenic autoantibodies in SLE.(1)**

| Antigen specificity | Prevalence, % | Main clinical effects |
|---|---|---|
| dsDNA | 70–80 | Kidney disease, skin disease |
| Nucleosomes | 60–90 | Kidney disease, skin disease |
| Ro/SSA | 30–40 | Skin disease, foetal heart problems |
| La/SSB | 15–20 | Foetal heart problems |
| Sm | 10–30 | Kidney disease |
| NMDA receptor | 33–50 | Brain disease |
| Phospholipids | 20–30 | Thrombosis, pregnancy loss |
| C1q | 40–50 | Kidney disease |

*Serologic Biomarkers*

Clinical serologic correlations in SLE fall into two categories of patient (1) Concordant: Those with clinically and serologically active disease and those with clinically and serologically inactive disease, and (2) Discordant: Those with clinically active serologically quiescent disease (CASQ) and those with serologically active, clinically quiescent disease (SACQ). Concordant patients can be easily assessed and managed as the antibody mirrors disease activity and outcome can be predicted. Conversely, patients with SACQ pose a management quandary. These patients represent a small but clinically important group within our SLE population and can flare late and these can be mild; 59% after a median of 3 years. Therefore, prudent therapy for these patients would be close observation to discern which SACQ patients will go on to flare. Therefore, when looking at enriching a population with anti-DNA antibody it is important to identify whether the patient has been concordant or discordant in the past and ensure this population does not include SACQ patients, as they will favor the placebo group.

The use of autoantibodies as biomarkers for the prediction of neuropsychiatric events in SLE has been studied in the SLICC study, which examined an inception cohort of 1047 SLE patients to determine which autoantibodies at enrolment predicted subsequent neuropsychiatric events.(2) Multivariate analysis of the autoantibodies present in this cohort of patients showed that the only predictors of neuropsychiatric manifestations were lupus anticoagulant (stroke) and anti-ribosomal P (psychosis). Neither of these were present at 100% and each only predicted one phenotype of disease and are therefore not useful biomarkers in this situation.

*Experimental Biomarkers*

These biomarkers include genetic, epigenetic and cytokine/chemokine biomarkers and, although they can provide insight into susceptibility to lupus, they are not good disease biomarkers yet.

4.  Comorbidities

Lupus patients are living longer, with patients in 1974 having only had 75% chance of survival at 5 years, by 2010 patients could expect a 95% chance of survival at 5 years and 79% chance of survival at 20 years. These patients are therefore living with co-morbidities (e.g. atherosclerosis) and despite patients getting fewer atherosclerotic events early on in life (20-30 years old), they will eventually experience them as they are living longer. Professor Urowitz described subclinical events, with one third of patients, with no known history of coronary artery events, having abnormal scans; thus, highlighting that clinical events are just the 'tip of the iceberg' and that these patients should be monitored for subclinical events that predict future events. In addition, preclinical events are important with several patients having experienced myocardial infarction (MI) prior to their lupus diagnosis, and within the first 2 years of diagnosis, indicating that lupus may have had a significant causal effect on the patients MI.(3) The factors influencing such effects have been described by Arbukle et al (2003 (Figure).(4) Therefore, the genetic and environmental influences on benign and pathogenic autoimmunity that underlie atherosclerosis and lupus should be considered carefully.

**Figure: Phases in the development of pathogenic autoimmunity.(4)**
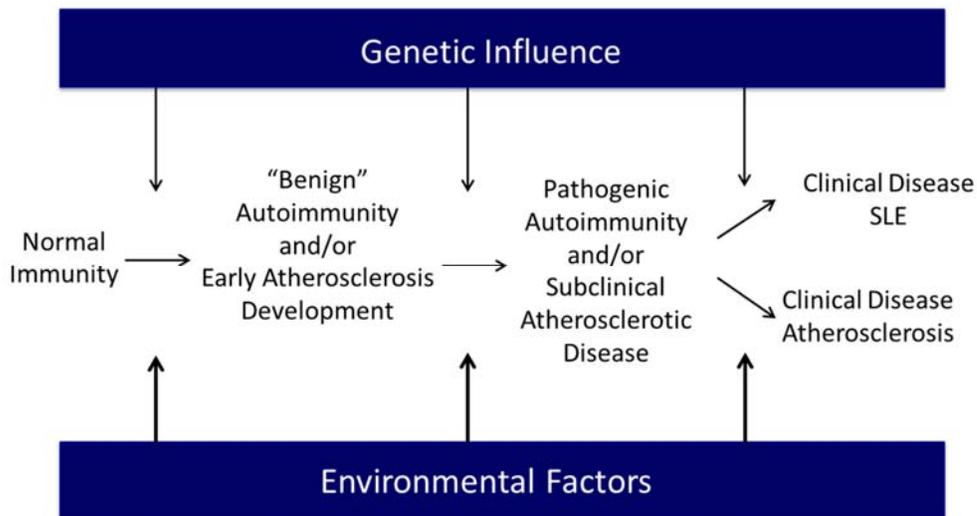


Professor Urowitz concluded noting that the 'elephant in the room' (i.e. Which lupus is it?) is one of many parts (i.e. organ involvement, disease course, biomarker and comorbidities) and that we can no longer say we are going to treat the elephant. It is necessary to identify which part of the elephant needs treating, and which part of this part needs treating—it is now important to phenotype the disease.

## Keynote Lectures: Phenotyping and Pathogenic Mechanisms in Lupus

**Understanding pathogenic B-cell functions in SLE: Where are we with new therapeutic targets: Thomas Dörner (Germany)**

Professor Dörner reviewed the function and type of post-activated B cells in the pathogenesis of SLE, the role of peripheral plasmablasts of systemic and mucosal origin as a key finding of SLE activity and described the pathogenic rationale guiding the treatment of SLE

The pathogenesis of systemic lupus erythematosus (SLE) appears to be complex and is possibly as heterogeneous as the disease itself. However, the majority of data point towards the role of type I interferon and the impact of B cells giving rise to autoreactive plasma cells that produce a plethora of autoantibodies, also involved in the formation of immune complexes. How type I interferon is interconnected with the formation of autoreactive plasma cells, including the role of abnormal T cell activity in SLE, has not been fully delineated.

Recent insights in the role of B cells comprise the diminished function of regulatory B cells,(5) including the reduced capacity of B cell cytokine production upon TLR9 activation(6) and BCR signaling responses.(7) The latter findings build the basis that B cells are considered to be in a postactivation status with reduced responsiveness, very similar as has been reported for CD8 and CD4 T cells. These observations are in striking contrast to textbook knowledge considering "B cell hyperactivity" as important in lupus pathogenesis. Since peripheral plasmablasts are a key finding of SLE activity described originally by our group(8) and recently characterised as a mixture of systemic and mucosal origin,(9) the data point toward a defect of selection within the germinal centre reaction in SLE, which can also be influenced by type I interferon as well as BAFF/BLys.

Pathogenic considerations provide the basis of innovative therapeutic approaches in SLE directly or indirectly impacting on B/plasma cells, which comprise targeting BAFF/BLys by belimumab, blocking IL12/23 by ustekinumab, Jak1/2 inhibition by barictinib as well as rituximab in refractory cases.

## Keynote Lecture: Classification Criteria for Lupus

**Evolution of SLE classification criteria: Ian Bruce (UK)**

Professor Bruce reviewed the classification criteria for SLE, noting that the classification criteria necessary for comparative studies can easily be misinterpreted as diagnostic criteria in inexperienced hands. SLICC 2012 and more recent criteria must consider the fundamental biology of SLE and its heterogeneous nature through robust methodology and improved sensitivity and selectivity.

Evolution of SLE classification criteria
Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with a wide range of clinical manifestations and having evidence of autoantibody production; the clinical features of SLE do not all need to be present at the same time. In contrast to many clinical conditions such as infection, anti-GBM disease etc., the fundamental nature of SLE remains elusive and ultimately may be a cluster of inter-related syndromes within the connective tissue disease spectrum. All of these present challenges for early diagnosis, prevention and predicting disease evolution over time.

Classification criteria are however necessary for comparative studies, for consistent trial inclusion etc. One challenge is that classification criteria easily morph into diagnostic criteria in inexperienced hands. A number SLE classification criteria sets have been published since 1971. The 1982 American College of Rheumatology criteria(10) have had considerable evaluation in the field but the 1997 revision(11) was not validated at the time. Other approaches have included classification trees, weighting of criteria etc.,(12) however these did not gain widespread use or acceptance.

The 2012 Systemic Lupus Collaborating Clinics (SLICC) criteria(13) maintained the spirit of the earlier criteria sets and improved face validity by including a wider spectrum of cutaneous and neuropsychiatric features as well as hypocomplementaemia. For the first time, biopsy proven lupus nephritis with a positive autoantibody was developed as stand-alone criteria. The SLICC Criteria have subsequently been shown by other groups to perform well in a range of contexts.(14)

What remains with SLICC 2012 and beyond into more recent criteria sets, is our continuing ignorance of the fundamental nature of SLE, whether it is a single entity and the continuing concern that any classification criteria set will still get used as diagnostic criteria. The next 20 years will be spent addressing questions of the fundamental biology of SLE so we can more precisely diagnose, classify, treat and eventually cure or prevent this challenging condition(s).

New SLE classification criteria: Beyond SLICC

Classification criteria are needed to identify more homogeneous groups of patients for inclusion into research studies.(15) The European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) supported a four-phase international effort to develop new classification criteria for systemic lupus erythematosus (SLE).

The validity of antinuclear antibody as an entry criterion was evaluated through systematic review and meta-regression of the literature.(16) Candidate additive criteria were collected through an international Delphi exercise,(17) an early patient cohort(18) and a patient survey. Items were reduced in number by nominal group technique (NGT). Multi-criteria decision analysis identified criteria weights. Criteria definitions, weights and threshold score were refined in a derivation cohort of 1001 subjects. The final criteria set was evaluated comparatively against previous criteria sets in a validation cohort of 1270 subjects. ANA ≥1:80 were identified as an entry criterion.(16) Of the 140 candidate additive criteria evaluated, 21 were chosen by Delphi and NGT, grouped into 10 hierarchically clustered domains and weighted from 2 to 10.3-5 Using a threshold score of ≥10, the new criteria had a sensitivity of 96.3% and specificity of 94.1%, compared to 82.8% sensitivity and 93.4% specificity of the ACR 1997 and 96.7% sensitivity and 83.7% specificity of the Systemic Lupus International Collaborating Clinics (SLICC) criteria.

Using rigorous methodology, multidisciplinary, and international input, the new classification criteria provide excellent sensitivity and specificity. Use of an entry criterion, hierarchically clustered and weighted criteria reflect current thinking of SLE and provide a new paradigm for SLE research.

## Plenary I: What's New in Lupus Nephritis

### Classification of lupus nephritis: What's new? Brad Rovin (USA)

Professor Rovin reviewed kidney biopsy and classification of lupus nephritis and the need to better identify predictive and prognostic markers for optimum (personalised) therapy through both biopsy and molecular expression patterns.

The kidney biopsy has been one of the most important tools in understanding the effects of lupus on the kidney. It has been in use for several decades and over that time has been used to classify lupus nephritis (LN) based on light microscopic features.(19) Besides providing a histologic diagnosis, the biopsy has been expected to guide therapeutic decisions and predict prognosis. However this was not realised with the original World Health Organization classifications of LN, so the International Society of Nephrology and the Renal Pathology Society (ISN/RPS) developed a new system for classifying LN in 2003 to address these clinical needs.(20) Arguably the ISN/RPS did not succeed at

this and there is now a movement to update the classification.(21) We suggest that in the age of molecular medicine and the quest for personalised treatment, kidney histology by routine microscopy, no matter how well described, will not be adequate to identify optimal therapies or quantify prognosis. The classification of LN should now move to combining histologic findings with molecular expression patterns from the kidney biopsy.(22) Furthermore, forecasting accurate prognosis likely requires repeat biopsy to understand changes in the kidney due to therapy.

## Plenary I: What's New in Lupus Nephritis

**Emerging therapies for lupus nephritis: Liz Lightstone (UK)**

Professor Lightstone reviewed standard of care for lupus nephritis before highlighting the place for better combinations of existing therapies and new agents targeting novel therapeutic pathways.

Professor Lightstone's presentation reviewed the standard of care for lupus nephritis, namely mycophenolate mofetil (MMF) and steroids or the Eurolupus regimen. Whilst we have good evidence for long term efficacy in those who respond, a significant proportion do not respond by one year and are more likely to reach end stage renal failure and face premature mortality, hence there is a need for better combinations of existing therapies and new agents targeting novel therapeutic pathways.

Calcineurin inhibitors

There is a growing evidence, mostly from China, that adding the calcineurin inhibitor (CNI), tacrolimus to low dose MMF and "low dose" oral steroids, leads to greatly improved and more rapid complete remission rates. However, these improvements are not necessarily maintained over time and approach has yet to be validated with tacrolimus in a more diverse population. Voclosporin, a new CNI with much flatter dosing (does not require levels to be measured) and purportedly less nephrotoxic and diabetogenic than tacrolimus, has shown promise in a (as yet to be fully published) Phase II randomised control trial.

B-cell depletion

Rituximab is used regularly for refractory lupus nephritis and, in our unit, as first line therapy for lupus nephritis – however, the trial data are lacking to support this approach. I will very briefly discuss the RITUXILup Trial, the results of which will be reported later this year. However, the study had to terminate early and I will discuss why and what this has taught us. I will also mention recent data using ofatumumab.

Other emerging therapies

There are a number of therapeutic approaches under evaluation at present and I will briefly explore the rationale and progress – this will cover belimumab, anifrolumab and complement inhibition.

Emerging therapeutic strategies

Whilst there is clearly unmet need for new therapeutic targets there is also a need to reduce the toxicity of current approaches, not least by reducing steroids. I will briefly review the data from the Cruces group, the control arm of the voclosporin study and our own data. Finally, no therapy will work if not taken new strategies to assess adherence are critical and if time permits Monitoring hydroxychloroquine levels is important as low levels are associated with increased risk of flare of nephritis.

## Plenary I: What's New in Lupus Nephritis

**Lupus nephritis: Dialysis and transplant: Evandro Klumb (Brazil)**

Professor Klumb highlighted the current treatment concepts for end stage renal disease in patients with SLE, before reviewing the outcomes of different vascular access for haemodialysis and complications associated with different treatment modalities and pre-emptive renal transplantation.

Glomerulonephritis is one of the most severe clinical presentations of systemic lupus erythematosus (SLE). Notwithstanding the availability of new drugs and modern laboratory biomarkers, end stage renal disease (ESRD) occurs in up to 30% of these patients. US data reveal that almost 1% of all patients starting ESRD treatment have lupus nephritis (LN).(23) At the same time, most patients initiating haemodialysis do not have a permanent vascular access [arteriovenous fistula (AVF) or graft (AVG)] adequately placed and patients frequently undergo treatment with a temporary central venous catheter, which has poorer outcomes in comparison to AVF or AVG.

Pre-emptive kidney transplantation (TX) presents better outcomes and is suggested for all patients with ESRD who are candidates for this treatment modality, however less than 10% of renal TX among SLE patients occur preemptively. Variables found associated with graft and global survival include delayed allograft function, HLA antibodies, type of donor kidney (living or deceased), donor illness and medical center factors. Since most LN patients who achieve ESRD progress slowly and are more likely to receive a living donor kidney (OR=3,6 CI95%-3.3-4.5)(24) that may be preemptive, rheumatologists should be should be encouraged to refer early these cases to the renal transplantation team as soon as GFR is lower than 30 ml/min. Current data obtained in different studies, mostly with deceased donors, demonstrate graft survival in 5, 10 and 15 years from 72% to 94%, from 58% to 94% and from 58% to 71% respectively.(25-29) SLE patient survival for 15 years was found to be 76% to 98%, which is better than rates achieved in haemodialysis. Preemptive transplant recipients present lower risk of graft failure [HR= 0.69; 95%; CI- 0.55‑0.86] and lower risk of recipient death [HR= 0.55; 95% CI- 0.36‑0.84] in adjusted analyses. At the same time, patient survival may also be influenced by the time spent on dialysis prior to renal transplantation though the longer the time on dialysis the worse the overall survival after transplantation. The concern of disease recurrence after renal treatment should not restrict preemptive procedures since the results are found to be better than treatment after haemodialysis.

## Plenary II: Treat-to-Target: Clinical and Patient Outcomes

**Current treatment targets in lupus: Rich Furie (USA)**

Professor Furie reviewed the current treatment and emerging treatment targets in lupus, highlighting the heterogeneous nature of SLE and associated difficulties in setting treatment goals for the individual patient. Evolving composite metrics aim to simply and improve outcomes in patients with SLE.

The clinician engaged in the care of lupus patients is faced with clinical heterogeneity not seen in any other disease. This makes the assessment of disease activity as well as the creation of treatment goals particularly difficult. Even for seasoned "lupologists", challenges abound. During a typical encounter, most healthcare providers rely on a combination of "clinical gestalt" and laboratory test results to assess the status of the patient. However, clinical research, particularly drug development clinical trials, mandates the use of formal metrics. Whereas several different disease activity instruments have been developed, the Systemic Lupus Erythematosus Disease Activity SLEDAI) and British Isles Lupus Assessment Group (BILAG) indexes have risen to the top. Based on

FDA draft guidance, issued in 2005, along with a post-hoc analysis of the Phase II belimumab trial, a composite index was born. Known as the SLE Responder Index (SRI), it was used as the primary endpoint in the successful Phase III belimumab program. A parallel outcome measure, BILAG-based Composite Lupus Assessment (BICLA), was created shortly thereafter. Efforts to refine these composite metrics with the goal of making assessments simpler and more clinically meaningful are underway.(30-35)

## Plenary II: Treat-to-Target: Clinical and Patient Outcomes

### Remission and low disease activity as treatment targets in lupus: Ronald van Vollenhoven (Netherlands)

Professor van Vollenhoven reviewed the treat to target for the management of SLE, highlighting definitions of remission and low disease activity and how their application in clinical practice can support improvement in treatment outcomes for patients with SLE.

There is evidence in many chronic diseases that treating-to-target (T2T) gives better outcomes. For systemic lupus erythematosus (SLE) this has not strictly been proven, but an international task force has recommended that, in analogy to those other diseases, T2T should be employed for SLE as well.(36) In order to do so, the target must be defined in measurable terms.

In parallel, those who design clinical trials for SLE have proposed outcomes that emphasise disease state rather than the change from baseline, again with the need for accurately defined quantifiable outcomes.(37)

Remission is intuitively understood as a highly desirable disease state, but defining it accurately has been challenging. The international "DORIS" (definitions of remission in SLE) task force proposed a framework for developing remission definitions and for testing their validity,(38) and this work has now led to a series of publications on possible definitions of remission in SLE. In parallel, the Asia Pacific Lupus Group developed and validated a definition of low disease activity (LDA), the Lupus LDA state, LLDAS.(39)

Thus, the development of accurate and quantitative LDA and remission definitions has accelerated and has now reached the stage where, I believe, the lupus community will be able to unite around a "core-set" of outcomes including both LDA and remission that can be used as end points in clinical trials, as outcomes in other forms of clinical research and as the target in clinical care, leading to better long-term outcomes for the patients.

## Plenary II: Treat-to-Target: Clinical and Patient Outcomes

### Quality of life as a treatment target in lupus: Matthias Schneider (Germany)

Professor Schneider reviewed the importance of assessing health related quality of life (HRQoL) as a treatment target in the management of SLE, considering both physicians' and patients' on therapeutic outcomes as measured by current domains.

The prognosis of lupus patients is essentially defined by the cumulative damage they suffer from their disease and the undesirable effects of their therapy. According to today's understanding, the main factors for this damage are disease activity and the use of glucocorticoids, both of which have a corresponding significance in the criteria for remission and low disease activity. Because it is known that fatigue and participation have an influence on long-term prognosis, the FDA also sees health-

related quality of life (HRQoL) as the primary endpoint of clinical trials. In 2009, the European League Against Rheumatism also recommended that HRQoL be included as an outcome parameter in clinical studies. Although HRQoL is an independent variable for the prognosis, it is not found in the therapy goals for lupus. There are also sufficient and validated tools available to capture the complex aspects of HRQoL. Why does the use of HRQoL as a therapy goal fail?

## Plenary III: Management of Lupus

**Biomarkers to predict flares: Judith James (USA)**

Professor James presented the clinical factors that can predict flares in patients with SLE. Despite some challenges in validating biomarkers for lupus flares, understanding of immune pathway activation is revealing candidate biomarkers for flare prediction in SLE.

Systemic lupus erythematosus (SLE) is a systemic disease characterised by waxing and waning disease activity, where periods of relatively mild disease may be punctuated by periods of intense and debilitating disease activity. Despite improved treatment regimens and the use of clinical instruments to measure disease activity, patients with SLE may experience an average of 1.77 disease flares per year. The frequency and severity of flares are important prognostic indicators for long-term outcomes because both disease flares and the major immunosuppressants used to treat flares can cause irreparable damage. Robust predictors of clinical SLE flares are needed to optimise the timing of aggressive treatments while safely minimising immunosuppressant use during periods of low disease activity.

Although predictors of SLE flares have been difficult to identify,(40) significant work is underway. In the SLICC inception cohort,(41) disease activity in the first year corresponded with annual relapse rates and average SLEDAI scores over 5 years of followup. In a post-hoc analysis of the placebo arms of belimumab trials,(42) the best baseline predictors of moderate-to-severe flare over the following year were renal involvement, anti-dsDNA>200, BLyS levels >2, low complement levels, or vasculitis/ neurologic involvement.

In recent biomarker studies,(43, 44) circulating proinflammatory mediators increased and regulatory mediators decreased prior to SLE flares, predominantly in T-helper, interferon-related and TNF-related pathways. Although the altered pathways varied among patients, an algorithm that simultaneously surveyed multiple immune pathways predicted impending flares with high sensitivity and specificity. In a paediatric lupus study a plasmablast expression signature was the most robust biomarker of disease activity(45) and personalised immune-monitoring identified correlates of disease activity that stratified patients into seven major groups. Finally, among adult SLE patients who stopped their background immunosuppressants and received intramuscular steroids until disease suppression, early flare was associated with baseline CD11b/ITGAM overexpression, CD11bhi neutrophils and monocytes, CD86hi B cells and lower IL-1RA and TNFR1. This talk will discuss highlights of current biomarker development and future directions for moving biomarkers into clinical care and improving outcomes.

## Plenary III: Management of Lupus

**Preventing damage (atherosclerosis, bone disease, infection and malignancy) David Isenberg (UK)**

Professor Isenberg presented details of the SLICC damage index, emphasizing that prevention of damage early in the disease process is critical to increase the life span of patients with SLE. Damage may be the result of lupus, concomitant disease such as atherosclerosis, bone disease infection and malignancy, and complications of therapy.

To assess a lupus patient completely requires the ability to distinguish activity (implying ongoing inflammation, potentially remediable to therapy) and damage (implying permanent change which anti-inflammatory medication cannot alter), as well as a recognition of the importance of the patient's perception of their disease.

It has long been established that damage acquisition is important as it predicts both the development of further damage(46) and early death.(47) Twenty years ago the Systemic Lupus Erythematosus Collaborative Clinics group (SLICC) published a damage index for lupus that is still in use today.(48) It remains the only one of its kind.

The SLICC index deliberately avoids attempting to ascribe the precise cause of an individual item of damage as this may be multiple and/or complex in origin. Damage items in the index are identified under twelve headings and damage can never improve only stay the same or worsen. Many studies in the past two decades [eg Petri et al 2012(49)] have, however, attempted to identify the important causes of damage in systemic lupus erythematosus (SLE). In broad terms, the disease itself, a concomitant disease (approximately 30% of SLE patients have a second/third/fourth autoimmune condition) or therapy may all give rise to damage.

Professor Isenberg highlighted the important contribution to damage [discussed in detail elsewhere(50)] brought about by atherosclerosis (SLE patients between 35 and 44 are fifty times more likely to have a heart attack); bone disease (principally osteoporosis invariably linked to steroid therapy); infection (both SLE itself and the immunosuppressive drugs often used to treat it increase the risk) and malignancy (non-Hodgkin's lymphoma is the "stand-out" cancer linked to lupus).

Remaining mindful of the likely determinants of increased damage is extremely important to minimise its development and help increase the lifespan of patients with SLE.

## Plenary IV: CNS Disease

**Clinical phenotypes and the management of neuropsychiatric lupus: Bevra Hahn (USA)**

Professor Hahn presented the current perspective on pathogenesis of neuropsychiatric SLE (NPSLE), highlighting the features of disease that indicate a neuropsychiatric problem may be due to SLE. Neuropsychiatric problems can be ascribed to the vasculopathy or inflammation associated with SLE and it is these that are treatment targets.

The pathogenesis of neurologic disease resulting from systemic lupus erythematosus (SLE) can be viewed as consisting of two major attacks on brain/spinal cord. The first is vascular and can be bland vasculopathy which includes occlusions (most common), vasculitis, or clotting due to antiphospholipid or platelet disorders. The second is diffuse inflammation, which results from

several autoantibodies (to neurons, NMDA2, ribosomal P, phospholipids) being able to cross a disrupted blood brain barrier to cause complement fixation, cytokine release, damage to cells and interference with neurotransmitter signalling. Thus, the clinician approaching a patient with neuropsychiatric symptoms and SLE must decide first if the problem is due to SLE (it is usually not) and if it is due to SLE (more likely if the disease is active in other systems and studies of spinal fluid, EEG and images suggest disease compatible with SLE), whether the problem is vascular or inflammatory or both. Therapies depend on those answers. For example, strokes are treated with the current common approach to acute stroke (rapid imaging, removal of clots or dissolution of acute clots) followed by consideration of low-dose aspirin and, if a major problem, long-term anticoagulation with relatively high INR. If there is diffuse inflammation (acute confusion, psychosis, aseptic meningitis, etc.) appropriate treatment is moderate-to high dose glucocorticoids often with another immunosuppressive such as cyclophosphamide, mycophenolate, azathioprine, rituximab etc. For seizures, psychosis and mood disorders (depression is very common and can associate with active disease), treatment with medications for those disorders is appropriate, often in combination with anti-inflammatory approaches. This presentation will discuss several separate disorders seen in neuropsychiatric SLE, such as cognitive dysfunction, headache, psychosis, neuromyelitis optica, reversible posterior encephalopathy. Most of these disorders respond to current therapies.(51-54)

## Plenary IV: CNS Disease

### Update on imaging in neuropsychiatric lupus: Simone Appenzeller (Brazil)

Professor Appenzeller presented the key 'mimikers' of CNS involvement in SLE, highlighting the importance of utilizing MRI techniques to diagnose CNS involvement in SLE.

Neuropsychiatric manifestations in systemic lupus erythematosus have been more frequently recognized and reported in recent years, occurring in up to 75% of patients during the disease course. Magnetic resonance imaging is known to be a useful tool for the detection of structural brain abnormalities in neuropsychiatric systemic lupus erythematosus patients because of the excellent soft-tissue contrast observed with MRI and the ability to acquire multiplanar images. In addition to conventional magnetic resonance imaging techniques to evaluate the presence of atrophy and white matter lesions, several different magnetic resonance imaging techniques have been used to identify microstructural or functional abnormalities. In this lecture we will review the main mimickers of CNS involvement in SLE and discuss different MRI techniques to diagnosis NPSLE.(55-57)

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