

## 2nd Meeting of the Lupus Academy

Hilton Hotel, Buenos Aires, Argentina  
17–18 April 2013

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## FACULTY

Participant	Affiliation	Country
<b>Graciela S Alarcon</b>	University of Alabama at Birmingham, Alabama	USA
<b>Marta E Alarcón-Riquelme</b>	Universidad de Granada, Spain and Oklahoma Medical Research Foundation	USA
<b>Paula Alba</b>	State University of Cordoba	Argentina
<b>Mary-Carmen Amigo</b>	ABC Medical Centre	Mexico
<b>Zahir Amoura</b>	Groupe Hospitalier Pitie-Salpetriere, Paris	France
<b>Eloisa Bonfá</b>	University of Sao Paulo Medical School	Brazil
<b>Ian N Bruce</b>	University of Manchester	UK
<b>Luis J Catoggio</b>	Hospital Italiano de Buenos Aires	Argentina
<b>Ricard Cervera</b>	Hospital Clínic, Barcelona	Spain
<b>Andrea Doria</b>	University of Padova	Italy
<b>Thomas Dörner</b>	Charite University Hospitals, Berlin	Germany
<b>David A Isenberg</b>	University College, London	UK
<b>Meenakshi Jolly</b>	Rush University Medical Centre, Chicago	USA
<b>Elizabeth Jury</b>	University College London	UK
<b>Munther A Khamashta</b>	St Thomas' Hospital, London	UK
<b>Roger A Levy</b>	The State University of Rio de Janeiro	Brazil
<b>Liz Lightstone</b>	Imperial College London	UK
<b>Loreto Massardo</b>	Pontificia Universidad Catolica de Chile, Santiago	Chile
<b>Joan T Merrill</b>	University of Oklahoma	USA
<b>Marta Mosca</b>	University of Pisa	Italy
<b>Sandra V Navarra</b>	University of Santo Tomas, Manila	Philippines
<b>Bernardo A Pons-Estel</b>	Cardiovascular Institute of Rosario, Rosario	Argentina
<b>Murray Urowitz</b>	University of Toronto	Canada
<b>Ronald F van Vollenhoven</b>	The Karolinska Institute and Karolinska University Hospital	Sweden
<b>Victoria P Werth</b>	Philadelphia Veterans Affairs Medical Center	USA

## INTRODUCTION

The Lupus Academy is a long-term initiative that is committed to improving outcomes in patients with systemic lupus erythematosus (SLE) and allied diseases. The Academy is dedicated to sharing best clinical practice through the dissemination and discussion of cutting edge clinical research.

The Second Annual Meeting of the Lupus Academy was held in Buenos Aires, Argentina on 17–18 April 2013. The meeting was attended by approximately 185 healthcare professionals from over 30 countries who represented the specialties of rheumatology, internal medicine, clinical immunology, dermatology and nephrology. The objectives of the meeting were to facilitate improvements in clinical practice and outcomes for patients with SLE through:

- Understanding of the genetic and cellular mechanisms underlying disease pathogenesis
- Discussion of patient perspectives on the burden of lupus and how best to manage this burden
- Improved understanding of the cardiovascular, renal and cutaneous manifestations of lupus
- Awareness of the risk factors for infection and infection prevention measures
- Understanding of the risks associated with pregnancy and risk-minimisation strategies
- Evaluation of current and future treatment options.

The scientific programme, developed by a Steering Committee of international experts, was designed to provide a highly interactive forum for the exchange of information and clinical experience to inform the management of lupus across the globe. The meeting, which had full Continuing Medical Education (CME) accreditation, offered a faculty of 25 global experts and incorporated delegate feedback from the inaugural 2012 meeting to ensure the provision of a topical, world-class educational programme. This highlights report presents key content from the main meeting sessions, excluding the workshops.

**WEDNESDAY 17 APRIL 2013**

## Keynote lectures

### **The genetics of lupus: Where are we now?**

**Marta E Alarcon-Riquelme (USA)**

*Professor Alarcon-Riquelme's presentation examined current knowledge of the genetics of lupus. She commenced by explaining the tools employed to investigate the genotypes of complex diseases and then described the gradual accumulation of data concerning lupus-related genes, culminating in ongoing genetic analyses in the present day.*

In Mendelian monogenic diseases, such as haemophilia, genotype plays a considerable role. In contrast, in complex polygenic diseases, such as rheumatoid arthritis, the genetic contribution becomes reduced and environmental factors take on an increasingly important role.

#### *Tools for investigating genotypes*

A number of tools are available for studying the interaction between genotype and phenotype, including the recurrent risk ratio, heritability, degree of concordance and segregation analysis. In patients with lupus, studies have demonstrated a relatively high degree of concordance between monozygotic twins, despite the complex nature of lupus. The heritability of the disease is also high at  $66\pm 11\%$ , and it is thought that lupus fits within a polygenic additive genetic model where genetic effects contribute towards clinical expression of the disease.<sup>1</sup>

Cases and matched controls are used to assess the genotypes of complex diseases enabling researchers to compare gene polymorphisms of interest. Simple genetic tests, such as the chi-squared test and contingency tables, are then used to identify genetic associations. True genetic associations arise when a mutation or polymorphism has a functional effect. Direct associations can be identified where a marker is available, enabling the investigation of potential associations between genetic alterations and the disease phenotype to be made. Indirect associations reflect that a gene may be associated with a disease but no marker is available; in such cases, linkage disequilibrium is used to indicate the non-random association of alleles. Spurious associations can also occur where case and control populations are not well matched and result in false positive associations; spurious associations can be a problem in populations composed of highly mixed ancestries, such as in Latin America.

Contemporary genetic research uses genome-wide association studies (GWAS), in which a dense array of genetic markers that captures the common variations of the genome is compared in cases and controls. If a specific genetic variant is more frequent in patients with the disease, it is considered to be associated with the disease, and the genomic region where the variant lies is considered to influence the risk of developing the disease.

### **Identifying lupus-associated genes**

The first GWAS in lupus commenced in 2008 when a small number of genes had already been identified. Today, approaching 50 lupus-associated genes have been documented using this technique, including *HLA*, encoding human leukocyte antigen, *FcGRs*, encoding the Fc gamma receptors, and *PDCD1*, which encodes the programmed cell death 1 protein.<sup>2,3</sup>

Most of the key lupus-related genes have now been identified, although they explain only 18% of the genetic contribution to the disease.<sup>3,4</sup> The remaining unidentified genes are likely to be hidden within subphenotypes, rare variants and gene–gene interactions, all of which are challenging to replicate and study.<sup>5,6</sup> Analysis of different global populations provides some information, and, indeed, some of the most severe cases of lupus arise in mixed populations.<sup>7,8</sup> However, genetic contributions vary between populations due to differing ancestries, such that *HLA* has the strongest association with lupus in Europeans (odds ratio [OR], ~1.5), whilst, in Latin Americans, the interferon regulatory factor 5 gene, *IRF5*, is most strongly associated with lupus (OR, 2.5).<sup>9</sup>

Most of the genes contributing to lupus encode proteins that affect the immune response. Thus, B-cell scaffold protein with ankyrin repeats 1 (*BANK1*) and B lymphoid tyrosine kinase (*BLK*) are involved in interactions between T and B lymphocytes; signal transducer and activator of transcription 4 (*STAT4*) and tumour necrosis factor receptor superfamily, member 4 (*TNFRSF4*) focus the T cell lineage towards the appropriate helper cell response; integrin alpha M (*ITGAM*) supports the complement cascade; and *FcGRs* clear immune complexes. However, the roles of many of the contributory genes are yet to be identified and their effects on disease expression remain unknown.<sup>10</sup>

### **The *BLK* gene in lupus**

The *BLK* gene is currently being studied to determine its contribution to lupus. *BLK* is important in immune signaling and is expressed in B cells, plasmacytoid dendritic cells and some T cells.<sup>11</sup> GWAS have shown that risk alleles for *BLK* correlate with low levels of *BLK* mRNA,<sup>9</sup> and low *BLK* levels, in turn, are associated with altered B cell populations.<sup>12</sup> Furthermore, some healthy individuals carry risk alleles for *BLK*, show alterations in some B cell populations, and thus represent carriers of lupus risk alleles.<sup>10</sup> A rare mutation in *BLK* has been identified recently that is associated with the substitution of alanine for threonine in Exon 4, resulting in a shorter lifespan and lower levels of the *BLK* protein that, in turn, lead to B cell activation and lupus-associated B cell phenotypes.<sup>13</sup> *In vivo* studies are ongoing to investigate the effects of this and other genetic mutations on lupus phenotypes in order to develop a better understanding of the disease.

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## Decreasing morbidity and mortality and improving outcomes in SLE

**Murray B Urowitz (Canada)**

*In his keynote lecture, Professor Urowitz discussed the morbidity and mortality associated with systemic lupus, acknowledging the significant reduction in lupus-associated mortality achieved since the 1970s. He cautioned that morbidity rates have risen, due to the accumulation of global damage in patients living with the disease, and discussed strategies to improve outcomes in patients with lupus.*

Longitudinal data for patients with systemic lupus treated at the University of Toronto suggest that survival rates have increased from a 15-year survival rate of 53% in the 1970s to a 20-year survival rate of 79% in the present day.<sup>1</sup> Calculation of the standardised mortality ratio (SMR) for patients with lupus from the same population treated in the 1970s to the 2000s, indicates that the SMR has decreased substantially from 13.84 to 3.81 during that time period.<sup>2</sup> However, life expectancy remains low for a population composed largely of young patients.

Evaluation of the adjusted mean Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) from the same longitudinal data indicates that levels of disease activity have decreased from 8.45 for the 1970s cohort to 5.99 for patients treated in the 2000s, although patients continue to present with active disease.<sup>2</sup> In line with this finding, in the 1,613 patients from the same population for whom long-term data were available, the rate of prolonged remission was just 2.4%, of whom less than half demonstrated both negative serology and negative clinical features.<sup>1</sup>

Application of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index<sup>3</sup> to the longitudinal Toronto data shows an increase in damage from 0.63 for patients first treated in the 1970s to 3.49 for the same patient cohort in their fourth decade of treatment, suggesting a progressive accumulation of damage over time.<sup>1</sup>

Damages comprise those definitely related to the use of corticosteroids (musculoskeletal, ocular); those possibly related to steroids (cardiovascular [CV], neuropsychiatric, diabetes); and those unrelated to steroid use (skin, gastrointestinal, renal, pulmonary, gonadal, malignancies). Evaluation of damage accrual over time suggests that, at 15 years, a considerable 80% of damage in lupus patients is definitely or possibly related to the use of corticosteroids.<sup>3</sup>

### **Cardiovascular damage in lupus**

Cardiovascular disease accounts for a significant proportion of damage in patients with lupus<sup>4</sup> and is often the cause of death in patients with disease of 15 or 20 years' duration. Analysis of the Toronto patient population demonstrates an incidence of coronary artery disease (CAD) of 5–7% in the first decade, rising dramatically to almost 30% in the fourth decade.<sup>3</sup> Furthermore, studies have shown that a significant proportion of asymptomatic patients with lupus already have significant subclinical CAD.<sup>5</sup> Risk factors for atherosclerotic

disease in these patients include lupus-related factors, such as vasculitis and neuropsychiatric factors, and CAD risk factors, to which corticosteroids contribute significantly.<sup>6</sup>

### ***Neuropsychiatric damage***

Many forms of neurological disease can occur in patients with lupus, including vasculitis of the central nervous system, cortical atrophy and organic brain syndrome. As with CV disease, a substantial proportion of lupus patients who appear to be cognitively normal have cognitive impairment, which may be disease- or steroid-related.<sup>7</sup>

### ***Musculoskeletal damage***

The bone conditions osteoporosis and osteonecrosis represent significant causes of morbidity in patients with lupus. In a 5-year analysis of 205 patients with lupus for whom baseline bone mineral density data were available, osteoporosis was observed in 18% of patients.<sup>1</sup> The variables independently associated with osteoporosis were age and ACR/SLICC Damage Index, the latter suggesting that corticosteroids are a major causative factor in the development of this condition.<sup>1</sup> Osteonecrosis is associated with multi-joint damage and requirements for surgical procedures in relatively young women, and has a significant impact on patient quality of life (QoL).<sup>8</sup> Predictive factors for the development of osteonecrosis include cytotoxic drugs, arthritis and, again, corticosteroids.<sup>9</sup> The prevention of osteoporosis and osteonecrosis and a reduction in the use of steroids represent major unmet needs in the management of lupus in order to reduce damage and improve patient QoL.

Thus, strategies for the management of lupus, including the long-term use of corticosteroids, have resulted in affected patients experiencing a range of additional morbidities. Greater understanding of genetic predispositions towards these conditions may assist clinicians in targeting those patients who require more vigorous early treatment in order to achieve greater disease control and improved QoL.

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**THURSDAY 18 APRIL 2013**

## **Plenary I: Lupus manifestations**

### **Getting to the heart of the matter: Improving cardiovascular outcomes Ian N Bruce (UK)**

*In his plenary lecture on cardiovascular disease in patients with lupus, Professor Bruce discussed the roles of inflammation and therapy in driving cardiovascular outcomes, highlighting the significantly increased risk of cardiovascular events in patients with lupus compared with the general population. He considered the limitations of previous therapeutic approaches and discussed novel strategies for the practical management of cardiovascular disease in this high-risk patient population.*

Women with lupus face a significantly increased risk of cardiovascular (CV) disease compared with the general population. Studies have demonstrated a 50-fold increase in the risk of coronary heart disease in 35–44-year old female lupus patients<sup>1</sup> and a substantially higher incidence of stroke.<sup>2</sup> Furthermore, the age of onset of a first coronary event is substantially younger in patients with lupus than in the general population, with the majority of patients experiencing a first event before the age of 55 years.<sup>3</sup> Underlying these events is an earlier development of subclinical atherosclerosis that progresses at an accelerated rate.<sup>4</sup>

#### ***Risk factors for cardiovascular disease***

Of note, use of the Framingham risk score in one study to predict the risk of a first CV event in patients with lupus underestimated the risk by at least a factor of 5.<sup>4</sup> Risk factors for CV disease in female patients with lupus compared with age-matched women in the general population include a higher prevalence of hypertension and diabetes, earlier age of menopause, higher incidence of renal impairment, more sedentary lifestyle, higher waist:hip ratio, and higher levels of very-low-density lipoprotein cholesterol, triglycerides and homocysteine.<sup>5</sup> Furthermore, the prevalence of metabolic syndrome, which is associated with a risk of future CV events, is higher in lupus patients than in the general population, driven by high triglyceride levels, low levels of high-density lipoprotein cholesterol and elevated blood pressure.<sup>6</sup>

Analysis of lupus-related risk factors for CV disease has demonstrated that steroid, azathioprine and cyclophosphamide exposure are associated with increased risks of future CV events in this patient population, with azathioprine and cyclophosphamide exposure probably reflecting more severe lupus phenotypes.<sup>3,4</sup> Whilst higher steroid exposure over time seems to be associated with increased risks for CV disease and metabolic syndrome in lupus patients, robust evidence suggests that hydroxychloroquine provides a protective effect against future damage, including CV endpoints.<sup>6,7</sup>

Lupus is independently associated with endothelial dysfunction;<sup>8</sup> studies have demonstrated impaired flow-mediated dilatation and higher levels of endothelial microparticles, a marker of endothelial damage, in patients with lupus.<sup>9</sup> Of note, suppression of inflammation over time may be associated with an improvement in vascular endpoints in these patients.



### ***Therapeutic management of cardiovascular risk factors***

A number of therapies have been evaluated in randomised, placebo-controlled trials and substudies for their efficacy in reducing CV risk in patients with lupus.<sup>10–12</sup> Whilst studies have demonstrated a trend towards benefit with statin therapy, data remain inconclusive.

In the absence of robust evidence to support a specific therapeutic strategy for CV risk management in patients with lupus, Professor Bruce recommended a target-based approach to each of the individual CV risk factors. Patients with hypertension or elevated levels of low-density lipoprotein cholesterol should be managed using standard approaches, which might include weight reduction, increased exercise, smoking cessation, use of plant stanols, statin treatment and/or antimalarial therapy.<sup>13</sup>

Given the strong association between lupus and premature CV disease, rheumatologists play a key role in promoting the importance of CV risk factor assessment and management in this patient population within the setting of a multidisciplinary team.

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## **Clinical manifestations and evaluation of cutaneous lupus**

***Victoria P Werth (USA)***

*Professor Werth presented a detailed review of the clinical manifestations and diagnosis of cutaneous lupus. She considered the different forms of cutaneous lupus and presented strategies to differentiate these variants from other skin conditions with similar presentations.*

The incidence of cutaneous lupus erythematosus (CLE) is approximately 4.3 per 100,000 of the population and is similar to that of systemic lupus erythematosus (SLE). Most patients with CLE exhibit discoid lupus (DLE; incidence, 3.56/100,000), of whom approximately two thirds have localised DLE and one third generalised disease. Subacute cutaneous lupus (SCLE) is less common (0.63/100,000), whilst lupus panniculitis and bullous lupus occur rarely (0.07 and 0.03/100,000, respectively).<sup>1</sup>

Patients with CLE may meet the criteria for SLE due to dermatological criteria alone, thus not every patient with SLE is sick if their disease resides primarily in the skin.<sup>2</sup> In a Swedish study, 24% of patients with skin-predominant disease met the criteria for SLE at the time of diagnosis and a further 18% were diagnosed with SLE over the next 3 years.<sup>3</sup>

CLE exerts a considerable negative impact on quality of life (QoL) with respect to emotional well-being. In a study in 157 patients, CLE was associated with a similar or greater impact on mental health status compared to hypertension, type II diabetes, recent myocardial infarction and congestive heart failure.<sup>4</sup>

CLE skin lesions can be classified as lupus-specific or non-specific, depending on their histology and clinical–pathological correlation; non-specific lesions may be seen as features of other diseases. CLE can also be categorised into the subgroups, chronic CLE, SCLE and acute CLE.<sup>5</sup> Patients may exhibit more than one form of the disease; thus, in one study, 29% of patients had two types of lupus-specific skin lesion and 3% had three types.<sup>6</sup> Subtyping can be helpful in determining prognosis and appropriate treatment.

### *Chronic cutaneous lupus*

Chronic CLE may present as localised DLE, generalised DLE, hypertrophic DLE, lupus panniculitis or tumid lupus. Direct immunofluorescence of chronic CLE biopsy samples typically shows a granular pattern of immunoglobulin (Ig)G, IgM or complement at the dermal–epidermal junction. Descriptions of the subtypes of chronic CLE are provided in Table 1.

**Table 1. Subtypes of chronic cutaneous lupus**

Subtype	Description
<b>DLE</b>	<ul style="list-style-type: none"> <li>• Associated with erythema, scale, pigmentation, papules, scarring, alopecia</li> <li>• Inflammatory cells are present in the dermis, at the dermal–epidermal junction and around the blood vessels</li> <li>• Vacuolated areas in the basal layer of keratinocytes</li> </ul>
<b>Localised DLE</b>	<ul style="list-style-type: none"> <li>• Number of variant forms occur; acral variant can impact on patient QoL</li> </ul>
<b>Generalised DLE</b>	<ul style="list-style-type: none"> <li>• Carries 20% risk of meeting SLE criteria</li> </ul>
<b>Hypertrophic DLE</b>	<ul style="list-style-type: none"> <li>• Rare variant (2% of CLE patients); associated with scaling and thickened epidermis</li> </ul>
<b>Lupus panniculitis</b>	<ul style="list-style-type: none"> <li>• Associated with inflammation of the fat and overlying DLE-like erythema and scale on biopsy</li> <li>• Patients may develop lipoatrophy, which can be treated by lipoinjection</li> </ul>
<b>Tumid lupus</b>	<ul style="list-style-type: none"> <li>• Typically photodistributed and non-scarring with grey areas where glycans arise between collagen fibres of the dermis</li> <li>• Lack of defining antibodies, absence of inflammation of the dermal–epidermal junction or vacuolisation</li> <li>• Infrequent occurrence of systemic disease</li> </ul>

*CLE, cutaneous lupus erythematosus; DLE, discoid lupus erythematosus; QoL, quality of life; SLE, systemic lupus erythematosus*

### *Subacute cutaneous lupus*

SCLE is typically photosensitive, associated with anti-Sjogren's syndrome antibodies (SSA/SSB) and lower severity than other forms of CLE due to the low incidence of renal or central nervous system involvement. Biopsy of patients with SCLE typically shows less inflammation than other forms of CLE, whilst direct immunofluorescence may identify punctate staining in the epidermis, which is thought to correlate with the presence of anti-SSA/anti-SSB antibodies.

SCLE can be categorised into papulosquamous psoriasiform plaques and annular–polycyclic plaques; the latter may be subcategorised into vesiculobullous annular SCLE and toxic epidermal necrolysis(TEN)-like annular SCLE. The two main variants each present in approximately 50% of patients and both may be identified in the same patient. Unlike other forms of SCLE, bullous lupus is associated with the presence of neutrophils and the formation of bullae at the dermal–epidermal junction; bullae may arise in the mouth and on sun-exposed skin.

A number of medications have been associated with the occurrence of SCLE, including statins, thiazide diuretics, tumour necrosis factor inhibitors, antiepileptics, proton pump inhibitors, angiotensin-converting enzyme inhibitors, non-steroidal anti-inflammatory drugs and antifungals. In a study in 234 SCLE patients with matched controls, 71% of patients had at least one prescription for a suspected drug and more than one third had SCLE attributable to drug exposure that was reversible on drug cessation.<sup>7</sup>

### ***Acute cutaneous lupus***

Acute CLE may be associated with facial malar erythema, crusting, cheilitis, lip and oral lesions, periorbital oedema, photodistributed erythema and bullous or TEN-like lesions. This form of CLE often presents as more severe disease with patients meeting criteria for SLE.

### ***CLE in association with SLE***

Patients with CLE present a spectrum of disease severity, ranging from those with skin disease only (localised DLE, hypertrophic lupus, lupus panniculitis, tumid lupus), who meet the SLE criteria 5% of the time; those with generalised DLE, who meet the SLE criteria 20% of the time; those with SCLE (50%); and those with acute CLE (72%).<sup>6</sup> Approximately 15–20% of patients with SLE have chronic CLE, 10–15% have SCLE and 30–50% have acute CLE.<sup>8</sup> Thus, patients with acute CLE are more likely to have systemic disease and require careful monitoring.

### ***Lupus non-specific skin lesions***

Many forms of non-specific skin lesions are observed in patients with SLE, including several forms of vasculitis, vasculopathies, cutaneous vascular diseases and alopecia; non-specific lesions are typically seen in the active phase of the disease and are associated with increased disease activity.<sup>9</sup> Additional forms of non-specific lupus-related skin lesions can include sclerodactyly, rheumatoid nodules, calcinosis cutis, bullous lesions, urticaria, papulonodular mucinosis, cutis laxa and acanthosis nigricans. Non-specific skin manifestations that are most commonly associated with a worse prognosis in SLE include photosensitivity, alopecia, oral ulcers and Raynaud's disease.<sup>10</sup>

### ***Diseases that mimic cutaneous lupus***

A number of conditions mimic chronic CLE, SCLE and acute CLE (Table 2). Patients with rosacea, dermatomyositis and acute CLE, for example, may all present with malar rash, photosensitivity and positivity for anti-nuclear antibodies. Distinguishing acute CLE from dermatomyositis is particularly challenging, and research is ongoing to develop differentiation criteria.

**Table 2. Diseases that mimic cutaneous lupus**

Form of lupus	Diseases with similar presentations
<b>Chronic cutaneous lupus</b>	
<b>Discoid lupus</b>	<ul style="list-style-type: none"> <li>• Tinea, lichen planus, lichen planopilaris, Jessner's lymphocytic infiltrate, polymorphous light eruption, sarcoidosis, lymphocytoma cutis, lymphoma cutis, granuloma faciale, non-melanoma skin cancer</li> </ul>
<b>Hypertrophic discoid lupus</b>	<ul style="list-style-type: none"> <li>• Keratoacanthoma, squamous cell carcinoma, prurigo nodularis, verruca vulgaris, hypertrophic lichen planus</li> </ul>
<b>Lupus panniculitis</b>	<ul style="list-style-type: none"> <li>• Panniculitic lymphoma</li> </ul>
<b>Tumid lupus</b>	<ul style="list-style-type: none"> <li>• Jessner's lymphocytic infiltrate, polymorphous light eruption, reticular erythematous mucinosis</li> </ul>
<b>Subacute cutaneous lupus</b>	<ul style="list-style-type: none"> <li>• Dermatophytosis, photolichenoid drug eruption, granuloma annulare, figurate erythema, dermatitis, pemphigus foliaceus</li> </ul>
<b>Bullous lupus</b>	<ul style="list-style-type: none"> <li>• Dermatitis herpetiformis (due to similar presence of neutrophils), epidermolysis bullosa acquisita (due to similar reaction to Type VII collagen)<sup>11</sup></li> </ul>
<b>Acute cutaneous lupus</b>	<ul style="list-style-type: none"> <li>• Rosacea, seborrhoeic dermatitis, sunburn, drug-induced photosensitivity, dermatomyositis, pemphigus erythematosis, dermatitis, acne</li> </ul>

### **Diagnosis and treatment of cutaneous lupus**

Skin biopsy and clinical–pathological correlation are important to support a correct diagnosis of CLE and exclude conditions with similar presentations to enable appropriate treatment selection. Direct immunofluorescence to identify immunoglobulins or complement in the skin may also be beneficial to confirm a diagnosis if histological examination has been inconclusive. The involvement of an experienced dermatopathologist should be considered where achieving a correct diagnosis proves challenging. If data suggest CLE, an initial work up should be performed to rule out systemic disease, including complete blood count, urinalysis and testing for anti-nuclear and anti-SSA/anti-SSB antibodies. If initial tests for systemic involvement are positive, patients should be tested subsequently for double-stranded DNA, complement, creatinine and liver function.

The validated Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) was developed in 2005 to support the correct diagnosis of skin involvement in patients with CLE. The CLASI may assist clinicians in identifying appropriate treatments for patients with CLE.<sup>12</sup>

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## Hot topic lecture

### The burden of fatigue in lupus: From patient perspectives to effective management

**Meenakshi Jolly (USA)**

*Professor Jolly discussed the impact of fatigue on patients with lupus, focusing on patient perspectives on fatigue, factors that correlate with the severity of fatigue in lupus and pharmacological and non-pharmacological strategies to support patients in managing their fatigue.*

With improvements in medical management, survival rates in patients with lupus have improved.<sup>1</sup> However, extended survival may come at a cost for patients in terms of quality of life (QoL). A study in patients with chronic diseases showed that the effects of lupus on QoL were similar to those of congestive heart failure and depression, despite the much younger age of lupus patients.<sup>2</sup> Furthermore, a 2004 study demonstrated a poor correlation between patient-reported outcomes for QoL and measures of disease damage and disease activity,<sup>3</sup> suggesting that physicians are focusing on treating the symptoms and manifestations of lupus but not on the effects of those manifestations and treatments.

Lupus affects physical functioning, emotional functioning and social functioning and, particularly, vitality or fatigue.<sup>4-7</sup> Indeed, fatigue is one of the most prevalent symptoms in patients with lupus, with up to 90% of patients reporting fatigue and 50% reporting disabling fatigue.<sup>8</sup> Fatigue also contributes considerably to work disability in this patient population.<sup>9</sup> In a 2010 focus group study, patients reported struggling to avoid lifestyle restrictions as a result of fatigue,<sup>10</sup> whilst 87% of patients completing endorsement questionnaires in a separate study reported frequent pain and fatigue and scored both factors at a level of importance of at least four out of five.<sup>11</sup>

Variables independently associated with fatigue in patients with lupus include sleep, social support, exercise and, particularly, depression.<sup>12</sup> Sleep efficiency is significantly affected in patients with lupus reporting disabling tiredness, with increases in the number of arousals per hour in sleep, the amount of non-restorative sleep and levels of depression.<sup>13</sup> Studies assessing the potential association between disease activity and fatigue have yielded conflicting results but have suggested ethnic differences, with higher levels of fatigue, fibromyalgia and depression in Caucasian compared to African-American or Hispanic patients.<sup>14,15</sup>

A number of psychological interventions have been evaluated for their potential in assisting lupus patients to manage fatigue, including telephone counseling, stress management, cognitive behavioural therapy, expressive writing, exercise interventions, acupuncture, dietary changes and vitamin D therapy. Psychoeducational interventions<sup>16</sup> and exercise programmes<sup>17,18</sup> have demonstrated benefit, with patients reporting lower fatigue scores following the implementation of these strategies. Acupuncture therapy,<sup>19</sup> a low glycaemic index diet<sup>20</sup> and vitamin D supplementation<sup>21</sup> have also been associated with improvements in fatigue.

In terms of pharmaceutical interventions, both abatacept<sup>22</sup> and belimumab<sup>23</sup> have been correlated with improvements in measures of lupus-related fatigue, whilst benefits with dehydroepiandrosterone (DHEA) were inconclusive.<sup>24</sup>

Fatigue remains a common symptom in patients with lupus that arises as a result of multiple causes. Patients should be assessed for depression, pain and sleep, with appropriate referrals where necessary, and should be educated on health behaviours and offered social and psychosocial support from a multidisciplinary care team.

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## State-of-the-art lecture

### T-cell signalling in patients with SLE: What every rheumatologist needs to know!

Liz Jury (UK)

*The interaction between T and B lymphocytes is profoundly dysregulated in patients with systemic lupus. Dr Jury discussed the defects in T cell signalling pathways and alterations in lipid metabolism and glycolipid profiles that contribute to the abnormal molecular interactions in patients with lupus.*

#### *Defects in the T cell signaling pathway in patients with lupus*

In patients with lupus, a multitude of abnormalities have been identified in T and B cell signalling pathways that result in defects in actin reorganisation and cell adhesion, the formation of abnormal immune synapses, and abnormalities in gene expression, cytokine production, proliferation and apoptosis. There is a profound increase in phosphorylation events, an increase in the calcium response to cell signalling, increased expression of signalling molecules, reduced activity and expression of the membrane-bound kinase, LCK, as well as defects in molecules associated with nuclear transcription factors, abnormalities in cytokine-related signalling and defects in lysosomal degradation of signalling molecules.

In addition, a number of metabolic defects have been identified in T cells from lupus patients, including increased mitochondrial mass, altered mitochondrial membrane potential, increased mitochondrial calcium stores and alterations in signalling molecules that control mitochondrial activation. There is also increased oxidation and increased recycling of membrane receptors, including CD3, CD4 and CD1d.

#### ***Alterations in lipid metabolism in patients with lupus***

The plasma membrane is a complex mixture of lipids in which lipid rafts, areas of the membrane enriched in cholesterol and glycosphingolipids, form more stable, ordered regions.<sup>1,2</sup> Lipid rafts play an important role in regulating cell signalling events at the plasma membrane by bringing together functionally related signalling molecules in activated cells and keeping them apart in non-activated cells. Lipid rafts are abnormal in T cells from lupus patients, with increased levels of cholesterol and glycosphingolipids and abnormal signalling and function.<sup>3-5</sup>

T cells can be categorised into three distinct populations based on the level of order of lipids in the plasma membrane.<sup>6</sup> Those cells with high lipid order respond robustly to proliferation and activation and produce anti-inflammatory cytokines; those with intermediate order proliferate a little and produce predominantly pro-inflammatory cytokines; and those with low membrane order are largely anergic. Patients with lupus and rheumatoid arthritis demonstrate larger populations of T cells with intermediate lipid order, associated with the increased production of pro-inflammatory cytokines.<sup>6</sup>

#### ***Invariant Natural Killer T cells and CD1d***

Invariant Natural Killer T (iNKT) cells are a specialised subset of T cells that respond to lipid antigen presented via CD1d, a major histocompatibility complex (MHC)-like molecule on B cells. iNKT cells are able to produce cytokines rapidly after activation by B cells, enabling them to activate other cells of the immune response.<sup>7</sup> The expression and function of iNKT cells are significantly reduced in patients with lupus, associated with defects in the CD1d molecule. In healthy B cells, CD1d is distributed outside the lipid rafts and is associated with the production of anti-inflammatory cytokines, whilst, in B cells from lupus patients, CD1d lies within the lipid rafts and leads to a pro-inflammatory cytokine response.<sup>8</sup>

#### ***Alterations in glycolipid profiles in patients with lupus***

Glycosphingolipids represent an important component of lipid rafts in T and B cells.<sup>3-5</sup> Studies have demonstrated a profoundly altered distribution of glycolipids in T cells from lupus patients, which can influence cell signalling and cytokine production.<sup>9</sup>

Liver X receptor beta (LXR $\beta$ ) is a master lipid regulator molecule that controls glycolipid and cholesterol homeostasis and has been linked to lymphocyte proliferation. Triggering of LXR $\beta$  in healthy T cells leads to a transient increase in glycolipid expression that is quickly downregulated. In contrast, in T cells from lupus patients, the upregulation of LXR $\beta$  is sustained and expression of glycolipids in the membrane is increased, thus altering T cell signalling.<sup>9</sup>

### ***Ongoing research into therapeutic strategies for patients with lupus***

Treatment of T cells from lupus patients with atorvastatin is associated with the inhibition of cholesterol biosynthesis and normalisation of the defective phosphorylation of the signalling molecule, ERK, which leads to a change in lipid expression.<sup>10</sup>

The drug NB-DNJ, which blocks glycosphingolipid biosynthesis and is clinically approved to treat lysosomal storage diseases, is able to normalise the defects seen in T cells from lupus patients *in vitro*, including membrane lipid expression, cell signalling and cell proliferation.

A number of additional established and novel agents that target specific areas of T cell signalling are currently under investigation for their potential efficacy in the treatment of lupus. Research is ongoing to determine whether a common cause contributes to all of the cell signalling abnormalities seen in patients with lupus.

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## **Plenary II: New horizons in the basic science and clinical practice of SLE**

### **Immunopathogenic mechanisms driving SLE**

**Thomas Dörner (Germany)**

*Professor Dörner discussed the immune perturbations that occur in patients with lupus, outlining the disturbances in cytokine homeostasis and the abnormalities in B cell responses that characterise the disease.*

Approximately 45 risk alleles have been identified that seem to be important in driving the pathogenesis of lupus.<sup>1–6</sup> Abnormalities associated with the disease include defects in clearance functions, innate immunity, ligand recognition and receptor signalling, including aberrations in the Fc gamma receptor, C4, C1q, DNase1, three prime repair exonuclease 1 (Trex1) and toll-like receptor 7 (TLR7), all of which have been implicated in disease pathogenesis.<sup>7</sup> Over a period of 10–15 years, and with repeated exposure to environmental factors, genetically predisposed individuals experience recurrent activation of the innate and adaptive immune responses and develop auto-immunity and thence clinical manifestations of lupus.<sup>8</sup>



### ***Immune disturbances in lupus***

Patients with lupus demonstrate disturbed cytokine homeostasis, with increased levels of pro-inflammatory cytokines that correlate with disease activity. Levels of interleukin-6 (IL-6) are increased and drive the differentiation of B cells, in addition to elevated production of IL-21; raised levels of interferon alpha (IFN- $\alpha$ ) lead to increased expression of Siglec-1 on monocytes; and elevated levels of B lymphocyte stimulator (BLyS) correlate with higher immunoglobulin (Ig)G levels and increased anti-double-stranded DNA (anti-dsDNA) antibody titres.<sup>9-14</sup> Whether all patients display the same patterns of these pro-inflammatory cytokines or whether a number of signatures are associated with particular disease variants remains in question; however, patients with enhanced IFN- $\alpha$  production are known to have active disease, characterised by renal involvement, reduced complement levels and the production of anti-RNA binding proteins.<sup>15</sup>

In addition, patients with lupus exhibit enhanced activation of B cells that produce large quantities of immunoglobulins. Cells of the B1 lineage mature quickly into short-lived IgM-producing plasma cells; without strict T cell control, this lineage may enable the emergence of autoreactive immunoglobulins. Cells of the B2 lineage undergo central checkpoints in the bone marrow before differentiating into marginal zone B cells in the spleen, from where they may develop into short- or long-lived plasma cells or memory cells. The emergence of autoreactive B cells and long-standing auto-immune memory is thought to occur in the germinal centres. Following antigen stimulation, T helper cells are induced and B cells activated, and the dark zones of the germinal centres are formed, which are important for B cell clonal expansion and somatic hypermutation. Affinity maturation and immunoglobulin class switching or the selection of autoreactive clones, then take place in the light zone, to form plasma cells, memory cells or apoptotic B cells.<sup>16</sup>

Patients with lupus exhibit additional abnormalities, consistent with over-activation of the immune response. These include the presence of CD95-positive naïve B cells and the expansion of circulating IgD-negative, CD27-negative plasma cells in the peripheral blood, which are also seen in patients with sepsis;<sup>17</sup> these abnormalities correlate with the level of disease activity.<sup>18</sup> A predominance of human leukocyte antigen (HLA)-DR-high plasmablasts is also observed in the peripheral blood and bone marrow, which correlate with elevated anti-dsDNA antibody titres and increased disease activity levels.<sup>19</sup>

Approximately one third of lupus patients exhibit elevated levels of T follicular helper cells, the founder cells for the germinal centres, under the control of the transcription factors Bcl-6, IL-6 and IL-21, in the lymphoid and peripheral organs. The germinal centres are associated with B cell aggregates, leading to the emergence of autoreactive cells that lack proper regulation by T cells and follicular dendritic cells.

### ***B lymphocyte stimulator***

BLyS is expressed by multiple immune cells of the innate and adaptive immune responses, including neutrophils, monocytes, dendritic cells, activated T cells, plasma cells and B cells. It is a member of the tumour necrosis factor (TNF) receptor family and exists in membrane-bound and soluble forms, of which the trimeric soluble protein is the only active form. BLyS binds to the BLyS receptor 3 (BR3), transmembrane activator-1 and calcium

modulator and cyclophilin ligand-interactor (TACI) and B cell maturation antigen (BCMA) receptors and is important for B cell maturation, differentiation and survival.<sup>20–22</sup>

BLyS causes the activation of nuclear factor kappa B (NFκB), leading to the upregulation of anti-apoptotic genes, particularly the transcription factors Bcl-2 and Bcl-x, and blockade of the pro-apoptotic gene, Bim. BLyS is associated with a reduced rate of apoptosis and the possible occurrence of long-standing populations of autoreactive cells in patients with lupus;<sup>23</sup> BLyS signalling is blocked by belimumab.

### ***Persistence of B cell populations following B cell depletion therapy***

Following B cell depletion therapy with rituximab in patients with rheumatoid arthritis, there is a persistence of peripheral plasmablasts, termed steady-state plasmablasts, in the peripheral blood. These steady-state plasmablasts are IgA-positive and express chemokine receptor 10 (CCR10) and the adhesion molecule B7 integrin, which are important for mucosal trafficking.

These data suggest that a population of mucosal B cells in patients with lupus may not be susceptible to rituximab-induced B cell depletion.<sup>24</sup> A greater understanding of such treatment-resistant immune populations and the events occurring in the tissues of patients with lupus is critical if effective disease control is to be achieved.

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## **Biologics in lupus: Clinical practice to clinical trials...and now...**

**David A Isenberg (UK), Joan T Merrill (USA)**

*Professor Isenberg and Professor Merrill discussed clinical trials of biologics in lupus, overviewing the history and development of biologics in lupus, presenting data from pivotal trials, and discussing ongoing challenges in the design and performance of clinical trials in this setting.*

The first use of targeted biologics to treat lupus was attempted 10–15 years ago. Since then, knowledge of the immune response has increased substantially and it is now possible to block many of the key molecules that contribute to immune pathways. Numerous biologics

are now under investigation in the treatment of lupus, most notably abatacept, rituximab, belimumab, epratuzumab and atacicept (not discussed here).

### ***Abatacept***

Abatacept is composed of an Fc region from immunoglobulin (Ig)G1 and the Fab region from the cytotoxic T lymphocyte antigen 4 (CTLA4) molecule. It blocks the link between the antigen-presenting cell and the naïve T cell and has been used in the treatment of both rheumatoid arthritis (RA) and lupus.

A 12-month, placebo-controlled study of abatacept in 175 patients with lupus demonstrated no significant difference in the number of new British Isles Lupus Assessment Group (BILAG) A/B flares between the two treatment groups. However, *post-hoc* analyses demonstrated BILAG A flare in 40.7% of abatacept-treated patients *versus* 54.5% of placebo-treated patients, suggesting some utility for abatacept in patients with non-life-threatening lupus.<sup>1</sup>

### ***B cell depletion therapy: rituximab***

Rituximab is a chimeric monoclonal anti-CD20 antibody that was approved by the US Food and Drug Administration (FDA) in 1997 for the treatment of non-Hodgkin's lymphoma and subsequently demonstrated therapeutic benefit in patients with RA.<sup>2</sup>

Efficacy of rituximab in RA suggested that B cell depletion therapy may also offer benefit in patients with lupus. Fifty patients with active lupus who were poorly- or non-responsive to immunosuppression received rituximab 1 g, cyclophosphamide 750 mg and methylprednisolone 100–250 mg, administered on two occasions 2 weeks apart, to achieve B cell depletion. At 6 months, 42% of patients achieved full remission and 47% achieved partial remission, and treatment was associated with improvements in BILAG score, C3 levels and anti-double-stranded DNA (anti-dsDNA) antibody titres.<sup>3</sup>

B cell depletion with rituximab in patients with lupus is associated with reduced titres of antibodies to DNA, phospholipid, C1q and cardiolipin but no changes in the levels of antibodies to Ro, La, Sm, ribonucleoprotein (RNP), measles and tetanus toxoid. Data also suggest that patients can be treated safely with repeated B cell depletion therapy.<sup>4</sup> Factors associated with a risk of disease flare following B cell depletion include anti-extractable nuclear antigen (ENA) antibody positivity and anti-Sm antibody positivity, whilst low baseline serum C3 is correlated with faster time to flare.<sup>5</sup>

### ***Clinical trials of biologics in lupus: challenges in trial design***

Over the last two decades more than 40 clinical trials of biologics, including rituximab and abatacept, have failed to meet their primary or secondary endpoints, principally due to the concomitant administration of high doses of background medications.

In the phase III BLISS-52 trial of belimumab, patients received reduced doses of background medications and the trial demonstrated a higher degree of discrimination between belimumab and placebo treatment, with significant differences between the active and control arms.<sup>6</sup> Similarly, the phase II EMBLEM trial of epratuzumab imposed strict criteria

regarding background medication and demonstrated a greater difference between active and placebo treatment, such that the primary endpoint was met.<sup>7</sup>

A trial design is currently under investigation where background immune suppression is stopped on study entry in order to achieve low response rates in the placebo group and avoid clouding of the trial results; on experiencing flare, patients become permanent non-responders and can be re-started on immune suppressants.<sup>8</sup> Of note, data from the rituximab<sup>9,10</sup> and belimumab<sup>11</sup> trials have demonstrated that, in subsets of sicker patients, use of background medications does not impede the ability to observe efficacy benefits with active *versus* placebo treatment and can be continued.

Recent trials have also assessed the efficacy of biologics in minimising requirements for corticosteroids.<sup>12,13</sup> Administration of rituximab to patients with lupus in one study was associated with complete remission in 78% of patients with new or relapsing lupus at 37 weeks, and only 2 of 50 patients required oral steroid therapy after 2 years.<sup>12</sup>

A number of patient-related factors, including anti-dsDNA antibody positivity and circulating levels of B lymphocyte stimulator (BLyS), are currently under investigation in clinical trials for their potential to predict target patient populations for biologic therapies.<sup>14,15</sup> Such trials are in their infancy but highlight the increasing sophistication of clinical trials in lupus.

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## SUMMARY

The Second Meeting of the Lupus Academy provided useful insights into the biology and management of lupus and covered a wide range of topics that are integral to clinical practice and research in the field of lupus and allied diseases.

Our knowledge of the genetics of lupus is growing; advances in gene identification and increased understanding of the genetic basis of this disease are enhancing our awareness of disease pathways in specific global populations. In the future, the development of more precise disease classification criteria that incorporate both serological parameters and molecular information will gain increasing importance to support the development of accurate diagnostic tools that promote individualised and cost-effective treatment decision-making.

Survival rates have improved substantially for patients with systemic lupus; however, life expectancy remains low for this largely young patient population, with low rates of prolonged disease remission and increasing levels of disease- and treatment-related damage. Cardiovascular (CV), neurological and musculoskeletal disease, often related to the use of corticosteroids, account for a significant proportion of the damage in lupus and are associated with considerable morbidity and mortality. Reduced usage of corticosteroids represents a major unmet need in order to reduce morbidity and improve quality of life (QoL) for patients with lupus.

Patients with lupus face a significantly increased risk of CV disease compared with the general population, despite the young age at disease onset. Lupus is independently associated with endothelial dysfunction, whilst higher steroid exposure over time is associated with increased risks for CV disease and metabolic syndrome. Stringent CV risk factor assessment and management from a multidisciplinary care team are critical in order to minimise the risk of premature CV morbidity and mortality in these young patients.

Cutaneous lupus exerts a considerable negative impact on patient QoL with respect to emotional well-being. A number of variants of cutaneous lupus exist and patients may exhibit more than one form of the disease across a wide spectrum of disease severity. A number of conditions closely mimic the subtypes of cutaneous lupus, which presents particular challenges to clinicians. Accurate diagnosis of cutaneous lupus is crucial in order to develop an accurate prognosis and identify appropriate treatments and monitoring requirements.

Fatigue is one of the most prevalent symptoms in patients with lupus, contributing to work disability and imposing lifestyle restrictions on affected patients. Sadly, data suggest that physicians are focusing on treating the manifestations of lupus but not on the effects of those manifestations and their treatments on patient QoL. Patients should be educated on health behaviours and offered social and psychosocial support in order to minimise the impact of their fatigue on daily life.

Defects in cell signalling, and particularly in T and B lymphocyte interactions, play an integral role in influencing the immunopathogenesis of lupus and affect a diverse range of pathways, including metabolic processes and nuclear transcription factors. Membrane lipids are known to be defective in lymphocytes from patients with lupus, due to dysregulated glycosphingolipid expression and function, and research is ongoing to determine the impact of such defects on cell signalling abnormalities in these patients. In recent years, signalling molecules and lipids have become a focus of scientific research in lupus. This has resulted in the development of novel therapies for the treatment of lupus and also the evaluation of existing agents that target signaling molecules and lipids, such as statins.

Patients with systemic lupus demonstrate a range of immunological disturbances, including defects in cell clearance, innate immunity, ligand recognition and receptor signalling. Over time, and with repeated exposure to environmental factors, genetically predisposed individuals experience recurrent activation of the innate and adaptive immune responses and the development of auto-immunity. Levels of pro-inflammatory cytokines are substantially increased, activation of B cells is enhanced and rates of apoptosis are reduced,

with the subsequent emergence of long-standing populations of autoreactive B cell clones and auto-immune memory.

Numerous biologic therapies are currently under investigation for the treatment of lupus, including abatacept, rituximab, belimumab and epratuzumab. Sadly, many potentially effective treatments for lupus have failed to meet their primary or secondary endpoints in clinical trials, largely due to the co-administration of high doses of background steroids and other medications. Contemporary trials are imposing strict criteria with regard to the usage of background medications in order to avoid the clouding of trial results by background noise. Early studies are also evaluating patient-related factors for their potential to identify patient populations most likely to benefit from specific treatments, which, if successful, could support more effective, tailored treatments for patients with lupus.

## CONCLUSIONS

The Second Annual Meeting of the Lupus Academy was extremely successful. The vast majority of delegates who provided feedback (>95%) rated the quality and educational content of the presentations very highly. The interactive workshops were particularly enjoyed and the delegates valued the independent nature of the meeting and the absence of commercial bias. Many delegates considered that the programme content offered the potential to lead to positive changes in their clinical practice, with the presentation and interactive discussion of cutting-edge data from leading global experts and researchers.

The Third Annual Meeting of the Lupus Academy is planned to take place on 7–9 March 2014 in the Maritime Hotel, Berlin. The programme for the 2014 meeting will be based on delegate feedback following the Second Annual Meeting and promises to build on the foundations created in Barcelona and Buenos Aires to support us in striving to improve patient outcomes in SLE.