Inaugural Meeting of the Lupus Academy

Fira Palace Hotel, Barcelona, Spain
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Meeting Report

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INTRODUCTION

The Lupus Academy is a long-term initiative committed to improving patient outcomes in SLE 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.

The inaugural meeting of the Lupus Academy was held in Barcelona, Spain, in March 2012, with the goal of reviewing and discussing insights into advances in global research and clinical practice in lupus and associated diseases. It marked the beginning of a long-standing initiative to communicate, educate, and treat patients with lupus.

The scientific programme, developed by a Steering Committee of six international experts, was intended to provide a highly interactive forum through which information and experiences about the management of lupus across Europe could be exchanged. The meeting was attended and well-received by approximately 300 healthcare professionals from 30 countries.

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

SATURDAY 17TH MARCH 2012

B cells and Biomarkers

B cells in the Pathogenesis of Lupus: *Claudia Mauri (UK)*

Professor Mauri's presentation provided some basic science insights into the role of regulatory B cells in the pathogenesis of SLE, highlighting the importance of distinguishing suppressive from pathogenic B cells, when targeting therapy to further improve patient care.

B cells have different pleiotropic roles in the immune system. Beyond their capacity to produce antibodies, B cell subsets can produce either pro- or anti-inflammatory cytokines, similar to the way that different T cell subsets produce different cytokines. A third subset of B cells (regulatory B cells, Bregs) produce the powerful anti-inflammatory cytokine IL-10, which together with TGF-β, inhibits harmful immune responses.[1] This important finding has contributed to the understanding of autoimmune diseases and to the development of new therapeutic strategies; agents that affect B cells may have far-reaching consequences for other parts of the immune system.

Regulatory B cells are contained within the mature B cell subset, whereas IL-10-producing B cells are part of the immature B cells group. When T cells are stimulated with anti-CD3, they spontaneously upregulate IFN-δ and TNF-α, but this is inhibited by 50% when they are cultured with immature B cells, suggesting that they have acquired a suppressive capacity and can dampen inflammation via a cascade reaction.[2]

Although the immune response varies among patients with SLE, depletion experiments indicate that B cells may be defective in this disease. Expression of the B cell surface marker CD1d, which presents lipid antigens via invariant natural killer T (iNKT) cells, is reduced in immature B cells of patients with SLE. The number and function of iNKT cells is also reduced in these patients. SLE iNKT cells do not proliferate in response to lipid stimulation through the glycolipid α-galactosylceramide (α-GalCer) and IL-2 pathway,[3] and the rate of CD1d internalisation on Bregs is increased in patients with SLE. The iNKT and CD1d defects were reversed in patients with SLE who had good clinical response to the anti-CD20 agent rituximab.

Biomarkers in SLE: *Matthias Schneider (Germany)*

Professor Schneider's presentation highlighted the complexity of biomarkers in SLE and the importance of viewing these biomarkers as a small part of the overall diagnostic picture that supports the physician's clinical investigation.

New biomarkers are being identified and researched continually. Proteomic studies have identified proteins involved in the pathogenesis of lupus nephritis, and how protein expression is altered in patients with SLE.[4] The importance of monitoring changes in biomarkers over time is highlighted in several studies.[5, 6] Early clinical response to immunosuppressive therapy was the best predictor of good long-term renal outcome in the Euro-Lupus Nephritis Trial,[5] while chemokine monocyte chemoattractant protein-1 (MCP-1) increased in patients with inflammatory glomerulopathies,[6] the levels increasing as early as two to four months before renal flares occured.

Improved clinical validation in randomised clinical trials is essential for biomarkers to be used in future studies. Anti-C1q antibodies have been omitted from the new SLICC criteria for SLE, but their importance as prognostic indicators in lupus nephritis has been clearly demonstrated. In combination with C3 and C4, anti-C1q antibodies provide the best biomarker for predicting renal flares. Brain antibodies have also been identified as biomarkers for disease activity in patients with CNS manifestations of SLE and some of these have been associated with an increased future risk of intracranial thrombosis and lupus psychosis.[7] Interferon-regulated chemokines have been identified as biomarkers of SLE disease activity and careful monitoring can assist in clinical decision making. Serum biomarker signatures have been identified that identify patients with SLE and can predict its severity.[8]

Prognostic Insights in Lupus Nephritis

End-stage Renal Disease in SLE: *Liz Lightstone (UK)*

Dr Lightstone reviewed the histological and clinical characteristics of poor prognostic lupus nephritis, while highlighting the importance of early diagnosis and treatment, blood pressure control and end stage renal failure (ESRF) prevention strategies.

Although the 5-year mortality of patients with lupus nephritis has declined dramatically since the 1970s, the proportion of patients reaching ESRF within 5 years remains at around 7−8%. Preventative strategies are important; patients with lupus nephritis need prompt diagnosis, effective treatment to induce response and prevent flare, stringent control of their blood pressure and monitoring for the signs of proteinuria.

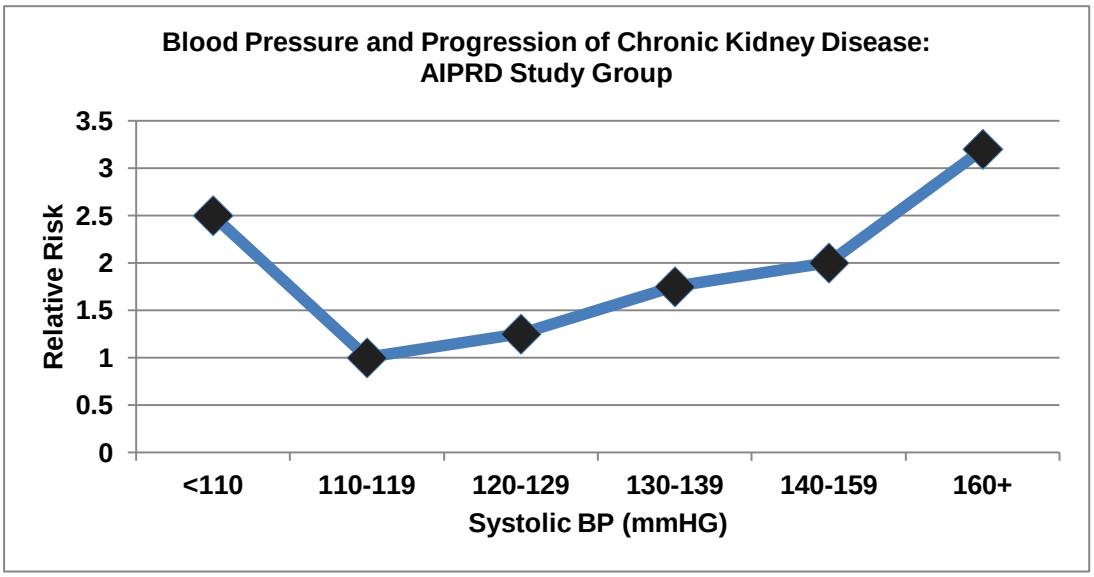
Monitoring of Proteinuria

Proteinuria should be measured using the protein:creatinine ratio (PCR) rather than 24-hour urine collections. If creatinine levels are over 100 mg, the patient should undergo a renal biopsy to determine the class of nephritis, assess glomerular lesions, determine the degree of tubulointerstitial damage and inflammation, and determine the presence of vascular involvement and/or antiphospholipid syndrome.

Once diagnosed, lupus nephritis is usually treated with either mycophenolate mofetil (MMF) or pulsed cyclophosphamide in conjunction with steroids (steroids should not be used alone: they are the main cause of long-term damage in patients with lupus). Hydroxychloroquine can be added to prevent flare. Maintenance with azathioprine or MMF is required for at least 3 years.

Control of Blood Pressure

Control of blood pressure is also very important in patients with lupus nephritis. There is clear correlation between the risk of ESRF and increasing blood pressure (*see Figure*). Stringent control using angiotensin blockade is necessary to achieve a target of 130/80 mmHg in patients with a PCR of <100, and a target of <125/75 in patients with PCR >100.



In a meta-analysis of 11 studies including 1800 patients with non-diabetic kidney disease, there increased risk of chronic kidney disease (CKD) progression with increased blood pressure.[9] AIPRD, ACE inhibition of progressive renal disease.

Chronic kidney disease is the strongest predictor of cardiovascular disease (CVD) and is a major cause of death. Lupus patients are at increased risk of CVD, and their CKD contributes to this risk. Cardiovascular risk factors should be treated aggressively in these patients, bearing in mind that impaired renal function may affect the choice of drugs available. NSAIDs should be avoided.

Patients with very severe disease and rapid progression, poor prognostic lesions, recurrent flares, treatment-resistant disease and children are likely to have poor outcomes. Treatment-resistant disease occurs in those with severe disease and leads to accrual of damage.

Management of Membranous Lupus Nephropathy (MLN): *Chi Chiu Mok (Hong Kong)*

Dr Mok highlighted the importance of improving prognosis in MLN through greater understanding of the prevalence of MLN in patients with lupus nephritis, differences in clinical and histological features of MLN (vs. SLE) and evidence-based treatment options for MLN.

The histological classifications of lupus nephritis have evolved over the last 40 years. Membranous lupus nephritis is an uncommon histological class of lupus nephritis, which accounts for 8–20% of all biopsy-confirmed lupus nephritis cases. Renal biopsy reveals either spike-like projections from the basement membrane, patent capillary loops and no evidence of endocapillary proliferation, or mild mesangial proliferation with patent capillary loops and slight thickening of the basement membrane.[10]

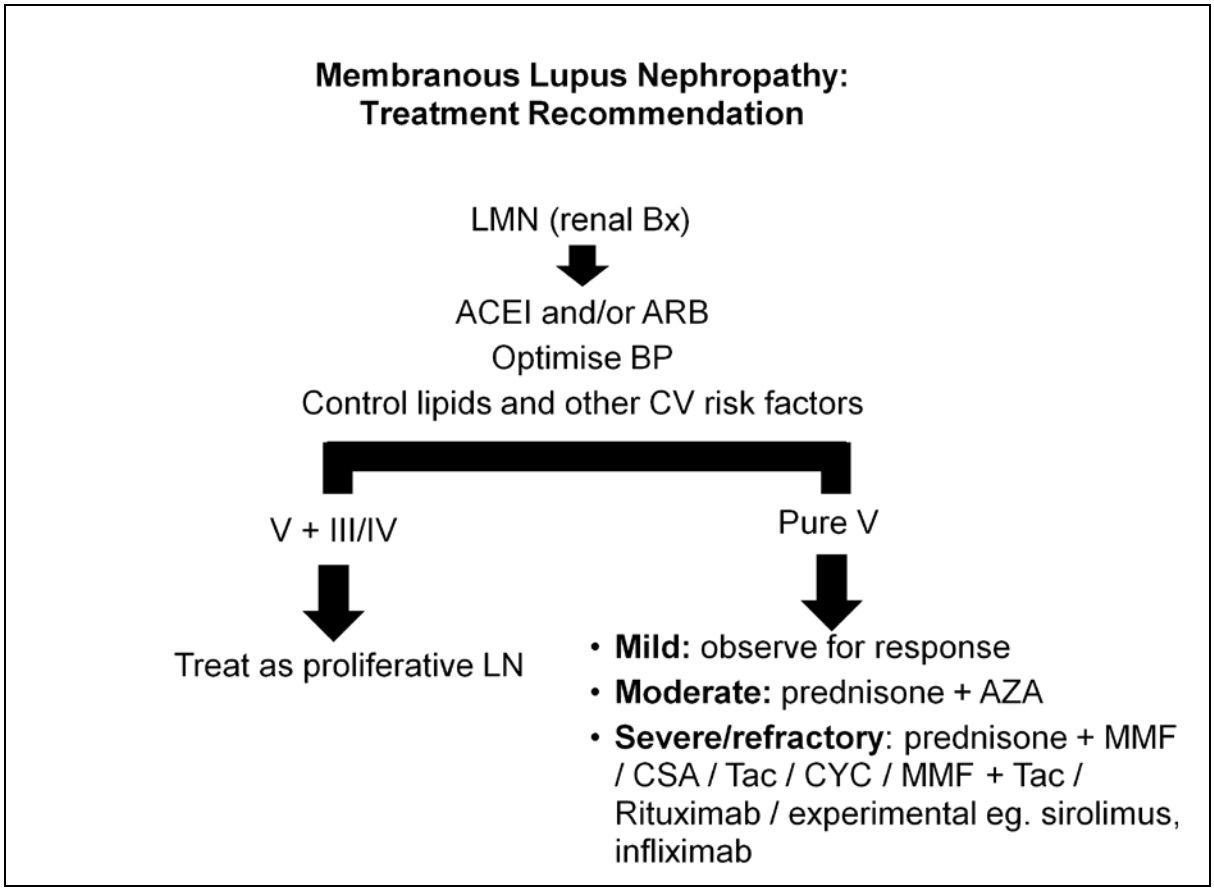
Clinically, MLN occurs in 31–100% of patients with nephrotic syndrome. Comparing MLN with proliferative disease, patients with MLN are more likely to have severe proteinuria and nephrotic syndrome, better renal function, lower anti-DNA titres, normal complement levels, lower SLE Disease

Activity Index (SLEDAI) scores, and they are less likely to have extra-renal manifestations of arthritis.[11] Fewer patients with MLN achieve remission in the first 6 months of treatment than patients with proliferative disease because patients with MLN respond more slowly to therapy.

Adverse prognostic features for MLN include higher serum creatinine at presentation, the presence of proliferative lesions, and persistent, nephrotic-range proteinuria despite treatment. Patients with MLN have a higher risk of venous and arterial thrombosis.

The probability of remission in patients with MLN at 12 months is highest in patients treated with prednisone (1 mg/kg qad) + cyclosporin A (5 mg/kg/day).[12]

A number of open-label, uncontrolled studies have provided insights into various treatments for MLN, perhaps the most interesting being the use of rituximab + cyclophosphamide (CYC), which improved proteinuria and serology compared to mycophenolate mofetil (MMF) + steroids.[13-21] The conclusion from studies to date is that MMF is the therapy of choice, having equal efficacy and less toxicity when compared with CYC.



ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; AZA, azathioprine; CSA, cyclosporine A; CYC, cyclophosphamide; MLN, membranous lupus nephropathy; TAC, tacrolimus

Renal Microangiopathy and Antiphospholipid (APS) Syndrome in Lupus: *Maria Tektonidou (Greece)*

Dr Tektonidou presented the clinical characteristics of APS-associated nephropathy (APSN) and highlighted the importance of the pathologists' awareness of APSN in patients with SLE as well as the therapeutic management of APSN.

Kidney involvement in APS has been poorly recognised. Thrombotic microangiopathy (TMA) is the most commonly-described intra-renal vascular lesion in primary APS and SLE-APS. Characterised by the presence of fibrin thrombi in the glomeruli and/or arterioles and the absence of inflammatory cells or immune complex deposits, TMA has no association with lupus nephritis. The most common lesion among patients with APS is fibrous intimal hyperplasia, in which myofibroblastic intimal cellular proliferation leads to fibrous intimal hyperplasia of the interlobular arteries and branches of the kidney. The most common clinical manifestations are hypertension, renal insufficiency, proteinuria and microscopic haematuria. Non-inflammatory renal TMA is associated with lupus anticoagulant and with higher morbidity from thromboembolic events.

Antiphospholipid Syndrome-associated nephropathy occurs in 23% of patients with SLE who demonstrate biopsy-proven renal involvement with the presence of antiphospholipid antibodies (aPLAs), in addition to, and independently of, lupus nephritis.[22] Patients with APSN have a higher incidence of hypertension, raised serum creatinine levels and progression of histologic lesions, although it does not predict renal insufficiency and end stage renal failure (ESRF) in long-term follow up.

The need for additional anticoagulation therapy in patients with definite APS (primary or SLE-APS) has not been evaluated in prospective clinical trials, but should be considered in patients with an aPLA profile which is persistently positive for anticardiolipin antibodies in medium-high titres, is positive for lupus anticoagulant, and is triple-positive for lupus antigen + anticardiolipin + anti-β2-glycoprotein I (β2GPI). Additional anticoagulation therapy should also be considered for patients with coexistent manifestations associated with APS, including thrombocytopenia, livedo reticularis, heart valve disease, epilepsy, and for those with adverse renal pathology.

Renal pathologists should be aware of the histological characteristics of APSN when they examine kidney biopsies of patients with SLE. Where APSN lesions are apparent, aPLA testing is recommended.

Treatment Challenges in Antiphospholipid Syndrome (APS)

Clinical Features and Pathogenesis of APS: *Munther Khamashta (UK)*

Professor Khamashta presented the key clinical and laboratory classification criteria for APS before describing both obstetric and thrombotic manifestations of APS and reviewing data that support treatment decisions for APS.

Antiphospholipid Syndrome is caused by the autoimmune production of antiphospholipid antibodies (aPLAs). The major clinical features of APS are recurrent arterial and venous thrombosis, recurrent pregnancy loss, thrombocytopenia, and livedo reticularis. Stroke, seen in 20% of patients with APS, and miscarriage are the major manifestations. Other features include leg ulcers, transverse myelitis, headache, chorea and epilepsy, cognitive disorders, heart valve lesions, haemolytic anaemia, and pulmonary hypertension. It is not known how aPLAs cause these clinical manifestations, but thrombosis is likely to be involved in the pathogenesis. Anticoagulants can be effective and biopsies

from leg ulcers indicate the presence of thrombotic microangiopathy, similar to that observed in the renal biopsy of patients with APS-associated nephropathy (APSN).

Clinical diagnosis of APS requires the presence of vascular thrombosis (venous, arterial or small vessel), or pregnancy morbidity (defined as either at least three consecutive miscarriages (<10 weeks), or at least 1 foetal death (<10 weeks), or at least one premature birth (<34 weeks due to severe pre-eclampsia / placental insufficiency). To confirm the diagnosis of APS, laboratory tests for lupus anticoagulant, anticardiolipin antibodies and β2GPI are required.

Many of the manifestations of SLE result from APS. Treatment of these patients with anticoagulants will be more effective than treatment with immunosuppressing agents. Very few patients with APS go on to develop SLE. Among patients with SLE, 30–40% are aPLA positive, and of these around half will develop APS over 10 years.[23]

Antiphospholipid Syndrome is the most common treatable cause of pregnancy loss. Fifteen percent of women suffering miscarriage in the first trimester will have aPLAs. Thirty percent of women suffering pregnancy loss in the 2nd or 3rd trimester have aPLAs, and for those who have intrauterine growth restriction or stillbirth, 40% are aPLA-positive. However, treatment with anticoagulants leads to successful pregnancy outcomes in 90% of cases.

Stroke is the most common neurological complication of APS, with one in five strokes in people <45 years old due to aPLA. Among patients with CNS lupus, aPLAs were significantly associated with cerebrovascular accident, epilepsy and headache.

Treatment of APS must consider patients who are aPLA-positive, and who have recurrent thrombosis, thrombocytopenia, or pregnancy loss. It is unclear why some patients have thromboses but not pregnancy loss, or vice versa, and as many as 70% of people with aPLAs are asymptomatic, but it is essential to understand the aetiology to provide optimal treatment. It appears that aPLA alone is not sufficient to cause the clinical manifestations of APS, and a potentiating factor is required. Potential candidates are infection, surgery, smoking, oral contraceptives, pregnancy, and air travel.

Data now suggest that the antibody profile in patients with APS is important, specifically the combination of anticoagulant, anticardiolipin and β2GPI antibodies present in individual patients. Patients who have all three antibodies can be considered high risk for thrombotic events.

Treatment

Immunosuppressive drugs plus steroids do not protect against recurrent thrombosis in APS. The current treatment to prevent recurrent thrombosis is long-term warfarin; for a first venous event, the INR should be between 2.0 and 3.0. For a first arterial event, or for recurrent thrombosis, the INR should be 3.0–4.0, and in all cases treatment should be continued even if the patient becomes aPLA negative. For patients who have recurrent thromboses despite warfarin treatment, various options have been suggested, mainly adding other therapies such as antiplatelet therapy (low-dose aspirin/clopidogrel), immunosuppressive drugs, statins, hydroxychloroquine, low molecular weight heparin, or rituximab. Other potential strategies include haematopoietic stem cell transplantation (HSCT), or the use of new oral direct anticoagulants such as dabigatran and rivaroxaban.

Thrombocytopenia is not rare and mostly mild, not requiring intervention. Bleeding is uncommon in these patients and it is important not to stop warfarin therapy because low platelet counts do not protect against thrombosis. Careful monitoring is advocated for mild-moderate thrombocytopenia, and corticosteroids are recommended for severe cases.

Aspirin and/or heparin are recommended for aPLA-positive women, depending on their obstetric history.[24] For the 10–15% of women for whom these regimens fail, low dose steroids or other immunosuppressive drugs can be given together with heparin and aspirin.

Improving CV, CNS and Pregnancy Outcomes in Patients with SLE

Assessing Cardiovascular Morbidity in SLE: *Ian Bruce (UK)*

Professor Bruce presented the CV risk profiles of patients with SLE, highlighting the importance of careful assessment of risk factors, targeted approaches to risk factor modulation and the cardioprotective effects of antimalarial drugs.

Cardiovascular risk is significantly increased in patients with SLE, with over 50% of first coronary events occurring under the age of 55 years. Young women with SLE have 50 times the risk of myocardial infarction (MI) than young women without SLE. These women already have a significant burden of subclinical atherosclerosis.

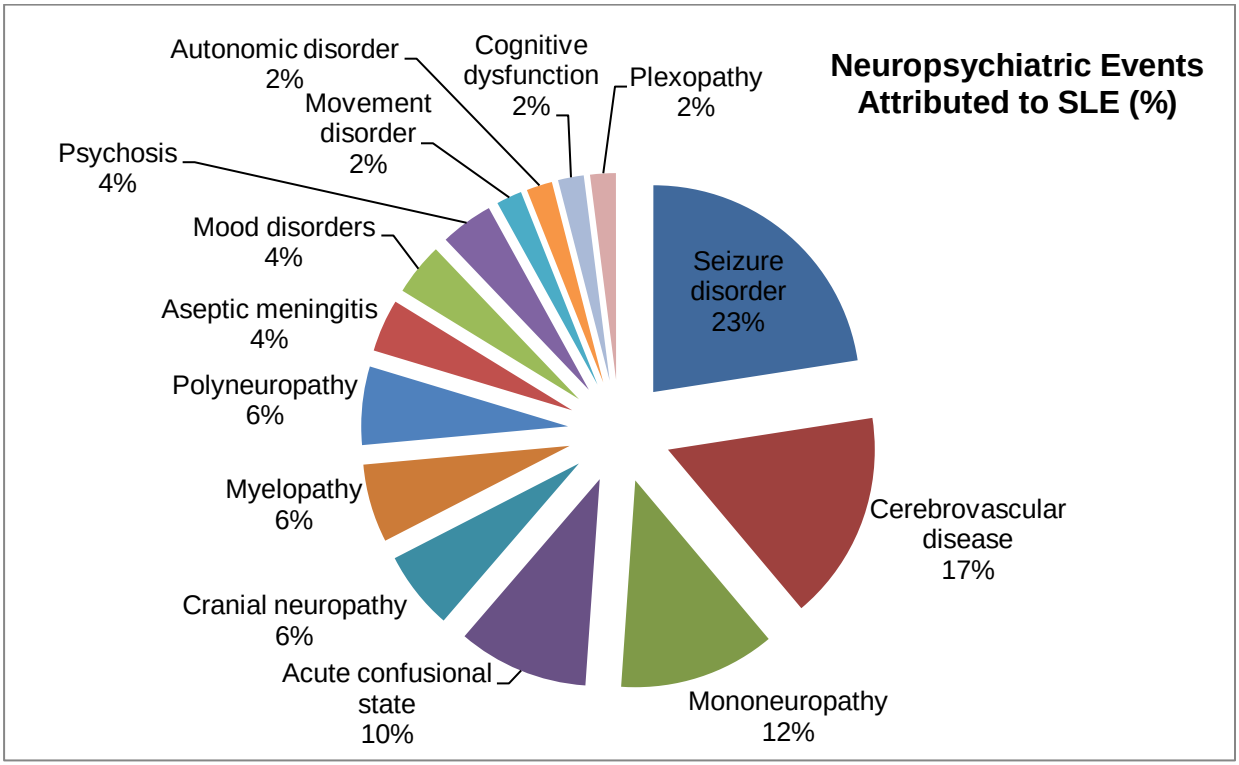
There is an increased prevalence of both classic and metabolic risk factors for MI in patients with SLE, including hypertension, hyperlipidemia, and a family history of coronary heart disease. Persistent lupus activity contributes to the risk, as does menopause, which is occurs earlier in women with SLE. Patients with SLE are more likely to be insulin-resistant with an adverse metabolic profile.

Steroid exposure may adversely affect lipid parameters, but antimalarial drugs reduce triglyceride and lipoprotein levels and patients appear to accrue less CV damage over time when treated with these agents. Active disease is also associated with increased risk of developing carotid plaque, and there is some evidence that antiphospholipid antibody drives atherogenesis directly. Use of biological therapies as anti-inflammatory agents reduces risk only in those patients who respond to treatment. Patients with SLE also have reduced ability to produce endothelial progenitor cells to repair ongoing damage.

Instruments to Measure Outcomes of Neuropsychiatric (NP) Manifestations of SLE: *John Hanly (Canada)*

Professor Hanly presented the broad classification criteria for NPSLE, before reviewing outcome measures for individual and global events and the impact of these on patient quality of life (QoL).

Reliable measures exist to record the clinical outcome of NP events in patients with SLE from both the physician and patient perspective. The Neuro-Psychiatric Systemic Lupus International Collaborating Clinics (NP-SLE SLICC) Study has now enrolled 1800 patients with early SLE, 30% of whom have one of the 19 NP manifestations described in the ACR case definitions; further analysis suggests that one-third of these events may be due to SLE (*see Figure*).[25]



Neuropsychiatric events resulting from autoimmune and inflammatory disease activity may be reversible, but those resulting from damage caused by disease activity are likely to be irreversible. Both impact on the patient's quality of life.

Potential outcome measures of NP events include clinical assessment, biomarkers and neuroimaging. There are many well-validated instruments for measuring clinical disease activity in SLE, including SLE Disease Activity Index (SLEDAI), Systemic Lupus Erythematosus Activity Measure (SLAM), British Isles Lupus Assessment Group (BILAG), European Consensus Lupus Activity Measurement (ECLAM) and others, which require attribution of the NP event to SLE. The NP event must occur within Day ten and Week four of assessment. The only validated index of damage is the SLICC/ACR damage index, which measures irreversible change not due to active inflammation, and attribution of NP events to SLE is not required. The NP event must have occurred since diagnosis of SLE and persisted for at least 6 months.

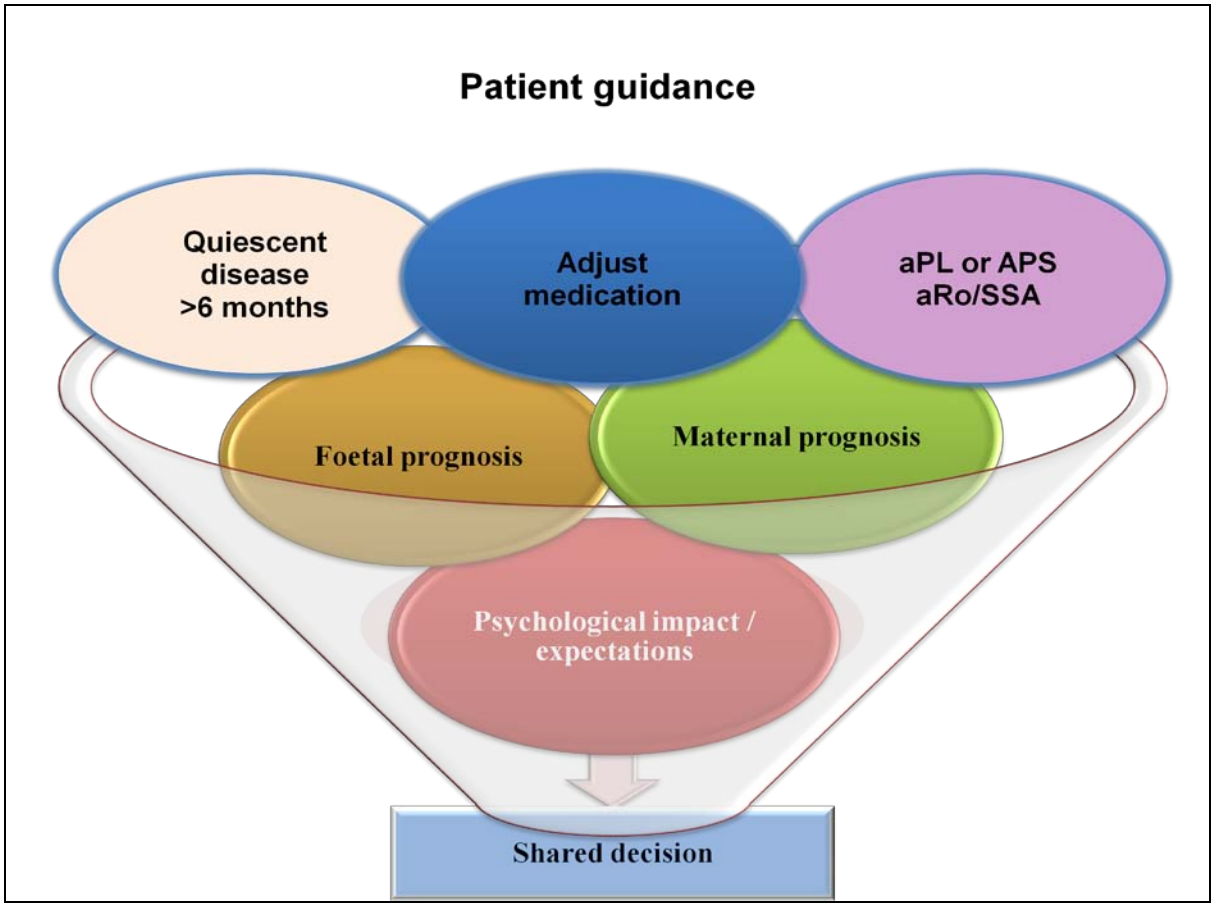
Events can be assessed by physicians using a Likert scale, which can distinguish between resolution of events attributable to SLE and those that are not. Patients completing modified Short Form (SF)-36 rating scales provide further assessments, and there is good correlation between the two.

Cognitive impairment can be used as a global outcome measure for brain function. Patients with SLE have a higher frequency of cognitive impairment, which may fluctuate over time. Patients who have had an NP event have gradual deterioration in their cognitive function over time, while patients who do not experience NP events remain stable for cognitive function.

Pregnancy in SLE: *Roger A. Levy (Brazil)*

Professor Levy highlighted the importance of preconception counselling, medication timing and clear communication between the physician and the pregnant patient with lupus for a successful pregnancy. Several other important characteristics were presented to differentiate between and normal pregnancy and lupus pregnancy.

Pregnancy can affect, and be affected by, rheumatic diseases. Although considered a Th2-predominant state, several Th1-related cytokines are vital to early pregnancy. The effect of pregnancy on SLE is unpredictable, but using improved treatment and biomarkers, and with careful timing and clinical management, most women with SLE can now have safe and successful pregnancies.



aPL, antiphospholipid; APS, antiphospholipid Syndrome; aRo; anti-Ro; SSA, Sjoren's Syndrome antibodies

Pre-conception counselling is recommended for women with SLE. Planning pregnancy to occur after 6 months of remission, particularly avoiding periods of active nephritis, CNS manifestations, and pulmonary hypertension, is advised. Women should wait for 2 years post-diagnosis, and for 2 years post-stroke before trying to conceive.

Patients want to know which drugs are safe for them to use during pregnancy and breastfeeding, and how pregnancy will affect their disease. Drugs that should be avoided include cyclophosphamide, methotrexate, leflunomide, mycophenolate mofetil, and bisphosphonates. Hydroxychloroquine, azathioprine, and low-dose steroids are all safe for use during pregnancy and breastfeeding. Oral contraceptives do not increase the risk of flare in SLE, and a systematic review has suggested that the benefits outweigh the potential risks. An intra-uterine device (IUD) may be the ideal option for women with SLE and antiphospholipid Syndrome (APS) who require long-term contraception.

SLE flare occurs in 10–30% of women who conceived while in remission. However many common signs of mild-to-moderate lupus flares, especially fatigue and musculoskeletal complaints, are frequently observed in normal pregnancy. Those flares that do occur are mostly mild and occur in the third trimester. They are positively predicted by active nephritis or CNS disease at the time of conception, recent flares or withdrawal of antimalarial drugs. A history of previous episodes of nephritis increases the risk of pre-eclampsia, foetal loss and pre-term delivery,[26] requiring careful follow-up of high-risk patients.

The probability of the neonate developing SLE is around 2%, and is predicted by the presence of maternal anti-Ro (aRo) antibodies. As congenital heart block (CHB) is also a risk in pregnant women with SLE, echo Doppler imaging of the foetal heart is recommended every 1−2 weeks from 18 weeks of pregnancy. The prevalence of CHB in babies carried by women with SLE is 2%, mortality is high, and pacemakers will be required in 65–100% of infants, with 10% requiring a heart transplant.

Risk factors for pregnancy loss in first trimester lupus pregnancies include proteinuria, APS, thrombocytopenia, hypertension and poor treatment adherence.

Complications of pregnancy in patients with APS include recurrent foetal loss, intra-uterine growth restriction (IUGR), foetal distress, premature rupture of membranes (PROM), infertility and IVF failure. Thrombo-embolism is increased five-fold due to both changes in levels of clotting factors and mechanical factors. These patients should be closely followed, with treatment depending on previous thrombotic history (*see Table*).[27-29]

All patients (control risk factors):	**Close foetal and maternal surveillance Peripartum THROMBO PROPHYLAXIS!**
aPLA (+) no past history	General care or LDA (start before conception)
OB APS: Early miscarriages	LDA If fails: LDA + LMWH (prophylactic dose)
OB APS: foetal losses	LDA + LMWH (prophylactic dose) If fails: LDA + LMWH (full dose) If fails: Add IVIG
APS with previous thrombosis	LDA + LMWH (full dose) – may use Coumadin from 12th week gestation. If fails: Add IVIG

aPLA, antiphospholipid antibody; APS, antiphospholipid Syndrome; IVIG, intravenous immunoglobulin; LDA, low-dose aspirin; LMWH, low molecular weight heparin; OB, obstetric

SUNDAY 18TH MARCH 2012

Treating Lupus: Old and New Treatments and Ethnic Considerations

Trial Design (Success Arises From Failure): *Richard Furie (USA)*

Professor Furie presented the challenges of SLE clinical trial design, highlighting how various issues have been addressed and touched on how to identify opportunities to improve the designs and outcomes of future clinical trials in SLE.

Clinical trials in SLE have faced several challenges, underscoring the importance of stringent patient selection criteria and endpoints. Early trials required only a history of measurable antibody, but not necessarily at baseline or at screening. Therefore a sizeable proportion of the study population was clinically active but serologically negative. Although endpoints of change in SLE Disease Activity Index (SLEDAI) or time to first flare were not met in these early trials, post-hoc analyses demonstrated significant clinical efficacy in patients with serologically active disease. Background therapies also present problems when designing a trial. Both steroids and immunosuppressive agents have an effect, but there is no consensus on whether they should be tapered during the study, and if so, what the schedule should be.

The entry criteria were therefore modified in all subsequent trials to include patients with both clinically and serologically active disease. The introduction of a more stringent efficacy measure known as the SLE Responder Index (SRI), and implementation of progressive restrictions on background medications throughout the study

Finally, there may be regional safety differences, for example the rates of opportunistic infections may be endemic in some regions of the world, potentially influencing the outcomes in global trials.

Clinical Efficacy of Biologics in SLE: *David Isenberg (UK)*

Professor Isenberg noted that we have reached the limits of benefit from conventional immunosuppression in SLE, and we are beginning to benefit from our improved understanding of immune response and targeted therapies for SLE, notably B-cell targeted therapies.

Although there have been improvements in survival since the 1950s, a significant number of patients with SLE still die early in the disease course. This is an indication that more effective treatments are required. With a better understanding of the pathogenesis underlying SLE, targeted therapies may provide improved treatment options. One key defect in the pathogenesis of SLE is the failure of immune cells to remove post-apoptotic material, exposing intracellular nuclear material to immunologic processes. New agents are being designed to target B cells, T cells, antigen-presenting cells, and interferon.

B cells are involved in antibody production, antigen presentation, T cell activation and polarisation, dendritic cell regulation, and cytokine and chemokine production. The CD20 molecule is present on the surface of B cells during part of their life cycle, and has been implicated in the development of RA. Rituximab, a monoclonal antibody that depletes B cell populations and which was originally developed for the treatment of non-Hodgkin's lymphoma, was found to be effective for the treatment of RA, and has subsequently shown efficacy in SLE.

B cell depletion leads to a reduction in some antibodies, including anti-dsDNA, anti-nucleosome, anti-C1q, and anticardiolipin. Anti-Ro, anti-LA, and anti-Sm are not affected. The UK-BIOGEAS Registry

has collected data on patients with lupus nephropathy treated with rituximab.[30] Around two-thirds of patients achieved full or partial remission within 12 months of treatment. Targeting the B cell population a second time is equally effective as initial treatment, with a good toxicity profile. Once B cells have repopulated, the time to return of clinical features of SLE also varies widely.

The failure of the LUNAR[31] and EXPLORER[32] trials to replicate the success of rituximab for SLE treatment in clinical practice is likely due to issues with study design rather than lack of efficacy of the monoclonal antibody. Despite apparent clinical failure, rituximab provided clear evidence of biological activity, as evidenced by serological changes in these studies. The Phase IIb epratuzumab EMBLEM study met clinical endpoints for efficacy at some doses, and early studies with tocilizumab in SLE have also shown promising results.[33] The most encouraging evidence to date, supporting B-cell targeted therapy in patients with SLE, comes from two landmark trials using the B-lymphocyte stimulator (BLyS) antibody (belimumab). Both trials met their endpoints in two parallel studies, which included over 1,600 patients with lupus.[34, 35]

Recently a "rituxilup" treatment regimen is being studied as a new low toxicity, steroid-sparing therapy for all new and relapsing lupus patients who are not already taking steroids and who do not have cerebral lupus. Complete remission (CR) was achieved in 39 patients (78%), with the median time to CR occurring at 37.7 weeks.

Differential Drug Effects and Ethnicity: *Sandra Navarra (Philippines)*

Professor Navarra presented the ethnic and racial differences in treatment outcomes for clinical trials in patients with SLE. Particular focus on ethnic subpopulations in key biologics trials provided insights into clinical decision making when selecting treatments for individual patients with SLE.

Pharmacogenetic variations among ethnic groups may influence the efficacy and tolerability of a drug; genetic polymorphisms can determine drug metabolism ability and drug target as well as the affect the disease pathway.

The treatment effects of drugs for SLE tested in clinical trials have shown interesting ethnic variations in response. The Euro-Lupus Nephritis Trial enrolled predominantly Caucasian subjects.[36] It showed no significant differences in the probability of renal remission and the cumulative probability of renal flare between patients given low-dose IV cyclophosphamide (CYC) compared with those on high-dose IV CYC. At the 10-year follow-up, there was no difference in the probability of death, end stage renal failure (ESRF), and sustained doubling of serum creatinine between groups. However, these results are applicable to a Caucasian population.[37]

Mycophenolate mofetil (MMF) and CYC gave very similar results in Asian patients, but not in Caucasian patients. Another meta-analysis, showing that MMF was as efficacious as but safer than CYC for the treatment of proliferative lupus nephritis, also found that non-White and non-Asian race contributed significantly to heterogeneity of renal remission.[38]

In the ALMS trial (MMF vs. CYC for induction treatment of lupus nephritis), the study population comprised three similar-sized groups: Asian, White, and Black and Other.[39] Overall, there was no difference between MMF and CYC treatment, but analysis by ethnicity found more patients in the combined Black and Other group responded to MMF compared to CYC and, among Blacks, more responded to MMF than to CYC.

The LUNAR study did not meet its primary endpoint overall, but among Blacks, rituximab-treated patients had higher response rates compared with placebo treatment.[31] In the EXPLORER rituximab trial, although the primary and secondary endpoints did not show any difference between placebo and

rituximab,[32] a *post hoc* analysis by ethnic group demonstrated a beneficial effect of rituximab in the African American and Hispanic subgroups.

Patients in the BLISS trials of belimumab were not only stratified for SELENA-SLEDAI and proteinuria, but also for race (African descent or indigenous American vs. other).[34, 35] There was a better response to belimumab among those with more active disease, high anti-dsDNA, and lower complement levels, but no significant differences in response between different ethnic groups per se (see table).

Study	Caucasian/ White	Asian/ Asian-Pacific	African Carib/ Black	Others*
Euro-Lupus Trial	76	6	8	-
ALMS (MMF)	147	123	46	54
LUNAR (RTX)	45	7	40	52
EXPLORER (RTX)	144	11	64	36
BLISS 52 (Bel)	229	327	30	279
BLISS 76 (Bel)	569	28	118	103

*Overview of patients with SLE in biologics trials by ethnicity.*Hispanics, American Indian, Alaska Native, Indigenous Americans Bel, belimumab;MMF, mycophenolate mofetil; RTX, rituximab*

Clinical trials in SLE have enrolled a range of ethnicities and highlighted differences in responses to various drugs, clearly demonstrating that drug choice in clinical practice must be individualised to patients.

Hydroxychloroquine: *Guillermo Ruiz-Irastorza (Spain)*

Professor Ruiz-Irastorza highlighted the basic immunomodulatory effects of antimalarial drugs before presenting the clinical benefits of hydroxychloroquine in lupus and potential antimalarial side effects to look out for.

Antimalarials are effective for suppressing flares in SLE, and data indicate that they reduce damage accrual.[40] They are also steroid-sparing and anti-thrombotic. A systematic review of individual studies has highlighted many other beneficial effects on lupus nephritis remission and serum lipid levels, as well as being protective against osteonecrosis and atherosclerosis. These beneficial effects may also protect against miscarriage in antiphospholipid Syndrome (APS), prevent congenital heart block in babies with anti-Ro antibody, and protect against infections.[41] It is not necessary to withdraw hydroxychloroquine in periods of high activity, in long-term remission or in pregnancy and breastfeeding. Several studies also suggest that antimalarials may improve overall survival in SLE. Furthermore, antimalarials are universally available and inexpensive.

Retinal toxicity is the most serious adverse event associated with antimalarials, particularly chloroquine, although it is rare in patients with cumulative doses <1000 g. Other events are anecdotal, but can include cardiac and neuromuscular toxicity. Hydroxychloroquine is safe to use in pregnancy, and is not associated with any increased risk of congenital defects, spontaneous abortions, foetal death, premature delivery, or decreased numbers of live births in patients with autoimmune diseases. It is important not to reach the cumulative dose of 1000 g too rapidly. Patients will need annual ophthalmological review.

Immunosuppressive Drugs for SLE: *Ricard Cervera (Spain)*

Professor Cervera provides a comprehensive review of changing immunosuppressive regimens in SLE and supporting evidence (meta-analyses) since the 1960s, with a view to providing a solid foundation to support treatment decisions in SLE.

Since the introduction of immunosuppressive therapies in the 1960s, survival at five years in patients with SLE has increased from 50% to more than 95% at present. Classic immunosuppressive treatments include steroids, cyclophosphamide (CYC), azathioprine (AZA), cyclosporin A, methotrexate, IV immunoglobulins, and plasma exchange. Although CYC was the gold standard for treatment at the time, side effects were an issue.

New treatment regimens aim to increase long-term survival and to decrease side effects of treatments, particularly amenorrhoea. The Euro-Lupus regimen[36] comprises a short course of IV CYC as therapy for induction of response (six pulses of 500 mg every two weeks), followed by AZA as maintenance therapy. However, despite long-term efficacy over 10 years and a good side effect profile, mortality remains at 8% with this regimen.

The introduction of mycophenolate mofetil (MMF), a drug with similar efficacy to CYC, provided an advance in treatment. Meta-analyses show that MMF may be better for induction of response than CYC, and MMF is superior to AZA for maintenance of response.[42] Two trials were carried out to prospectively assess these effects; the Euro-Lupus MAINTAIN Nephritis Trial found that induction with low-dose CYC followed by maintenance with either MMF or AZA found similar efficacy in both arms with fewer side effects in the MMF arm.[43] The ALMS trial investigated induction with either IV CYC or MMF, followed by maintenance with either MMF or AZA.[39] Results showed that MMF was superior to CYC for induction. Recent meta-analyses of all trials concludes that MMF is as efficacious as, but safer than, CYC.[42]

Another immunosuppressive drug introduced for the treatment of SLE, tacrolimus (TAC), has been studied mainly in Asia. Addition of TAC to MMF induced response in patients who had failed to respond to MMF alone. These new treatment regimens have been responsible for significant improvements in long-term outcomes for patients with SLE.

Early Aggressive Treatment: *David D'Cruz (UK)*

Professor D'Cruz's presentation highlighted the importance of early diagnosis, personalised treatment plans, damage prevention strategies and careful chronic disease management in improving prognosis in patients with SLE.

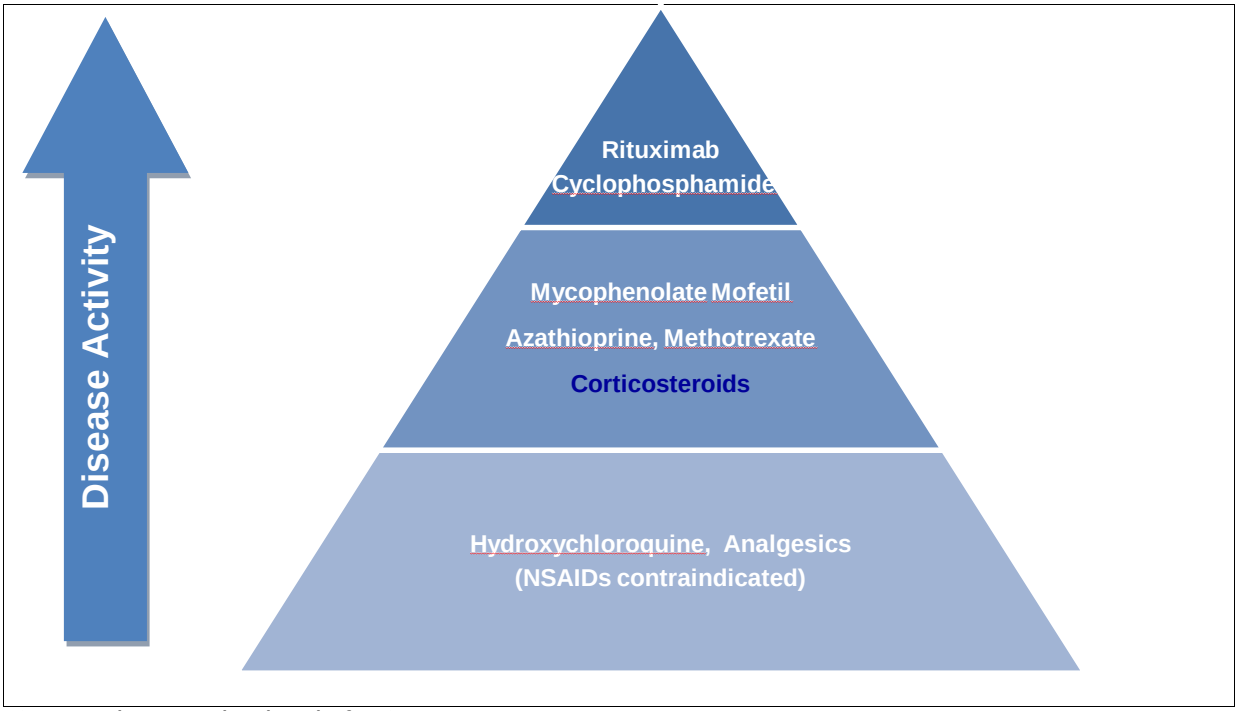
It is well recognised that SLE is a disease with a wide spectrum of manifestations from mild to severe. Early diagnosis is important, but SLE is difficult to diagnose and a delay of 2–4 years after first symptoms appear is common.

Serological abnormalities may appear several years before symptom onset, but diagnosing SLE is entirely clinical. American College of Rheumatology and SLICC criteria are useful reference aids, but are designed for classification not diagnosis. When assessing SLE, measures are used to monitor disease activity, damage caused by treatment, and quality of life (QoL).

Patients at high risk of poor outcomes can be identified; higher disease activity predicts damage accrual, and lupus nephritis predicts poor outcome. Risk factors for lupus nephritis are young onset of disease, Black ethnicity, positivity for anti-dsDNA, anti-Sm and LA. Not surprisingly, patients with SLE and co-morbid antiphospholipid Syndrome (APS) have poor outcomes. The main cause of death in patients with SLE is renal disease, with a Standard Mortality Ratio (SMR) of nearly 8. Factors

associated with increased mortality include female gender, younger age, disease duration of <1 year and Black ethnicity. There has, however, been a dramatic decline in mortality between 1970 and 2001, probably due to reduced numbers of deaths from infection (probably related to lower doses of steroids) earlier diagnosis and improvements in treatment. Conversely, there has been a slight rise in CV deaths.

The primary aim of treating SLE is to reduce inflammation, prevent thrombosis, and avoid long-term damage, as damage predicts premature mortality. The choice of treatment depends on the extent of organ involvement and the risk of thrombosis. Pregnancy and fertility issues must also be considered. The variable severity and course of clinical disease make it unwise to treat the disease based on laboratory values alone, but each patient should be treated individually. Antimalarials should be considered as first-line treatment for all patients with SLE, as they provide effective thromboprophylaxis and improve survival. Steroid treatment is controversial. The lowest effective dose should be used for the shortest period of time. The current therapeutic triangle for SLE is shown in the figure below.



Current therapeutic triangle for SLE.

Early aggressive treatment is indicated for those patients who may present with mild clinical disease, but who have serological risk factors predicting poorer outcomes. Rather than a watch and wait approach, early treatment with a biologic followed by mycophenolate mofetil or azathioprine combined with hydroxychloroquine and low dose aspirin can be initiated. This approach may incur immunosuppressive risks, but it may also provide better disease control and possibly prevent the development of lupus nephritis.

Better outcomes can be achieved not only by improved drug treatment regimens, but also by careful management of patients with regards to treatment compliance, adherence and follow-up, management of cardiovascular and thrombosis risk, prevention of glucocorticoid bone loss and vitamin D deficiency, and ensuring patients are immunised to protect against the risk of infection. Management of fatigue and psychological issues is also beneficial for patient outcomes. Poor compliance is difficult to measure, and predicted by lower socioeconomic status and educational attainment, cognitive dysfunction and depression. Fatigue is the single most important symptom for patients. A multifactorial symptom, fatigue persists through disease remission. Patients with fatigue often have poor aerobic fitness, but exercise and weight loss can have positive benefits.

SUMMARY

The immune response varies among patients with SLE, but it is clear that B cells have an important role in this disease. As new data emerge, therapies that target B cells are being developed for SLE. New biomarkers are constantly being identified and validated to improve monitoring of both disease state and drug treatment.

Lupus nephritis remains a significant cause of mortality in patients with SLE. Preventative strategies are important; while the five-year mortality of patients with lupus nephritis has declined dramatically since the 1970s, the proportion of patients reaching end stage renal failure within five years remains at around 7−8%. Prompt diagnosis, effective treatment, and stringent control of blood pressure and proteinuria are essential.

Membranous lupus nephritis (MLN) is an uncommon histological class of lupus nephritis, which accounts for 8–20% of all biopsy-confirmed lupus nephritis cases. Mycophenolate mofetil (MMF) is the first choice of treatment for these patients, but recent studies suggest that rituximab may also be effective in patients with MLN.

Antiphospholipid Syndrome (APS) occurs in some patients with SLE with antiphospholipid antibodies. Stroke, seen in 20% of patients with APS, and miscarriage are the major manifestations, and additional anticoagulation therapy should be considered in high-risk patients. With careful planning and management, most women with SLE and APS can have a safe and successful pregnancy.

Although there have been large improvements in survival since the 1950s, a significant number of patients with SLE have a shortened lifespan, and more effective treatments are still needed. Now that more is understood about the pathogenesis underlying SLE, new therapies may provide more targeted treatment approaches.

The failure of the LUNAR and EXPLORER trials to confirm the success of rituximab for treating SLE, which has been observed in many clinics, is likely related to issues of study design rather than lack of drug efficacy. Clinical trials in patients with SLE have enrolled a range of patient ethnicities and highlighted differences in response to various drugs, clearly demonstrating that ethnicity may affect drug response, and drug choice in clinical practice must be individualised per patient. The most encouraging evidence to date comes from two landmark trials using the B-lymphocyte stimulator (BLyS) antibody (belimumab).[34, 35]

Antimalarials may be overlooked when selecting a treatment regime. Whilst glucocorticoids and immunosuppressives manage lupus manifestations, hydroxychloroquine can be used for the *treatment* of lupus itself, used as a baseline treatment particularly in antiphospholipid antibody positive patients. Hydroxychloroquine can be used continually in periods of high activity, in long-term remission, and throughout pregnancy and breastfeeding.

New treatment regimens aim to increase long-term survival and to decrease side effects of treatments. Mycophenolate mofetil is better for induction of response than cyclophosphamide (CYC), MMF is superior to azathioprine for maintenance of response, and it is widely agreed that MMF is as efficacious as, but safer than, CYC. Early aggressive treatment is now advocated for those patients who present with mild clinical disease, but who have serological risk factors predicting poorer outcomes.

CONCLUSION

Following this inaugural meeting of the Lupus Academy, many delegates provided positive feedback and relevant insights into their research and clinical interests. Given the advent of targeted therapy for Lupus, notably the first new treatment to be licensed in 50 years (belimumab) and several other targeted therapies in phase III trials, exciting changes in the way Lupus and allied diseases are managed are afoot. As real world data and case studies emerge from targeted therapies in clinical practice, our understanding of how best to treat our individual patients will be well invested for improved patient outcomes in future.

The 2nd Annual Meeting of the Lupus Academy will take place 17–18th April 2013 in Buenos Aires, the programme for which has been based on delegate feedback following the inaugural meeting. The meeting promises to build on the foundation created in Barcelona and bring us closer to the vision of improving patient outcomes in SLE.

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