Asian Lupus Summit

Radisson Blu Hotel Cebu

Cebu City, Philippines

31st March to 1st April 2014

Meeting Report

Contents

Participants

Participant			Affiliation	Country
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Dr	Daniel	Tak Mao Chan	University of Hong Kong, Queen Mary Hospital, Hong Kong	China
Professor	Bevra	Hahn	University of California, Los Angeles	USA
Dr	Laniyati	Hamijoyo	University of Padjadjaran Bandung	Indonesia
Dr	Aisha	Lateef	National University Health System,	Singapore
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Professor	Shue-Fen	Luo	Chang Gung University	Taiwan
Dr	Mo-Yin Temy	Mok	The University of Hong Kong, Hong Kong	China
Professor	Sandra	Navarra	University of Santo Tomas, Manila	Philippines
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Introduction

The Lupus Academy is a long-term initiative committed to improving patient outcomes in systemic lups erythematosus (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.

Now in its third year, the Lupus Academy continues to grow in its commitment to providing high quality and clinically relevant education to support better patient outcomes in SLE. This first satellite meeting, held in Cebu City, Philippines, brings a programme of cutting edge insights into advances in global research and clinical practice in lupus and allied diseases.

The scientific component of this programme, developed by the Lupus Academy Steering Committee, aimed to create a highly interactive forum through which to develop a logical approach to the management of lupus across Asia and the rest of the world. More than 100 healthcare professionals from the Asia-Pacific region had the opportunity to meet world-leading clinicians and scientists and, through the sharing of clinical experience, develop knowledge in this high-profile therapeutic area.

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

Asian Lupus Summit by the Lupus Academy

LupusAcademy
Communicate. Educate. Treat.

Radisson Blu Hotel Cebu
Cebu City, Philippines
31st March to 1st April 2014

Programme

Monday 31st March 2014

13:00	Registration	
Case Study Workshops		
14:00	*Moderator/Facilitator:* Lyndon J.Q Llamado *(Philippines)* Difficult lupus	Mo-Yin Temy Mok *(Hong Kong, China)* & Worawit Louthrenoo *(Thailand)*
	Moderator/Facilitator: Evan Glenn S. Vista *(Philippines)* Lupus nephritis	Daniel T.M. Chan *(Hong Kong, China)* & Yingyos Avihingsanon *(Thailand)*
	Moderator/Facilitator: Sargunan Sockalingam *(Malaysia)* Cardiovascular disease in SLE	Bevra H. Hahn *(USA)* & Laniyati Hamijoyo *(Indonesia)*
15:30	Coffee	
Case Study Workshops		
16:00	*Moderator/Facilitator:* Lyndon J.Q Llamado *(Philippines)* Difficult lupus	Mo-Yin Temy Mok *(Hong Kong, China)* & Worawit Louthrenoo *(Thailand)*
	Moderator/Facilitator: Evan Glenn S. Vista *(Philippines)* Lupus nephritis	Daniel T.M. Chan *(Hong Kong, China)* & Yingyos Avihingsanon *(Thailand)*
	Moderator/Facilitator: Sargunan Sockalingam *(Malaysia)* Cardiovascular disease in SLE	Bevra H. Hahn *(USA)* & Laniyati Hamijoyo *(Indonesia)*
17:30	Close	

Tuesday 1st April 2014

08:00	Opening Address	Roger A. Levy *(Brazil)*
Plenary I: *Moderators:* Mandana Nikpour *(Australia)* & Cesarius Singgih Wahono *(Indonesia)*		
08:15	Lupus in Asia: unmet needs	Chak-Sing Lau *(Hong Kong, China)*
08:40	Infections in SLE	Sandra Navarra *(Philippines)*
09:05	Current concepts in antiphospholipid syndrome	Roger A. Levy *(Brazil)*
09:30	Discussion	
09:50	Coffee	

Plenary II: *Moderators:* Thomas Dörner *(Germany)* & Chak-Sing Lau *(Hong Kong, China)*		
10:35	Special concerns in children and adolescents	Christine B. Bernal *(Philippines)*
11:00	Pregnancy and SLE therapy	Aisha Lateef *(Singapore)*
11:25	Discussion	
11:50	Lunch	

Plenary III: *Moderators:* Ricard Cervera *(Spain)* & Shue-Fen Luo *(Taiwan)*		
13:00	Update on the diagnosis and management of neuropsychiatric SLE	Sargunan Sockalingam *(Malaysia)*
13:25	Update on the management of lupus nephritis	Daniel T.M. Chan *(Hong Kong, China)*
13:50	Treat-to-target in SLE	Mandana Nikpour *(Australia)*
14:15	Discussion	
14:45	Coffee	

Plenary IV: *Moderators:* Sandra V. Navarra *(Philippines)* & Nan Shen *(China)*		
15:10	Optimising outcomes in SLE: best practice	Bevra H. Hahn *(USA)*
15:35	Advances in SLE therapy	Ricard Cervera *(Spain)*
16:00	Discussion	
16:20	Summary and close	Sandra V. Navarra *(Philippines)*

Plenary I

Lupus in Asia: unmet needs: ***Chak-Sing Lau (Hong Kong, China)***

Professor Lau's presentation provided an overview of lupus in Asia, showing how care has lagged behind more developed countries with poorer outcomes for patients, especially those with renal disease.

The large lupus population in the Asia-Pacific region (around 2 million people), and the concentration of patients in a small number of tertiary referral centres, provides a great opportunity to study changes in epidemiology as a result of ongoing industrialization.

Many studies have shown that Asian patients with systemic lupus erythematosus (SLE) have worse clinical outcomes than patients of other ethnicities,[1] and in particular there is a higher rate of renal involvement in Asian patients than in Caucasian patients.[2] It is clear that lupus damage in the first year after diagnosis predicts mortality,[3] particularly in those patients with renal damage.[4]

Infections and active disease are key contributors to early death in developing countries, in addition to immunosuppressive treatment, the endemic nature of certain infections poses a particular threat to patients in developing countries.[5] In addition to disease and damage, there is a clear correlation between these and negative impact on quality of life; in fact the impact of lupus on quality of life is comparable to other chronic diseases (eg. RA, diabetes, AIDs). With adequate and early treatment, quality of life improves.[6]

Developments in lupus care in Asia lag behind that of the rest of the world and there remains a disparity in the level of care for lupus patients due to both inadequate resources and training, and also to lack of awareness of the impact of lupus in the community, with few patient advocacy groups and charities. The prognosis for lupus patients in Asia has improved over the last 30 years in terms of survival,[5] but there is more work to be done, particularly to improve patients' quality of life.

Infections in SLE: ***Sandra Navarra (Philippines)***

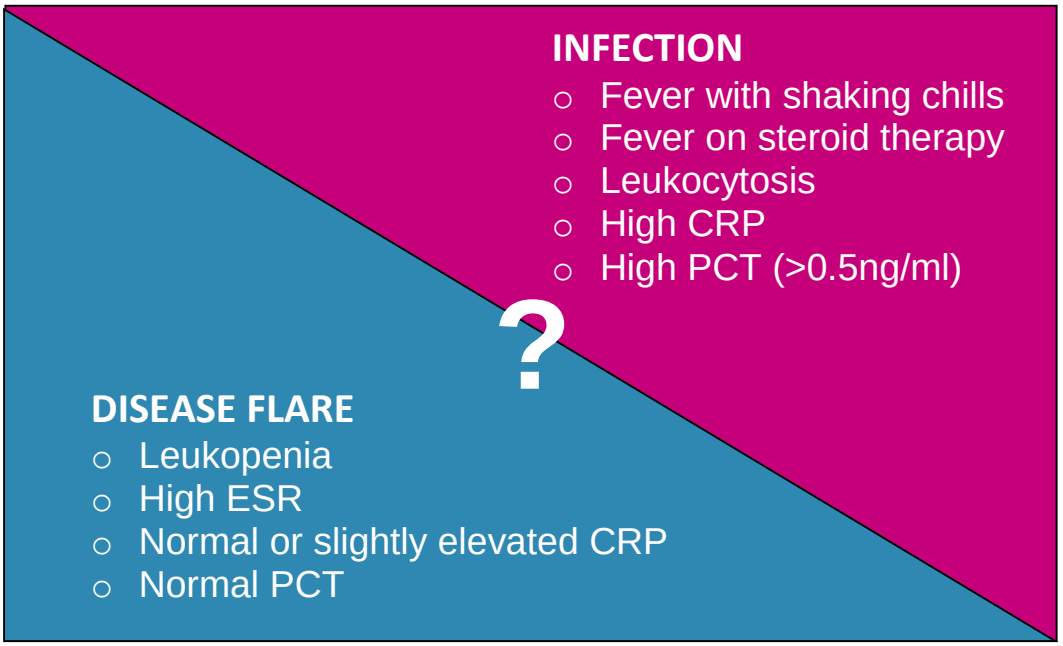
Professor Navarra presented an overview of the topic, emphasising that infections in SLE must be approached with utmost vigilance and investigated thoroughly.

Patients with systemic lupus erythematosus (SLE) are susceptible to common and opportunistic infections due to both inherent immune abnormalities and the use of immunosuppressive therapies. Infection leading to hospitalisation is a leading cause of morbidity and mortality among SLE patients,[7] both globally and in the Asia-Pacific region, where infections such as tuberculosis (TB)[8] and Salmonella are endemic. The respiratory tract is a common site for infections in SLE, as well as the urinary tract and skin, and the rate of death from infections is estimated at 25–70%.[5,9] Risk factors for infections in SLE include active renal disease and higher disease activity overall, but the double-edged sword is that many treatments for SLE such as steroids also expose the patient to risk for infections, although anti-malarial agents such as hydroxychloroquine may be protective.[10]

SLE is the most frequent underlying disease in patients with Salmonella bacteremia.[11] Similarly, TB is more frequent in SLE patients than in the general population particularly in endemic areas, with use of corticosteroids being a risk factor for its development.[12,13] Vaccination of SLE patients should follow guidelines, which advocate avoiding the use of live vaccines in immunocompromised patients.[14-16]

Treating the febrile lupus patient is a challenge; inflammatory manifestations of systemic infection may be masked in SLE or may simulate SLE activity (Figure 1). Procalcitonin (PCT) may be a better marker than C-reactive protein (CRP) to rule out bacterial infection during lupus flare but not during lupus remission.[17-19] Whether infections lead to flare, or flare leads to infections, remains to be resolved.

Figure 1. The clinical challenge of diagnosing fever in SLE.



Current concepts in antiphospholipid syndrome: *Roger A. Levy (Brazil)*

Professor Levy explained that classification is not the same as diagnosis for patients with APS, but should be based on experience in daily clinical practice rather than just the strict criteria used in epidemiological studies.

Antiphospholipid syndrome (APS) is the most frequent type of acquired thrombophilia. There is overlap between APS and systemic lupus erythematosus (SLE); like SLE, APS has a wide spectrum of clinical manifestations and is a systemic disease. As well as recurrent arterial or venous thrombosis and inflammation, APS is associated with spontaneous abortion, and patients have detectable lupus anticoagulant (LA) and or elevated levels of IgG and/or IgM antiphospholipid antibody (aPL) either anticardiolipin (aCL), or anti-β2 glycoprotein-I (anti-β2GPI) antibodies.

The classification criteria for APS[20] are strict and diagnosis must meet at least one clinical (vascular thrombosis or pregnancy morbidity) and one laboratory (LA, aCL, anti-β2GPI) criterion.

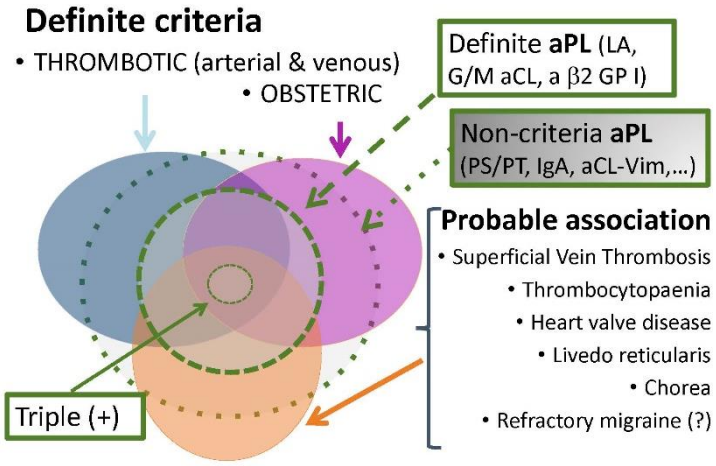
The AntiPhospholipid Syndrome Alliance For Clinical Trials and InternatiOnal Networking (APS ACTION) group have tried to identify a 'clinically significant aPL profile' through analysis of the literature. They estimated the overall frequency of aPL at 6% in patients with pregnancy morbidity, 13.5% in patients with stroke, 11% in myocardial infarction (MI), and 9.5% in those with deep vein thrombosis (DVT),[21] suggesting APS may be under-recognised. Most patients with APS are positive for aCL or LA, so this should be the first-line testing strategy. Those patients who are triple positive are at higher risk for a thrombotic event than those positive for one or none.[22]

Those who test negative for the classical antibodies are termed as having 'seronegative APS' or SN-APS, and may account for 28% of all patients,[23] but opinion is divided about what this means in practice. Approximately 80% of patients with Sneddon's syndrome, a rare disorder characterised by cerebrovascular disease associated with livedo reticularis, have an aPL marker,[24] leading some to consider Sneddon's syndrome as part of a wider spectrum of seronegative APS-like disease.

Potential indicators of APS

Many clinical signs have been proposed as indicators of APS, and how they might fit into the overall picture is shown in Figure 1. Thrombocytopaenia is found in 16–38% of patients with primary APS and more frequently in SLE-associated APS, and some authors believe it should be considered as part of the classification criteria for APS. Renal microangiopathy can also indicate APS; in patients who have no other features of APS apart from nephropathy and who are persistently positive for aPL, the diagnosis of APS should be considered. Heart valve disease occurs frequently in APS and lesions may be progressive despite anticoagulant and/or antiplatelet therapy.

Up to 50% of patients with APS have CNS involvement which can extend beyond stroke to include multifocal lesions on MRI and features related to chorea, cognitive impairment, migraines, epilepsy and psychiatric alterations.[25]



Treatment of APS involves daily care and lifelong treatment. In the acute phase of the disease, treatment is the same as any other thrombosis, with full-dose heparin followed by coumadin to maintain INR at recommended levels: 2–3 for those with past venous events and 3–4 for those with past arterial events. It is important not to stop therapy after 6 months, as there is a 20% of a recurrence, including major stroke. In pregnancy, women should be treated according to their past obstetric history; all patients should receive low-dose aspirin with low molecular weight heparin up to 6 weeks post-partum, while patients with a history of thrombosis should be restarted on coumadin post-partum. The control of additional classic thrombotic risk factors is mandatory. Future trends in treatment may include oral direct thrombin or anti-Factor Xa inhibitors, but more data on long-term outcomes are needed.

Plenary II

Special concerns in children and adolescents: ***Christine B. Bernal (Philippines)***

Dr Bernal reviewed the challenges of managing paediatric-onset SLE, which often follows a more severe course than in adults, aiming to ensure patients' adherence to treatment and prevent damage induced by medication side effects

Childhood onset or paediatric systemic lupus erythematosus (pSLE) accounts for 10–20% of all SLE cases, with an incidence of 0.3–0.9/100,000, and a prevalence of 3.3–24/100,000. The wide variation in prevalence is due to the influence of ethnicity and age at onset.

Whether pSLE is the same as adult SLE is a controversial topic. Although there are similarities in immunopathogenesis, classification criteria, clinical and laboratory findings, and response to medications, the presentation is different in children, with a more abrupt onset, higher rates of organ involvement (particularly in the kidneys), and a more aggressive clinical course (Table 1).[26] Children with SLE and renal involvement are more likely to have severe kidney disease (WHO class III/IV lupus nephritis) than adults.[27]

Table 1.: Clinical features of paediatric-onset SLE compared with adult-onset SLE.[26]

Clinical features	Paediatric–onset SLE	Adult–onset SLE
Fever	20–67%	43–55%
Lymphadenopathy	6–36%	0–1%
Malar rash	22–79%	35–59%
Discoid lupus	0–19%	2–29%
Oral ulcers	9–49%	13–40%
Photosensitivity	23–53%	20–57%
Arthritis	22–88%	67–94%
Nephropathy	67–82%	33–53%
Pericarditis	16–26%	13–33%
Pleuritis	6–48%	6–33%
Neuropsychiatric disease	15–95%	33–60%
Leucopaenia	46–64%	41–57%
Thrombocytopaenia	25–37%	6–25%
Haemolytic anaemia	10–76%	3–13%

Higher disease activity score, both at presentation and over time, is a feature of pSLE,[27] and although both diseases are treated with the same medications, children have more severe disease for a longer time than adults, leading to a need for higher doses over a longer duration (Table 2).

Table 2. Differences in medication use between children and adults in the LUMINA cohort.[28]

	Paediatric Onset SLE	Adult Onset SLE	
Steroids	96.8%	85.4%	
Maximum dose	49.1 mg	13.4 mg	P=0.061
Average dose	34.9 mg	9.1 mg	P=0.080
IV cyclophosphamide	16.1%	4.2%	P=0.088

Damage in pSLE is related to both disease and medication. Paediatric patients have longer disease activity, remission is uncommon, and consequently the frequency of irreversible damage is high. Most damage occurs within the first year of disease, and increases with disease duration, leading to growth failure, delayed puberty and nephrotic-range proteinuria. Organ damage occurs in up to two-thirds of children within 2 years.[29]

The 5 year survival rate for pSLE has significantly increased since the 1950s due to better recognition

and treatment, and now stands at more than 90%. However, longer life expectancy brings with it a greater chance of morbidity, particularly an increased risk of premature atherosclerosis resulting from the complex immune dysregulation of SLE. While the incidence of myocardial infarction is the same for both pSLE and adult-onset SLE, patients with pSLE have a 100–200-fold risk of death from cardiovascular disease in early adulthood.[30] Higher rates of dyslipidaemia are evident in pSLE (50–80% vs general population).[31,32] Hyperlipidaemia is a feature of pSLE at diagnosis, but the disease mechanisms surrounding dyslipidaemia are poorly understood.

There is also a high risk of developing osteopaenia in pSLE, as patients have not yet achieved peak bone mass before the onset of disease. One study has shown a rate of reduction in bone mass of 3.4% over a year, compared with an age-related annual increase of bone mass of 8% in normal children.[33]

Finally, pSLE patients have poorer quality of life, due to the onset of disease in adolescence coinciding with a vulnerable period of intellectual and emotional development.[27,34,35] Active disease, worsening of disease and effects of damage all lead to a risk of fatigue, joint symptoms and headaches.

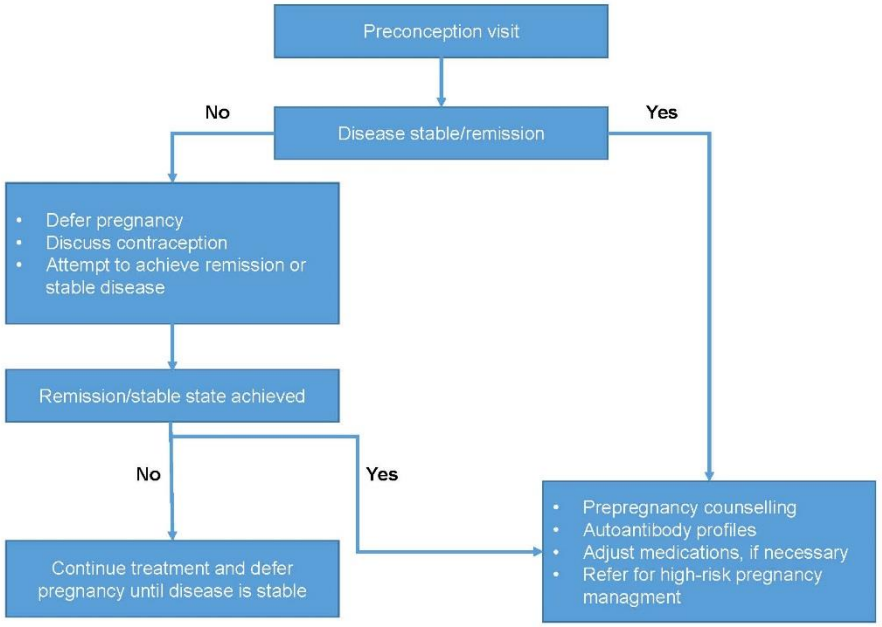
Pregnancy and SLE therapy: ***Aisha Lateef (Singapore)***

Dr Lateef explained that pregnancy in the setting of SLE is increasingly common but remains high-risk. She stressed the importance of a pre-conception assessment prior to the planned pregnancy, and the need for close monitoring and high-risk surveillance during pregnancy to achieve good outcomes.

Pregnancy in systemic lupus erythematosus (SLE) is increasingly common.[36] However, pregnancy remains a high-risk situation, with higher rates of maternal and foetal complications and poorer obstetric outcomes than in the general population. Pregnancy in SLE poses a unique challenge in terms of balancing the interests of mother and child and judicious use of medications.[37]

To achieve the best outcomes, pregnancies should be planned and if necessary deferred until disease is stable or in remission (Figure 1).[38] In the real world, pregnancies occur when disease is active, and these patients should be counselled about the effects of SLE on pregnancy and the risks of maternal and foetal complications. It is important to discuss continued medication use and the need for close monitoring.

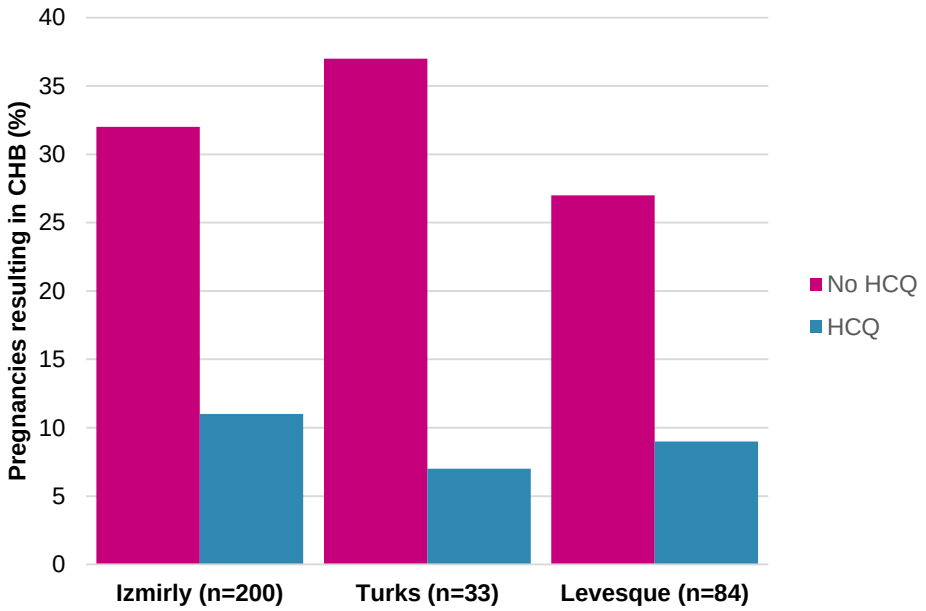
Figure 1. Algorithm for planning a pregnancy in women with SLE.[38]



As part of preconception planning, the patient's autoantibody profile should be considered. Anticardiolipin antibodies pose a significant risk of pregnancy morbidity and loss, while anti-Ro antibodies have been associated with neonatal lupus syndromes (NLS) and congenital heart block. When maternal antibodies cross the placenta, 10–15% of foetuses develop passively acquired autoimmunity, manifesting as transient photosensitive rash, cytopaenias, or transaminitis, all of which resolve within 6–8 months.[38] Congenital heart block can result when the foetal heart reacts to maternal antibodies leading to fibrosis of the cardiac conduction system and high foetal morbidity and mortality. It is much less common, occurring in fewer than 2% of foetuses, but may recur in subsequent pregnancies. Close monitoring of patients at risk of NLS is important, with weekly foetal echocardiography recommended between Weeks 16–26 and biweekly thereafter to detect early manifestations of impending heart block. Early treatment with fluorinated corticosteroids, dexamethasone and betamethasone may prevent progression to complete heart block, and

prophylactic treatment with hydroxychloroquine reduces the risk of cardiac neonatal lupus (Figure 2).[37,39]

Figure 2. The effect of hydroxychloroquine treatment on the risk of cardiac neonatal lupus.[22]



Antiphospholipid antibodies are associated with higher rates of pregnancy loss and morbidity resulting from pre-eclampsia, placental insufficiency and intra-uterine growth retardation (IUGR), and preterm delivery. Women with aPL require different strategies, based on the risk profile for each pregnancy. Asymptomatic women with no prior thrombotic event should take low-dose aspirin throughout the pregnancy, those with a history of recurrent early losses or one late foetal loss should take aspirin in combination with prophylactic dose of heparin, and heparin should be continued for 6 weeks postpartum. Those with systemic thrombosis should be treated with full therapeutic doses of heparin. Coumarin should be avoided, especially during the period of organogenesis.

There are certain situations where pregnancy is contraindicated in women with SLE, and these include:

- Severe lupus flare within past 6 months
- Active lupus nephritis within past 6 months
- Stroke within past 6 months
- Previous severe pre-eclampsia or HELLP syndrome despite therapy
- Severe organ damage, manifesting as:
    - Severe pulmonary hypertension (estimated systolic pulmonary artery pressure >50 mmHg or symptomatic)
    - Severe restrictive lung disease (forced vital capacity <1L)
    - Chronic renal failure (creatinine level >2.8 mg/dL)
    - Advanced heart failure

Medication Use During Pregnancy

Steroids should be used at the lowest possible dose, and pulse therapy considered if the patient has a flare. Hydroxychloroquine is safe to use throughout pregnancy and should be continued to reduce disease activity. In some situations, it can reduce the risk of congenital heart block in at-risk fetuses.[40]

Azathioprine is also safe to use during pregnancy, but doses should be limited to 2 mg/kg to avoid possible fetal cytopaenias and immune suppression with higher doses. Other safe immunosuppressants include azathioprine and the calcineurin inhibitors, tacrolimus and cyclosporine Medicines that should not be used in pregnancy include all other immunosuppressives, most of the antihypertensives (esp ACE inhibitors and ARBs), and antiplatelet agents other than aspirin.

Calcium and vitamin D supplementation should be prescribed to all pregnant women with SLE, especially those receiving corticosteroids and heparin, and should be continued until the end of lactation.

Plenary III

Update on the diagnosis and management of neuropsychiatric SLE: ***Sargunan Sockalingam (Malaysia)***

Dr Sockalingham explained that neuropsychiatric manifestations of SLE affect many patients. He reviewed the pathogenesis of this aspect of the disease and looked at options for diagnosis and treatment.

Neuropsychiatric SLE (NPSLE) has been defined by ACR nomenclature,[41] and the heterogenous nature of the disorder is reflected in the wide range of adults it affects (between 14% and 80%).[42] Secondary causes, such as infections, metabolic or endocrine disturbances, or even adverse drug reactions must be excluded during the diagnosis.

NPSLE occurs after a disruption of the blood-brain barrier allows autoantibody-mediated neuronal injury, leading to vasculopathy and cytotoxicity. Antibodies directed to the N-methyl-D-aspartate receptor (NMDAR) and to ribosomal P protein can be detected in the cerebrospinal fluid of patients with neuropsychiatric SLE, and can affect neuronal function and viability.[43] Around 30% of SLE patients have antibodies to NMDAR subunit 2, which is associated with cognitive defects, and other biomarkers for NPSLE include anti-MAP2, matrix metalloproteinase-9, and plasminogen activator-1.

Structural magnetic resonance imaging (MRI) is widely used to aid in the diagnosis of NPSLE. Neuroimaging studies show that 40–80% of abnormalities in NPSLE are multiple discrete lesions in the periventricular and subcortical white matter.[44] In those patients with neuropsychiatric symptoms who do not appear to have any abnormalities on MRI, positron emission tomography (PET), MR spectroscopy and single-photon emission computed tomography (SPECT) can be used to reveal lesions.

Guidelines on the management of NPSLE have recently been published.[45] Glucocorticoids remain the first-line therapy for NPSLE, along with hydroxychloroquine. In patients with aPL, anticoagulation is recommended, as well as immunosuppressive therapy. Second-line treatments for refractory NPSLE include intravenous immunoglobulins, plasmapheresis and rituximab. Anticonvulsants, non-steroidal anti-inflammatory drugs and psychotropic medications such as selective serotonin reuptake inhibitors (SSRIs) may be used for symptomatic treatment, and non-pharmacological approaches include cognitive behavioural therapy and psychosocial support. In the future, new drugs such as belimumab may be appropriate for NPSLE, while gene therapy and stem cell transplantation are still under investigation.

Update on the management of lupus nephritis: *Daniel T.M. Chan (Hong Kong, China)*

Professor Chan looked at how immunosuppressive treatment for lupus nephritis has evolved, with reference to early phase treatments for the induction regimen, and long-term maintenance immunosuppression regimens.

Lupus nephritis is still an important cause of death in many Asian countries. The prevalence of systemic lupus erythematosus (SLE) is between 500–1000 per million population, with renal involvement in 50–75%. Mortality has been reported as 40% over 4 years in Thailand, and 30% at 5 years in Singapore.[46]

In the 1970s, corticosteroids were the only drugs available to treat lupus nephritis but since then many others have been introduced, including cyclophosphamide (CYP) and mycophenolate mofetil (MMF). Today, treatment regimens may include corticosteroids + MMF or CYP, then mycophenolic acid or azathioprine, calcineurin inhibitors (CNI), or biologic therapies.

The treatment of lupus nephritis can be separated into two distinct phases. The early, or induction, phase involves use of immunosuppression treatment to induce remission or more realistically a satisfactory response. The second phase covers maintenance treatment in the long-term. A satisfactory response to induction treatment is important, as it is associated with good long-term renal survival[47] and patient survival.[48] Response is defined by reduction in proteinuria by 50% at 6 months, and is predicted by baseline factors including ethnicity, active serology, and stable renal function after 4 weeks of treatment.

Induction Treatment

In the 1970s, it was discovered that the use of cyclophosphamide (CYP) in SLE patients led to more sustained remission and a better renal outcome, although maintenance immunosuppression was necessary for good long-term outcomes even if flares were successfully treated. Despite this, there is still a trade-off as CYP treatment is associated with significant toxicity, including nephritic flares, end-stage renal disease, and death.[49] Reducing the toxicity of CYP while maintaining efficacy can be achieved by reducing or pulsing doses, and limiting the duration of treatment. Azathioprine is not sufficiently potent to manage this aggressive disease; while it is as effective as CYP at inducing remission, the rate of relapses and disease progression and the incidence of infections are all increased.[50]

MMF + prednisolone has similar efficacy to CYP + prednisolone when used as induction therapy in Chinese patients, with fewer adverse events, better quality of life and better long-term outcomes.[51] In the large two-phase Aspreva Lupus Management Study (ALMS),[52] MMF was compared with CYP. In the induction phase, there was no difference between the two groups in response rate, and MMF was not superior to CYP for renal outcomes. However, ethnicity was a factor in response to treatment: while there was no difference in response between White and Asian patients, more Black and Hispanic patients responded to MMF than to CYP.

Maintenance Immunosuppression

In the maintenance phase of the ALMS study, MMF was more effective than azathioprine at preventing treatment failure.[53]

A recent study has shown that patients who continue with MMF from induction through to maintenance

for a minimum of 24 months have better 5- and 10-year survival than those who moved to azathioprine after induction, suggesting it is better to maintain continuous MMF treatment.[51]

When assessing new treatments it is important to measure not only efficacy, but also to consider how the treatment will fit in with the overall management of lupus nephritis; for example a new drug may be best used as a steroid sparing agent, or to reduce relapses, rather than as an add-on therapy. The choices available today allow individualisation of treatment for patients with lupus nephritis.

Treat-to-target in SLE: ***Mandana Nikpour (Australia)***

Dr Nikpour explored the issues surrounding treating-to-target for SLE patients, and suggested that attaining remission or LLDAS was only one aspect of managing patients. Other considerations include patient-reported outcomes such as quality of life, management of co-morbidities, and special situations such as pregnancy.

The Variable Course of Disease

Systemic lupus erythematosus represents a spectrum of manifestations and severity requiring tailored therapy using a limited repertoire of drugs. Coupled with the variable manifestations is a variable disease course.[54]

Depending on the definition chosen, between 1.7 and 6.5% of patients are in remission at any one time, while 6.1% of patients will have serologically-active but clinically quiescent disease (SACQ). Between 40 and 65% of patients have relapsing-remitting disease, and up to 50% of patients will have a period of persistently active disease over a year. On top of this, about two-thirds of patients will have at least one flare in any given year.

Although mortality has improved over the last few decades, the standardised mortality ratio (SMR) remains high, measured at 5.3 in Hong Kong in the decade 1999–2008,[55] which translates to 19.7 years of life lost in women and 27.0 years of life lost in men. Deaths in lupus patients are caused by active disease, infection and atherosclerotic events, while mortality is predicted by male gender, coronary artery disease, cumulative disease activity, and organ damage as measured on the Systemic Lupus International Collaborating Clinics Damage Index (SLICC-DI).[36]

A number of measures are available to assess disease activity, including both subjective measures such as the physician global assessment (PGA) and more objective measures such as the British Isles Lupus Assessment Group index (BILAG). The EULAR guidelines for management of SLE advocate regular monitoring of disease activity (with application of indices of disease activity) to guide treatment.

The armamentarium of drugs available for the treatment of SLE is likely to change with the advent of biologic therapies such as belimumab, but corticosteroids are the cornerstone of current therapy. For maintenance therapy, a majority (>75%) of patients require long term immunosuppressive treatment and a significant proportion (30–50%) of patients are on long-term corticosteroids at varying doses.

The Need for Treatment Targets in SLE

A treat-to-target approach aims not just to achieve a significant improvement in disease as in clinical trials, but to reach a state (‘target’) where the patient is doing well, both in terms of current symptoms and risk of future complications. This approach will lead to better outcomes, less uncertainty about whether or not to escalate therapy, and is potentially cost-effective.

Remission would be an ideal target in SLE disease management, but prolonged complete remission in SLE is rare. In a large Canadian cohort, only 1.7% of patients met very stringent criteria for remission (SLEDAI-2K=0 for ≥5 years, with no corticosteroids or immunosuppression).[56] This has led to minimal disease activity (Lupus Low Disease Activity State or LLDAS) being proposed as a potential target to balance activity-related complications and treatment toxicity.

The Asia-Pacific Lupus Collaboration (APLC) has provisionally defined LLDAS based on a commonly used measure of disease activity that is easy to use in clinical practice, and also captures disease activity based on overall physician judgment and considers the toxicity of maintenance therapy.

APLC criteria for LLDAS in SLE

1. SLEDAI-2K ≤4 with no activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, haemolytic anaemia, fever) or gastrointestinal activity
2. No new feature of lupus disease activity compared to the previous assessment
3. PGA (0-3) ≤1 (0=no disease activity, 3=severe disease activity; 1-2= consider escalating therapy, 2-3= consider hospitalisation)
4. Current prednisolone (or equivalent) dose ≤7.5mg daily
5. Well tolerated standard maintenance doses of immunosuppressive drugs or approved biologic agents

The APLC is currently undertaking a longitudinal, two year study of between 1000–2000 consecutive patients to establish the frequency of LLDAS attainment and its ability to predict improved outcomes based on death, organ damage and quality of life.

Plenary IV

Optimising outcomes in SLE: best practice: ***Bevra H. Hahn (USA)***

Professor Hahn investigated best practice for management of SLE, looking at strategies for induction of improvement, maintenance of improvement and minimisation of damage over the long term, with particular focus on minimising kidney disease, infections and CVD, the major causes of mortality in SLE patients.

Early diagnosis and treatment of systemic lupus erythematosus (SLE) is necessary to reduce damage and mortality from SLE. Once the diagnosis has been made, the next stage is induction of improvement of disease, followed by maintenance of the improvement using target-to-treat strategies.

Revising the ACR guidelines for classification of SLE may enable diagnosis to be made earlier. The new Systemic Lupus International Collaborating Clinics (SLICC) group criteria, published in 2012,[57] include updates on skin disease, renal biopsy, neurologic manifestcyations, and immunologic criteria.

A recent large study on mortality in SLE confirms that the standardized mortality ratio (SMR) is in the range of 3.5–4,[58] with renal disease being the greatest cause of mortality, followed by infections and cardiovascular disease (CVD). Recent data have shown that response to treatment for lupus nephritis

can be predicted by measuring normalisation of complement biomarkers.[59]

If patients do not respond to initial induction therapy with MMF within 3–12 months, MMF should be exchanged for cyclophosphamide (CYP) or rituximab; the ACR guidelines do not include azathioprine for induction of response, even though it is a less expensive option.[60] The EULAR guidelines state that azathioprine can be used for induction, but that more flares are likely in the maintenance phase compared with MMF.[61]

Once improvements have been induced, they must be maintained. There are some specific considerations for Asian patients, particularly the use of oral CYP, which provides excellent long-term outcomes in Chinese patients,[62] using MMF at less than maximum dose,[63] and the use of multi-target therapy.[64] Both ACR and EULAR guidelines recommend maintenance with MMF or azathioprine for 3 years, although this may be prohibitively expensive in some areas. [60,61]

Remission may be an unrealistic target for the management of SLE, but many patients will be able to achieve LLDAS on low dose glucocorticoid plus oral hydroxychloroquine. Daily prednisone doses >6 mg present a risk for damage, and tapering is recommended, although patients with active arthritis and/or dermatitis may need to stay on higher doses. The RITUXILUP study has suggested that oral steroids can be safely avoided in the treatment of lupus by starting treatment with 2 doses of rituximab (1 g) and methyl prednisolone (500 mg) on days 1 and 15, maintained with MMF, although these data are controversial.[65] Belimumab has a small steroid-sparing effect, although it has not been studied in patients with active renal or CNS disease.

Adjunctive therapies for SLE include hydroxychloroquine, Angiotensin Converting Enzyme Inhibitors (ACEi) or Receptor Blockers (ARB) to maintain blood pressure ≤130/80 mmHg, statins to prevent atherosclerosis, aspirin and anticoagulants. Patients with stable SLE should be immunised against influenza, tetanus, and pneumovax to prevent infections, although live virus vaccines should be avoided in immunosuppressed patients (prednisone ≥20 mg/qd). Vaccination against varicella zoster virus should be considered to prevent shingles. Strategies to prevent bone loss and increase bone mass are also important.

Advances in SLE therapy: ***Ricard Cervera (Spain)***

Professor Cervera presented the most advanced immunosuppressive regimens that have been used to treat patients with SLE, analysing the trials performed to assess the safety and efficacy of immunosuppressive drugs.

Five-year survival among patients with systemic lupus erythematosus (SLE) has improved dramatically over the last 50 years, from just 50% in the 1960s to 95% in 2006, mainly due to better treatment strategies. However, currently-available drugs are associated with significant toxicity and the therapeutic challenge has moved away from survival in the acute phase towards long-term survival with fewer side effects.

Advanced immunotherapies introduced within the last few years include low dose IV cyclophosphamide (CYP), mycophenolate mofetil (MMF), tacrolimus, and biologic treatments. The ‘Euro-Lupus’ sequential regimen of low-dose pulse CYP followed by azathioprine achieved good clinical results in the very long term.[47] However, mortality remained high (8%), and other drugs were sought. MMF was introduced in 2000,[62] and subsequent studies have shown it has a similar efficacy to CYP but a better side effect profile.[66] Calcineurin inhibitors such as tacrolimus have been widely researched in Asia, and shown to be effective as an induction and maintenance therapy for lupus nephritis, particularly when used as

combination therapy with MMF.

Emerging Therapies

Calcineurin inhibitors are effective in non-renal SLE. Cyclosporin A and tacrolimus have both shown promise in proliferative lupus nephritis, while triple induction therapy with MMF+ tacrolimus + steroids (multi-target therapy) was better at inducing complete remission of class V+IV lupus nephritis compared with intravenous CYP, with particularly rapid reductions in proteinuria in the tacrolimus group.[64] Mizoribine behaves like MMF, while mammalian target of rapamycin (mTOR) inhibitors are effective in animal models of lupus.

Biologic therapies, which target specific cells in the immune system, are the most recent addition to the armamentarium of drugs for SLE. Targeted therapies include anti-CD20 antibodies, abatacept, atacicept, belimumab, and protein kinase C inhibitors. Belimumab, a human monoclonal antibody which targets the B Lymphocyte Stimulator (BLyS) - B-cell activating factor (BAFF) complex, is effective in SLE.[67-69]

Conclusion

The first satellite meeting of the Lupus Academy was a huge success, and many delegates provided positive feedback. The combination of interactive workshops and presentations from world-renowned experts in all aspects of SLE management provided delegates with new insights into this difficult disease. Current advances in the management of neuropsychiatric SLE, lupus nephritis and treat-to-target concepts were reviewed and discussed. Advances in SLE therapy and best practice for optimising outcomes will have a positive impact on current clinical practice

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