3rd Annual Meeting of the Lupus Academy

Maritim Hotel, Berlin, Germany

7–9th March 2014

Meeting Report

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<tr>
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<td>Amoura Hospitalier Pitié-Salpêtrière</td>
<td>France</td>
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<td>Professor Ian</td>
<td>Bruce The University of Manchester</td>
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<td>Dr Andrea</td>
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<td>Professor Dr Thomas</td>
<td>Dörner Charité University Hospital Berlin</td>
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<td>Fischer-Betz Heinrich-Heine-Universität Düsseldorf</td>
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<td>Furie North Shore-LIJ Health System</td>
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<td>Professor Bevra</td>
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<td>Professor Dr Tom</td>
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<td>Professor David</td>
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<td>Professor Munther</td>
<td>Khamashta St Thomas' Hospital London</td>
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<td>Professor Roger A.</td>
<td>Levy State University of Rio de Janeiro</td>
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<td>Dr Elizabeth</td>
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<td>Professor Eric</td>
<td>Morand Monash University Medical Centre</td>
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<td>Associate Professor</td>
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<td>Professor Sandra</td>
<td>Navarra University of Santo Tomas Hospital</td>
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<td>Professor Lars</td>
<td>Rönnblom University of Uppsala</td>
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<td>Associate Professor</td>
<td>Elisabet Karolinska University Hospital</td>
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<tr>
<td>Professor Murray B</td>
<td>Urowitz University of Toronto</td>
<td>Canada</td>
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<td>Professor Ronald</td>
<td>van Vollenhoven Karolinska University Hospital</td>
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<tr>
<td>Professor Arturo</td>
<td>Zychlinsky Max Planck Institute for Infection Biology</td>
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Introduction
The Lupus Academy is a long-term initiative committed to improving patient outcomes in systemic lupus erythematosus and allied diseases. By providing a highly interactive educational forum, the Lupus Academy is dedicated to sharing best clinical practice through the dissemination and discussion of cutting edge scientific and clinical research.

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

The 3rd Annual Meeting of the Lupus Academy was held in Berlin, Germany, in March 2014, with the aim of reviewing and discussing insights in global research and clinical practice in lupus and associated diseases. This two day meeting brought together >240 clinicians and scientists, with a specialist interest in lupus, from around the world. The meeting was CME accredited and was designated for a maximum of 10 European CME credits.

The scientific programme, developed by a Steering Committee of nine international experts, was intended to provide a highly interactive forum through which information and experiences about the management of lupus could be exchanged.

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

## Friday 7th March

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<tr>
<th>Time</th>
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<tr>
<td>18:30</td>
<td>Opening Address</td>
<td>Thomas Dörner (Germany)</td>
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<tr>
<td>18:50</td>
<td>Keynote Lectures</td>
<td><strong>Moderator: Ronald F. van Vollenhoven (Sweden)</strong></td>
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<td>18:50</td>
<td>Low disease activity: a realistic therapeutic goal in SLE?</td>
<td>Eric Morand (Australia)</td>
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<tr>
<td>19:30</td>
<td>NETs: from infection to autoimmunity</td>
<td>Arturo Zychlinsky (Germany)</td>
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## Saturday 8th March

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<td>07:00–08:15</td>
<td>Breakfast</td>
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<tr>
<td>08:30</td>
<td>Plenary I: Disease monitoring and management updates</td>
<td><strong>Moderator: Thomas Dörner (Germany)</strong></td>
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<td>08:30</td>
<td>Update on the diagnosis and management of neuropsychiatric SLE</td>
<td>Tom W.J. Huizinga (The Netherlands)</td>
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<td>09:00</td>
<td>Update on the management of lupus nephritis</td>
<td>Bevra H. Hahn (United States)</td>
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<tr>
<td>09:30</td>
<td>Use of activity indices to assess clinical involvement in lupus</td>
<td>David A. Isenberg (United Kingdom)</td>
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<tr>
<td>10:00</td>
<td>Discussion</td>
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### Case Study Workshops (AM)

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<tbody>
<tr>
<td>11:00</td>
<td>Case Study Workshop Difficult lupus</td>
<td><strong>Moderator: Murray B. Urowitz (Canada)</strong></td>
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<td>Sandra V. Navarra (Philippines) &amp;</td>
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<td>Eric Morand (Australia)</td>
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<td>11:00</td>
<td>Case Study Workshop Cardiovascular disease in SLE</td>
<td><strong>Moderator: Andrea Doria (Italy)</strong></td>
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<td>Elisabet Svenungsson (Sweden) &amp;</td>
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<tr>
<td></td>
<td></td>
<td>Ian N. Bruce (United Kingdom)</td>
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<tr>
<td>11:00</td>
<td>Case Study Workshop Bone health and vitamin D</td>
<td><strong>Moderator: Roger A. Levy (Brazil)</strong></td>
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<td>Ricard Cervera (Spain) &amp;</td>
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<td>Zahir Amour (France)</td>
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<td>11:00</td>
<td>Case Study Workshop Lupus nephritis</td>
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<td>Falk Hiepe (Germany) &amp;</td>
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<td>Richard A. Furie (United States)</td>
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#### Case Study Workshops (PM)

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<td>13.30</td>
<td>Murray B. Urowitz (Canada)</td>
<td>Difficult lupus</td>
<td>Sandra V. Navarra (Philippines) &amp; Eric Morand (Australia)</td>
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<tr>
<td>13.30</td>
<td>Andrea Doria (Italy)</td>
<td>Cardiovascular disease in SLE</td>
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<tr>
<td>13.30</td>
<td>Roger A. Levy (Brazil)</td>
<td>Bone health and vitamin D</td>
<td>Ricard Cervera (Spain) &amp; Zahir Amoura (France)</td>
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<tr>
<td>13.30</td>
<td>Bevra H. Hahn (United States)</td>
<td>Lupus nephritis</td>
<td>Falk Hiepe (Germany) &amp; Richard A. Furie (United States)</td>
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<td>Interferon as a therapeutic target in SLE: why and how?</td>
<td>Lars Rönnblom (Sweden)</td>
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<td>15.40</td>
<td>Doing small open trials in lupus: experiences with anti-TNF</td>
<td>Martin Aringer (Germany)</td>
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<td>16.10</td>
<td>Is there a place for kinase blockers in SLE?</td>
<td>Liz Jury (United Kingdom)</td>
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<td>17.00</td>
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### Sunday 9th March

#### Breakfast

07:00–08:15 Breakfast

#### Plenary III: Challenges in treatment

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<td>Treat-to-target in SLE</td>
<td>Marta Mosca (Italy)</td>
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<tr>
<td>09.15</td>
<td>Pregnancy issues in SLE</td>
<td>Rebecca Fischer-Betz (Germany)</td>
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<tr>
<td>09.45</td>
<td>Optimal management of hypercoagulability states in SLE</td>
<td>Roger A. Levy (Brazil)</td>
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<td>10.45</td>
<td>Glucocorticoid-free treatment for lupus nephritis: a paradigm shift in the making?</td>
<td>Liz Lightstone (United Kingdom)</td>
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<tr>
<td>11.15</td>
<td>Optimising outcomes in SLE: best practice</td>
<td>Andrea Doria (Italy)</td>
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<tr>
<td>11.45</td>
<td>Biologics: the future of SLE treatment?</td>
<td>Ronald F. van Vollenhoven (Sweden)</td>
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<td>12.15</td>
<td>Discussion</td>
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<tr>
<td>12.30</td>
<td>Summary and close</td>
<td>Sandra V. Navarra (Philippines)</td>
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<td>Ronald F. van Vollenhoven (Sweden)</td>
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**Keynote Lectures**

**Low disease activity: a realistic therapeutic goal in SLE?: Eric Morand (Australia)**

Professor Morand’s presentation provided insights into the potential value of a treat-to-target approach in SLE, highlighting the importance of developing a robust definition (LLDAS) and validation of the treatment target i.e., measuring a low disease activity state in SLE as a predictor of improved outcomes.

Despite patients receiving the best standard of care, current management of systemic lupus erythematosus (SLE) leaves too many patients with poor outcomes. Disease activity is classified on a continuum (Figure 1) and existing instruments used to quantify disease activity are either too complicated for everyday practice or not comprehensive enough given the heterogeneous nature of SLE and its multiple manifestations.

*Figure 1: Continuum of disease activity.*

Some new concepts in SLE have helped advance measuring disease activity over time, including measurement of ‘persistently active disease’, in which patients have a SLEDAI score of ≥4 for two consecutive visits. Another concept is the time-adjusted mean SLEDAI, which is a useful way of integrating disease activity overtime, which allows us to effectively quantify SLE disease activity over time. These concepts have allowed us to quantify differences in disease activity among patients of different ethnic origins. These instruments can also be used in biomarker studies, which are necessary to advance the validation of therapeutic targets. However, despite these measurement tools, mortality has plateaued at a level at which an unacceptable number of patients still die prematurely from SLE. Accrued organ damage, which is a key predictor of mortality, seems to be all too common, even in studies at leading centers, where organ damage is seen to increase over time despite receiving the best possible care. Given that disease activity drives damage there is a need for a treat-to-target approach SLE that focuses on lowering disease activity.

Treat-to-target approaches have resulted in improved outcomes in other disease areas including hypertension, diabetes, and rheumatoid arthritis (RA). RA studies have shown that treat-to-target approaches, with decision assisted treatment escalation, have resulted in lower disease activity states and better radiographic outcomes than with conventional treatment approaches. It is important to note that these improved outcomes were achieved through modifying approaches to treatment with existing drugs rather than with the introduction of new drugs.

Although there is a lot to learn from the RA treat-to-target experience, SLE is a highly heterogeneous disease where disease activity is more difficult to measure. Moreover, unlike RA, using remission as a target in SLE is not realistic as this state is achieved by only a small minority of patients and is therefore not useful as a measurement tool in clinical care/research. The Asia Pacific Lupus Collaboration
(APLC) is working on a core hypotheses that whereas active disease is heterogeneous, low disease activity (i.e. the desired outcome of therapy) is more homogenous and, therefore, the relative absence of disease could represent a feasible potential outcome measure. The APLC have developed a conceptual definition of a lupus low disease activity state (LLDAS) “A state which if sustained, is associated with a low likelihood of adverse outcome”. This serves as a foundation for reaching a consensus definition of LLDAS, through generating items for an empirical approach. Work to generate this definition is nearing completion and APLC investigators have commenced a multicentre longitudinal study to validate a definition of LLDAS against outcomes such as organ damage accrual.

**NETs: from infection to autoimmunity: Arturo Zychlinsky (Germany)**

Professor Zychlinsky’s presentation provided insights into the role of neutrophil extracellular traps (NETs) in limiting infection, activating the immune system and, importantly, their role in the initiation and exacerbation of autoimmune responses, notably systemic lupus erythematosus.

Neutrophils are the most abundant white blood cells in the immune system, yet they are hard to study as they develop in the bone marrow and only survive about 6 hours in circulation. Phagocytosis, the primary mechanism of neutrophil biology, was first reported in the 1880s and is essential for health. More recently, a second mechanism of neutrophil biology was discovered, the development of neutrophil extracellular traps (NETs), which have evolved to trap bacteria. NETs are made of processed chromatin bound to granular and other cytoplasmic proteins; their specific composition includes histone 2A, elastase and DNA. In addition to being components of the NETs, DNA, histones and neutrophil proteins are also main targets of autoantibodies in lupus.

**Mechanism of NET Formation**

The mechanism of NET formation, activation and their role in immunity and autoimmunity is complex and not yet completely understood. NETs result from a unique form of cell death, called NETosis, where neutrophils undergo dramatic morphological changes following activation by kinases. During NETosis enzymes (protease neutrophil elastase and myeloperoxidase) in the cytoplasm of the neutrophil travel to the nucleus to modify histones, which results in the relaxation of chromatin and the formation of NETs. After about 2 hours the expanded nucleus of the neutrophil expands and contracts until the cell membrane rupture and the cell’s contents, including the NETs, are released, where they perform their short lived role in the immune system.

**NETs and Infection**

NETs have an important role in fighting infection. The first function of the NET is to trap bacteria and prevent dissemination. Secondly they disarm bacteria by releasing components to degrade the bacteria before killing the bacteria. The antimicrobial activity of NETs has been shown to kill around 25% of a *shigella* and 35% of a *staphylococcus* infection in 20 minutes. Looking at NETs in experimental fungal infections, NETs completely cover yeast...indicating that fungi induce NETs easily.

The importance of the antimicrobial activity of NETs has been demonstrated in a patient with chronic granulomatous disease (CGD) and an aspergillus infection. This CGD patient could not produce his own NETs and succumbing to aspergillus infection, had spent 4 years in a lamina flow hood, yet the infection had not subsided. Restoration of NET formation using gene therapy resulted in subsequent killing of the aspergillus efficiently with the patient making a full recovery. Once the infection is under control, and inflammation reduces the NETs are degraded and removed by DNase1.
NETs and Autoimmunity
NETs must be balanced, too few and the body is left susceptible to infection, too many and there is a risk of autoimmunity. NETs have been found to be involved in preeclampsia, cystic fibrosis, asthma, sepsis, thrombosis and systemic lupus erythematosus (SLE) (Figure 1).

*Figure 1. Putative role of NETs in SLE.*

Neutrophils, specifically low density granulocytes (LDGs) in patients with SLE are more prone to making NETs. These LDGs make NETs without the need for activation and are present in lupus patients in varying degree; it is also likely that these LDGs are also present in other diseases. SLE antibodies trigger NETs and SLE patients are more responsive to antibodies than healthy donors (ie. Patients with SLE make more NETs in response to antibodies). The high titre of autoantibodies in SLE patients triggers neutrophils to make NETs, which in turn trigger dendritic cells to make interferon alpha and also promote presentation of the NET antigens. Moreover, some patients with SLE are deficient in DNAse1 and cannot degrade NETs. Analysis of such patients revealed some were carrying anti-DNAse antibodies and others anti-NETs antibodies. Correlation of the degraders and non-degraders showed that non-degraders are more likely to get lupus nephritis than degraders (70% vs 30%).
Plenary I: Disease monitoring and management updates

Update on the diagnosis and management of neuropsychiatric SLE:  
**Tom Huizinga**  
(The Netherlands)

Professor Huizinga’s presentation provided valuable insights into developments in the diagnosis of NP SLE. Starting with preclinical models in mice and translating learnings in clinical practice this presentation highlights the value of new imaging techniques in earlier diagnosis of NPSLE.

Up to 80% of patients with systemic lupus erythematosus (SLE) have neuropsychiatric symptoms, the diagnosis of which is often reached through a process of elimination. The pathogenesis of neuropsychiatric SLE (NPSLE) centers around autoimmune related vasculopathy and damage to the blood brain barrier. If a lupus patient presents with a psychosis it is important to always consider differential diagnosis first. A treatment strategy is triggered by pathogenesis (anticlotting and anti-CNS antibodies) and prognosis (waxing and waning symptoms) that determines the clinical course of the disease.

Preclinical Insights

Studies in mice suggest that anti-DNA antibodies may mediate brain damage in SLE by cross-reacting with NMDA receptors, subsequently mediating non-thrombotic and non-vasculitic abnormalities of the CNS. In another study, immunized mice were given lipopolysaccharide (LPS), following which anti-NR2 antibodies accessed the brain where they bound to hippocampal neurons, resulting in neuronal death and cognitive dysfunction. Another study showed opening the blood brain barrier at the amygdala with adrenalin resulted in a different emotional behaviour. There is some evidence that this also occurs in humans with SLE, where patients with anti-NMDAR antibodies exhibited more damage (p=0.001) in the amygdala than those without. Thus antigen binding in NPSLE does occur and produces neuronal damage at the binding site, resulting in specific NPSLE symptoms.

Clinical Practice Applications

It is also possible that lupus-autoantibodies can cause vasculopathy, microthrombosis and microinfarction through compliment (C1q and C4d) activation in patients with SLE, with C1d and C4d are more prevalent in patients with SLE versus controls. Moreover, C1d and C4d were found in vessels affected by vasculopathy and C4d was associated with microthrombi. It is antibody deposition that initiates compliment activation and subsequent vasculopathy, microinfarction and microthrombi, which are found diffusely throughout the brain in the vicinity of white matter hypersensitivities. Imaging (7Tesla MRI) does not always detect these abnormal pathologies (ie a normal MRI does not mean patients have not got NPSLE). Unlike qualitative MRIs, quantitative MRIs have a higher sensitivity for diffuse structural abnormalities. Magnetisation transfer imaging in patients with a history of NPSLE has clearly shown diffuse structural abnormalities, highlighting its importance as an imagine technique in the diagnosis and management of patients with NPSLE.
Update on the management of lupus nephritis: Bevra Hahn (USA)

Professor Hahn’s presentation provided a comprehensive update on the management of lupus nephritis, with an overview of current EULAR and ACR guidelines and treatment options with respect to induction and maintenance of improvement, prevention of damage and achieving good quality of life for patients.

Lupus nephritis (LN) is the result of complex interplay between the innate and adaptive immune systems. Since the 1990s we have learned that this begins with antibody deposition, activating complement, followed the activation of myriad of infiltrates, monocytes, macrophages, dendritic cells, B cells and T cells which release proteases, fibrosing growth factors, reactive oxygen species resulting in damage and the subsequent release of antibodies and then more autoantibody deposition.

Our improving understanding of the innate and adapted immune systems, including the complex plasticity of T cells and their interplay with B cells, cytokines and potential receptor targets, have allowed us to begin developing more targeted therapies for lupus. Current treatments for lupus nephritis (LN) include glucocorticoids (GC), which act on both innate and adaptive immune systems, hydroxychloroquine which acts on the innate immune system and cyclophosphamide (CYC), azathioprine (AZA), belimumab, mycophenolate mofetil (MMF) and rituximab, which act on the adaptive immune system.

Lupus Nephritis: Treatment Goals

Goals of therapy are induction and maintenance of improvement, prevention of damage and acceptable quality of life for the patient. Both EULAR and ACR guidelines state that immunosuppressive treatment (GC, MMF, CYC) of LN must be guided by renal biopsy. Treatment goals are defined as survival, maintenance of glomerular filtration rate (GFR), prevention of flares and minimising harm (Table 1).

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<td>Complete response (CR)</td>
<td>&lt;50 mg/mmol</td>
<td>Within 10% of starting levels</td>
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<tr>
<td>Partial response (PR)</td>
<td>≥50%</td>
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Induction of Improvement

Data from 1982, before dialysis and renal transplant options, show that high-dose corticosteroids are lifesaving and without them patients with type IV glomular nephritis often died within 2 years. There is much, however, that we don’t know about GCs such as if the initial IV GC pulse is necessary, what the best dose for induction is, most appropriate dose tapering schedules or even if long-term daily use of GCs is necessary.

For induction of improvement, EULAR recommends three pulses of IV GCs (methylprednisolone [MP] 500–700 mg) followed by 0.5 mg/kg/d for 4 weeks, tapering ≤10 mg/day by 4–6 months. In addition, MMF 3 g/day for 6 months or CYC 3 g over 6 months. Where there are adverse prognostic factors (ie. decreased GFR, crescents, fibrinoid necrosis), high dose IV CYC 0.75-1g/m² for 6 months or oral CYC 2–2.5 mg/kg for 3 months is recommended.

A recent meta-analysis of short term trials has shown that MMF is as good as CYC in induction of improvement at 6 months in LN; however, MMF was not shown to be safer, with higher rates of death and end stage renal disease (ESRD). There are also data showing that IV CYC is as good in low dose (500 mg CYC q2w for 6 months) as it is in high dose (500–1000 mg/m2 q/m for 6 months). There is,
however, a lack of knowledge about the effectiveness of CYC in different races; with African Americans, Latin Americans and Afro-Carribbeans less responsive to low dose CYC than Caucasians and Asians.  

**Maintenance of Improvement**

ACR guidelines recommend only using AZA for maintenance and not induction of improvement. Grootscholten et al (2006) found that induction with AZA, as opposed to CYC, resulted in doubling of serum creatinine over 10 years and a higher likelihood of relapse and renal failure. EULAR recommends AZA as an alternative to MMF or CYC in patients without adverse prognostic factors or when MMF/CYC are contraindicated/not tolerated, noting there is a higher flare risk.

An analysis of the ALMS trial has shown that patients are likely to be good responders to MMF or IV CYC if, following 8 weeks of treatment, they have a >25% reduction in proteinuria and normalisation of complement (C3 and/or C4). ACR guidelines for patients with class V LN and nephrotic range proteinuria (≥3 g/24h) recommend management with MMF 2–3 g/d plus prednisone 0.5 mg/kg/d for 6 months. If the patient’s symptoms improve, then maintenance treatment with MMF 1–2 g/d or AZA 2 mg/kg/d is recommended. If the patient’s symptoms don’t improve, then treatment with CYC 500–1000 mg/m2 monthly x 6 plus GC pulse, followed by prednisone 0.5–1.0 mg/kg/d is recommended.

EULAR guidelines for maintenance of improvement recommend MMF 2 g QD or AZA 2 mg/kg/d for 3 years in patients who have complete or partial response over 6–12 months, this constitutes about 50–75% of all patients. Patients showing with no response over 3–12 months should switch from MMF to CYC (vice versa) or add rituximab. If there is still no response after 6 months, then ACR guidelines recommend rituximab, a calcineurin inhibitor or other experimental treatments.

MMF, methotrexate (MTX) and CYC are teratogenic and contraindicated in women who are/wish to become pregnant; therefore pregnancy is a key reason for patients being switched to AZA. Long term data in patients induced with CYC, showed equivalent efficacy of MMF and AZA in maintaining improvement over a 5 years. Conversely, other data from the US in patients randomised to receive MMF or AZA (following a successful response to MMF or IV CYC in a 6 month induction phase) showed MMF to have superior efficacy over a 3 year period.

There is mixed evidence for rituximab, with open trials in Europe showing 70–80% response rates in patients failing other treatments, whilst other trials have shown no additive effect with rituximab in patients taking MMF, AZA or MTX plus prednisone and hydroxychloroquine. Patients have exhibited fewer flares when taking rituximab and steroids can be safely avoided when treating LN with IV rituximab (1 g) and MMF with high numbers of patients achieving PR (90%) and CR (72%).

Adjunctive maintenance therapy for all patients includes:

- hydroxychloroquine for reduction of renal damage
- angiotensin converting enzyme inhibitors (ACEi) or receptor blockers (ARB) for patients with urine protein/creatinine ≥0.5 g/24 hours for hypertension—maintaining ≤130/80 blood pressure
- statins for LDL >100 mg/dL
- aspirin if anti-cardiolipin antibodies (anti-CL) +, calcium plus vitamin D, immunisation with non-live vaccines
- anticoagulation if serum albumin <20 g/litre, especially if anti-CL+

**Managing Poor-/Non-Responders**

Even among good responders, flares and overall deterioration are not unusual as medications are tapered; this results in long term use of GC and immunosuppression. 20–25% of patients with LN do not have sustained CR or PR after 6–12 months of treatment and approximately 85% of patients with systemic lupus erythematosus (SLE) have persistent active disease or flares in 1 year of observation.
One choice for poor-responders is to stop immunosuppression, survival in renal transplant patients is good (88% at 1 year, 81% at 5 years and 71% at 10 years).\textsuperscript{45} Recurrence of SLE in renal biopsies is low with 25% of transplants rejecting and SLE recurrence in 3%.\textsuperscript{46}

Experimental treatment options are also being aggressively pursed in clinical trials and include therapies targeted at B-cells, T-cells, monocytes, cytokines, intracellular signalling molecules and proteasomes.\textsuperscript{47-49} Three phase III trials of the B lymphocyte stimulator-specific inhibitor belimumab in patients (n=1684) with SLE have shown a highly significant difference in treatment response with belimumab \textit{versus} placebo. Belimumab reduced flares, had a small steroid sparing effect, reduced fatigue and improved quality of life in patients with SLE.\textsuperscript{50-52} Abatacept has also shown evidence of biologic activity in patients with SLE, albeit not significant this was probably the result of a more stringent definition of success (CR) compared with clinical trials of other biologic therapies.\textsuperscript{53} Interestingly, Wolfsy \textit{et al} have shown that the definition of CR can determine whether or not a LN trial is interpreted as a success or failure and that different definitions support conflicting conclusions.\textsuperscript{54}

Management of LN has improved dramatically since the 1980s, with guidelines reflecting a greater understanding of what is needed for successful induction and maintenance of improvement and prevention of damage with current therapies. Importantly, there is also a renewed drive to discover and develop targeted therapies, which may further improve patient outcomes and quality of life.

Use of activity indices to assess clinical involvement: \textit{David A. Isenberg (United Kingdom)}

Professor Isenberg’s presentation provided insight into the value and importance of using disease activity indices, like BILAG and SLEDAI, in both clinical practice and clinical trials to allow identification and comparison of clinical disease features between different patients and from different centers.

When assessing patients with systemic lupus erythematosus (SLE) it is important to capture and distinguish disease activity from damage and understand the patient’s perception of the disease, which is usually different from the clinician’s perception. Patients often have many clinical features and some may be due to concomitant disease rather than SLE. Using a uniform system of assessment to allow comparisons between groups of patients is the ideal. From the mid-1980s, today’s global scoring systems (SLAM, ECLAM, SLEDAI) and individual organ/system (BILAG) were created and have since been refined in line with clinical practice. SLEDAI and BILAG are now the principle activity indices in use.

\textbf{British Isles Assessment Group (BILAG)}

Since 1984 BILAG have aimed improve global scoring by using the principle of the ‘physician's intention to treat’, originally through the division of SLE activity into 8 different systems/organs. This concept involved agreeing groups of clinical features and serological tests that would make physicians want to treat SLE with varying amounts of drug therapies (categories A, B or C) or no therapy at all (categories D and E). Focussing on group A, patients thought likely to be treated with 220mg of Prednisolone or an immnosuppressive drug we successfully tested the hypothesis across the five different BILAG centers.

In 2004 BILAG was updated to provide a more comprehensive system-based disease activity measure. BILAG 2004 scoring comprises five categories (Figure 1), which allow physicians identify disease activity patterns across time and the 9 organs/systems (Constitutional, Mucocutaneous, Neurological, Musculoskeletal, Cardiovascular & Respiratory, Gastrointestinal, Ophthalmological, Renal, Haematological).\textsuperscript{55} In practice, the physicians complete a patient assessment form, from which the A–E scores may be determined manually or using the iBLIPS computer system across 9 organs/systems.
Figure 1. An Example of the Assessment Systems in BILAG 2004 – Cardiovascular/Respiratory Disease.

Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)
In 2002 Gladman et al developed the SLEDAI following studies in which clinicians rated the importance of 37 variables defining SLE activity and subsequent analysis identified 24 of these to be the most important in contributing to the clinical judgment of disease activity across 9 systems.\textsuperscript{56}

Comparison of BILAG, SLEDAI and SLAM
Although these disease activity systems had been developed independently there are core similarities. Three studies showed good comparability between these three systems in terms of validation, reliability and sensitivity to change.\textsuperscript{57-59} Further confirmation of this comes from a study of 75 patients by Bencivelli et al.\textsuperscript{60}

In practice, BILAG requires the physician to ask questions about SLE disease activity in the 9 organs/systems, then clinical feature(s) in the past month should be assessed as not present (0), improving (1), the same (2), worse (3) or new/recurrent (4). These data, along with blood pressure, urinalysis and renal and haematology blood tests, are entered in to iBLIPS system. Similarly, SLEDAI requires the physician to ask questions about activity in a broad range of organs/systems, but it does not capture gastrointestinal or ophthalmic involvement and scoring sheets are normally completed by hand. Advantages and disadvantages of both systems are outlined in table 1.

There were issues around the sensitivity of global scores as even if the total score is the same at each subsequent assessment, the subscores may be different (ie. the total score can mask underlying damage).
Table 1. Advantages and disadvantages of original BILAG and SLEDAI.

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<th>Advantages</th>
<th>Disadvantages</th>
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<tr>
<td><strong>BILAG</strong></td>
<td>• Comprehensive</td>
<td>• Some systems (GI/ophthalmology) not involved &gt;95% of assessments</td>
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<td></td>
<td>• Relatively easy to complete most of the time</td>
<td>• More time-consuming with more complex patients</td>
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<td></td>
<td>• Computerised system available to determine the scoring</td>
<td>• Needs someone to enter the data</td>
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<td></td>
<td>• (Done right!) provides an accurate and complete assessment; of great value when comparing to activity with serology (and in clinical trials)</td>
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<td></td>
<td>• Distinguishes clinical features improving/deteriorating/staying the same</td>
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<tr>
<td><strong>SLEDAI</strong></td>
<td>• Reasonably comprehensive</td>
<td>• Not fully comprehensive</td>
</tr>
<tr>
<td></td>
<td>• Easy to complete and score</td>
<td>• The global score approach masks how the final number was arrived at</td>
</tr>
<tr>
<td></td>
<td>• Easy to compare to serology results</td>
<td>• Does not distinguish clinical features which have not changed/partially improved/ deteriorated</td>
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Updated BILAG (2004) and SLEDAI-2K Indices
Several studies have looked to test these indices further. A two centre study used BILAG showed patients with a lupus flare were treated as expected along the principles upon which BILAG was devised.\(^{61}\) Another 5 year study revealed death and damage increase were strongly predicted by high total disease activity (p<0.001) and the average number of ‘A’ flares (p=0.004).\(^{62}\)

The reasons for changing the BILAG system in 2004 included the need to take out items that recorded damage as opposed to activity, include adequate measures to capture gastrointestinal and ophthalmic involvement and refinements to renal scoring. Similarly, changes to the SLEDAI system have been made as the original was not validated and did not allow for measuring chronic persistent activity. Changes resulted in SLEDAI-2K, which allows for persistent activity in rash, mucous membranes, alopecia and proteinuria\(^{56}\). Both revised indices have been shown to be valid reliable and sensitive to change in many patients.\(^{53}\)

There is still progress to be made in capturing lupus activity. Although severe flares are well-defined, mild and moderate flares are less so. Testing these definitions in paper patient and real patient exercises and ultimately in clinical trials is important as is correlating these definitions with biomarkers.
Several observations have suggested an important role for the type I interferon (IFN) system in the aetiopathogenesis of systemic lupus erythematosus (SLE). Type I IFN administration can cause SLE, and the immunostimulatory effects of Type I IFN causes an immune activation resembling that seen in SLE. SLE patients have endogenous inducers of type I IFN production, and type I IFN-regulated genes (the interferon signature) are over-expressed, resulting in a prominent interferon signature, which is noticeable both early in the course of SLE and during severe flares. Gene variants in the type I IFN signalling pathway (production, regulation and response) increase risk of SLE.

Regulation of the type I IFN response is abnormal in lupus patients – people without SLE produce type 1 IFN as a response to infection, but when the infection clears these IFNs are switched off; in SLE, this capacity to switch off IFNs is disturbed, type I IFNs must be blocked another way.

There are several things to consider before starting type I IFN blockade. Type I IFNs constitute a large family of proteins (>15) and are important in SLE both for clinical disease manifestations (acute) and the central autoimmune process (long term). Several pathways are involved in the expression of the IFN signature, which is more complex in patients with SLE than a virus-induced signature. However, type I IFNs are our most important defence against viral infections, and infections that escape them are highly dangerous.

Plasmacytoid dendritic cells (pDCs) are the most potent producers of type I IFNs, contributing to immune homeostasis and protecting from viral infections. Immature pDCs are involved in immune tolerance, picking up autoantigens and migrating to the thymus, causing clonal deletion of autoreactive cells, inducing anergy and regulatory T-cells. However, under viral attack, pDCs become activated and secrete type I and type II IFNs and a number of other proinflammatory cytokines. As the pDCs mature, they get the phenotype of an antigen-presenting cell.

pDCs have a very low frequency in the body. They can produce up to \(10^9\) molecules of IFN in the 20 hours after they encounter a virus, and once activated, develop chemokine receptors, so they can migrate to areas of inflammation. A number of receptors sense nucleic acids, this is important for the body to identify viral intruders promptly, activate the inflammatory system and defend against attack.

The type I IFN activates >2000 genes, which affect major signalling pathways. If an IFN encounters an IFN receptor, IFN-stimulatory genes are expressed, triggering production of a protein to prevent viruses from replicating. Cell proliferation is slowed and immune response is activated. NETosis, chromatin, LL37 and amyloid fibrils can all trigger IFN production in pDCs. Many genes are associated with the IFN system and increased risk of lupus and, together with what is known about IFNs, scientists can produce a model of SLE.

pDCs produce IFN when they encounter a virus, but in lupus patients there is increased apoptosis and reduced clearance of apoptotic cell material and necrotic cells. This releases autoantigens which trigger autoantibody production by B cells (mimicking normal processes to fight infection, but in people without SLE, autoantibodies are cleared). The autoantibodies form immune complexes, such as NETs, which trigger the pDCs. Once IFN is produced, the pDCs mature and activate T-helper cells, which act as anti-presenting cells. IFN also promotes T-cell production and immunoglobulin production by B cells, creating a perpetuating cycle. Monocytes also mature to antigen-presenting cells and activate other cells, which can increase the pDC response; the monocytes down-regulate and control the natural killer (NK) cell's response, but this function is deficient in lupus patients, so they cannot control their NK cells.
in a normal way, which increases the IFN response. The IFNs produced by the pDCs affects a number of other cells (Figure 1) and subsequently affect their cytokine production. The cytokines in red have been blocked in SLE; but only anti-BAFF treatment have been approved so far.\(^67,68\)

**Figure 1. Cytokines in the lupus disease process.\(^68\)**

![Diagram of cytokines in the lupus disease process](image)

The different targets for controlling the IFN system each have advantages and disadvantages. Hypotheses about how therapy might develop include: more efficient inhibition of type I IFNs; targeting type III IFNs; individualised treatment of the IFN system (early versus late disease); targeting inducers of IFN production; and modulating signalling pathways.

**Doing small open trials in lupus: experiences with anti-TNF: Martin Aringer, (Germany)**

Randomised controlled trials are the gold standard for evidence, but sometimes other types of trial are appropriate. Dr Aringer outlines the times and reasons when this might be the case.

Infliximab was tested in small open trial in patients with systemic lupus erythematosus (SLE), and moderate disease activity. This trial had a primary endpoint of safety and secondary endpoints of proteinuria and joint count.\(^1\) Why was running this uncontrolled trial even considered? Earlier trials had shown that tumor necrosis factor (TNF) blockade worked in rheumatoid arthritis (RA),\(^2\) Crohn’s disease,\(^3\) psoriatic arthritis,\(^4\) and ankylosing spondylitis,\(^5\) but there was a perception that it would not work in SLE. There were several reasons for this. Earlier work on NZB x NZW F1 mice showed that recombinant TNF delayed disease onset, although it did not prevent disease, and some mice still went on to develop severe\(^6-8\) or very severe lupus.\(^9\) Under TNF blockade in RA, some patients developed new anti-dsDNA antibodies\(^10\) and occasionally lupus-like symptoms, resulting in concerns about the safety of TNF blockade in SLE. However, in other mouse models, mice made more TNF, and the more inflammation the mouse developed the more TNF was produced.\(^11\)

A trial of TNF blockade in patients with SLE was considered, since serum TNF is high in active SLE, which is not consistent with anti-SLE efficacy. However, the antibody question remained. Because of this, a large RCT was unrealistic, so a short-term, open, single-centre trial with very close clinical surveillance was initiated, with patients being included one by one (phase 1-like), and close surveillance of autoantibody levels throughout. Good long-term follow-up for as long as possible was planned to pick up other disease signals.

The results showed a decrease in SLE activity in patients without arthritis, but a decrease followed by
an increase at around week 12 after infliximab infusion in patients with arthritis. The treatment effect on the lupus arthritis had been lost, and the joint counts returned to pre-treatment baseline levels. Under anti-TNF therapy, anti-dsDNA levels increased, but there was no evidence of SLE flare, and C3c levels remained constant throughout. Anti-dsDNA, and anti-cardiolipin levels, which likewise increased under infliximab, returned to their earlier levels over time.\(^1\)

While long-term follow up of patients maintained on TNF blockade revealed a few severe adverse events (AEs) after many months or years of treatment, short-term TNF blockade resulted in no flares, one thrombotic event, one infusion site reaction and some bacterial infections.\(^1,13\) SLE nephritis under infliximab showed rapid reduction in proteinuria, and a long-term beneficial effect lasting up to 7 years.\(^14\)

Overall, the results from the open trial showed the following results: Safety – no SLE flares, 1 APS episode, and a transient increase in anti-dsDNA and anti-phospholipid antibodies; Preliminary efficacy – short-term effect on arthritis, and an unexpected long-term effect on proteinuria. The adverse event profile of short rem TNF blockade had been consistent with acceptable safety, and two placebo-controlled trials were planned, the first on infliximab and the other on etanercept. However, the safety concerns led to protocol changes, which ultimately prevented recruiting patients to run the trials, which were therefore abandoned.

Small open trials may address safety, but constant surveillance is essential. Underlying potential mechanisms of AEs must be studied in parallel, and parameters need to be quantifiable. At least two organ systems should be monitored to pick up potential efficacy signals.

**Is there a place for kinase blockers in SLE? Liz Jury, United Kingdom**

SLE immunopathogenesis is complex with defects in many aspects of the immune system. Kinases are important in cell signalling, and cell signalling defects are characteristic of SLE. Kinase targets in T- and B-lymphocytes from SLE patients are therefore also key, as are other therapeutic strategies that target cell signalling defects in patients.

Treatment strategies for systemic lupus erythematosus (SLE) include conventional immunosuppression, biologic therapies and use of small molecular-weight agents such as kinase blockers. Protein kinases are key regulators of cell function and ~30% of all human proteins can be modified by kinase activity which adds phosphate groups to proteins (phosphorylation). Kinase activation affects protein function in many ways: it changes enzyme activity and cellular localisation, and changes the way proteins interact with each other. Overall, kinases orchestrate the activity of almost all cellular processes, and are particularly prominent in signal transduction and co-ordination of complex functions, such as the cell cycle.

Protein tyrosine kinases and serine and threonine kinases are the most important in cell signalling. Lymphocyte specific protein tyrosine kinase p56(LCK) is a T lymphocyte-specific membrane-bound molecule associated with co-receptor CD4, it has two tyrosine residues which can become phosphorylated, turning it into active LCK allowing it to act on other substrates.\(^83\) The active kinase combines with T-cell receptors, triggering an intracellular signalling cascade, resulting in the phosphorylation and accumulation of downstream signalling molecules. Cell signaling results in a functional response by the T-cell such as proliferation or cytokine production. After T-cell activation has occurred, inhibitory kinases inactivate LCK again. Similar kinase molecules help control activation of B-cell receptor-associated signaling. Many different defects in T- and B-cell receptor signalling have been described in patients with SLE, all of which cause further increases in T- or B-cell activation.

Defects in cell signalling have been described in many cancers and these defects have been successfully targeted by inhibiting specific kinase signalling molecules and are now established treatments for some cancers. It has been proposed recently that molecules that inhibit kinases could also be used to treat autoimmune disorders in general including patients with lupus. However, although kinase inhibitors have
been seen to be effective in animal models of lupus disease, very few have been used on patients.

The spleen tyrosine kinase (Syk) family of tyrosine kinases are non-receptor cytoplasmic tyrosine kinases, e.g. Syk (in B cells/monocytes) and ZAP-70 (in T cells), which transmit signals from the B-cell receptor and T-cell receptor, FC receptor, and integrins. In T cells from SLE patients Syk (which is more active) replaces ZAP-70 in some cases. Fostamatinib is a small molecule Syk inhibitor which in clinical trials with rheumatoid arthritis patients shows acceptable toxicity and efficacy, reducing inflammation, but there have been no trials in SLE. An in vitro study shows that it suppresses calcium signalling in T cells from SLE patients and it is effective in NZB/NZW, MRL/lpr and BAK/BAX mouse models.

BTK activation could contribute to B-cell hyperactivity in SLE and early clinical studies suggest that ibrutinib blocks BCR signalling, which drives cells into apoptosis and/or disrupts cell migration. As before, it is effective in mouse models of lupus.

BTK and Syk could both be useful in lupus as they target more than one cell – in B-cells blocking BTK could inhibit autoantibody production and in monocytes inhibit abnormal cytokine production.

Mammalian target of rapamycin (mTOR) is a serine/threonine kinase that regulates cell metabolism, cell growth, cell motility, cell survival and proliferation, protein synthesis and transcription. It integrates signals from upstream pathways, including environmental, nutritional and stress signals, growth factors and energy availability. Defects in mTOR are described in a range of diseases including cancer, autoimmunity and obesity, and it is also important in aging. mTOR activity is upregulated in SLE T cells and contributes to T-cell hyperactivation. A pilot study suggests that mTOR inhibitors improves disease activity in patients by blocking mTOR in T lymphocytes.

JAK tyrosine kinases (JAK1, JAK2, JAK3 and TYK2) mediate cytokine and hormone signalling. When activated they phosphorylate downstream molecules (STATs) that regulate gene transcription. Inhibition of JAK kinases has been shown effective in RA, but is not yet approved for RA patients in Europe.

Cell signalling defects are common in patients with SLE and affect a diverse range of molecules from proximal T cell and B cell receptor-associated molecules to nuclear transcription factors and metabolic signalling pathways. Not all defects are seen in all patients, and although some kinase inhibitors have been developed, more research is needed to confirm their safety and efficacy in patients.
Plenary III: Challenges in treatment
Treat-to-target in SLE: Marta Mosca (Italy)

Dr Mosca discusses why T2T is important in lupus, and the considerations and limitations in the T2T approach.

There are many unmet needs in systemic lupus erythematosus (SLE) treatment. Even under treatment, patients have flares or persistent disease activity, damage accrues (eg. osteoporosis and cataracts), steroids are still the main treatment and quality of life and long term survival are impaired. Improving disease outcomes is important and a treat-to-target (T2T) approach has been seen to improve care and patient outcomes in rheumatoid arthritis (RA).

Developing a T2T approach requires identifying a defined measurable variable associated with a bad disease outcome, and treating it to an agreed level within a specified timeframe. Therapeutic options must be available for the target variable. If the target is not met within the prespecified timeframe, the therapy is adapted until it is reached: measure variable, adapt treatment; measure, adapt treatment, and so on. If the target is reached, treatment is maintained and a new target can be set for the future.

Importantly, with respect to drugs, T2T recommendations should be generic, since an optimal outcome should be sought irrespective of the availability of specific drugs. Lifestyle changes can be part of treatment, and this works well in RA and for diabetes control. In RA, T2T recommendations have been developed, and treatment outcomes are measured against these.

In SLE, there are reasonably well-established outcomes, and a number of objective measures, including validated disease activity indices, SLICC damage index and patient reported outcomes. There are also optimised protocols, and new treatment options are being developed. These can be used to guide the development of a T2T strategy, and a T2T steering group met to discuss the way forward: identify the targets, do a systematic literature review, define a research agenda, and develop and agree recommendations.

Targets include control of disease activity, limitation of damage accrual, minimisation of corticosteroids, improved patient survival and quality of life and reduction of drug toxicity and comorbidities. The committee identified 12 areas of key importance to be investigated by a systematic literature review: Disease activity (5 questions), Damage accrual (2 questions) and Treatment strategies (5 questions). They retrieved 814 papers and reviewed 440 of them. This resulted in 5 overarching principles and 11 recommendations, with the aim of treating patients to improve survival, reduce damage and improve QoL, control comorbidities and reduce corticosteroid use.

Disease activity correlates with outcomes (survival, damage, quality of life), and predicts mortality, so the recommendations were based on this principle, and a research agenda was decided for each recommendation.

The question remains: Is T2T in SLE feasible? SLE is a complex heterogeneous disease and the T2T approach will need to be tested in future years. In addition, a T2T approach may impact on outcomes, quality of care and healthcare costs. The research agenda for T2T includes a prospective randomised trial comparing a targeted to standard treatment in SLE; development of definition(s) of remission in SLE; defining a minimally acceptable level of disease activity or damage; development and/or refinement of flare definitions; and studies to determine if there is a ‘safe’ lower level of long-term glucocorticoid exposure.
Pregnancy issues in SLE. Rebecca: Fischer-Betz (Germany)

SLE patients have fewer children than women in the general population, and >50% of women diagnosed with SLE prior to the completion of family planning had fewer children than they hoped for. Their fertility was not reduced, but higher rates of pregnancy loss were associated with a smaller family size, as were concerns about well-being of mother and foetus during pregnancy.

As part of a German long-term study of patients with systemic lupus erythematosus (SLE), a reproductive history questionnaire was mailed to 800 women with SLE. 270 women responded who had never been pregnant. More than 60% had been told that their medication was contraindicated in pregnancy, >50% were worried about getting pregnant because of their illness, nearly 50% had been told not to have children by their doctor, and ~10% had been unable to get pregnant. When disease duration was considered, almost twice as many women with longstanding disease had been misadvised about pregnancy (29% vs 17%).

There are issues in pregnancy for both mother and foetus. For the mother, risks are lupus flare (during pregnancy and postpartum), renal impairment, pre-eclampsia and thrombosis. For the foetus, risks are miscarriage, foetal death, growth restriction, preterm birth and neonatal lupus. Risks were clearly shown in a study of over 16 million pregnancies, of which >13,000 were in lupus patients. Maternal mortality was increased 20-fold with leading causes being infections and thromboembolic complications, with pre-eclampsia occurring in over 20% of SLE patients. However, maternal deaths related to pregnancy in SLE have decreased from 17% in the 1950s to below 1% in 2000–2005, there was a decrease in overall flare rate (from 50–60% to 10–20% in recent publications), most flares are minor (with renal flares being very rare), and flare risk is low (<15 %) if remission ≥6 months. The live birth rate continuously improves and is now ~90% because of a decline in foetal loss, though preterm deliveries are still common. Moreover, a population-based cohort study in Australia found that women with SLE who have a perinatal death in their first pregnancy can expect a live birth for a subsequent pregnancy.

Women at highest risk of complications during pregnancy are those with high disease activity, acute lupus nephritis and high titres of antiphospholipid antibodies. Kwok et al prospectively evaluated 55 pregnancies (from 6 months preconception to 1 year post-delivery). There was a live birth rate of 89%, but women with a history of nephritis had a significantly higher risk for maternal and foetal adverse outcomes. Non-use of hydroxychloroquine (HCQ) was also a risk factor, as was higher disease activity at conception (cut off point, SLEDAI ≥4). The most accurate predictor of adverse foetal outcomes was a flare during pregnancy.

It is recommend that woman with SLE have a stable disease state for at least 6 months before conceiving, but a retrospective study in Korea of 183 SLE pregnancies (1998–2010) predicted a cut-off stable time for SLE pregnancies was 4 months. Pregnancy outcomes in lupus nephritis patients are mostly successful in patients with stable lupus nephritis and normal renal function at time of conception; they may achieve a live birth rate of around 90%. However, there is a risk of worsening renal function in these patients during the pregnancy. EULAR recommendations for pregnancy planning in lupus nephritis state that pregnancy may be planned in patients with inactive SLE and stable renal function for the preceding 6 months. Stable renal disease should be treated with the same drugs that are recommended during pre-pregnancy counselling (HCQ, prednisone, azathioprine) and HCQ should be continued. Aspirin is recommended to reduce the risk of pre-eclampsia, but mycophenolate mofetil and cyclophosphamide should not be used in the last 3 months.

Antiphospholipid antibodies can be detected in ~40% of patients with SLE, and are associated with
recurrent foetal loss (≥10 weeks gestation), as well as maternal thromboembolic events during pregnancy and postpartum; risk is modulated by the patient’s immunological and clinical profiles. Management of antiphospholipid antibody positive patients involves preconception counselling and expert care during pregnancy (rheumatologist, obstetrician, hemostaseologist). Aspirin plus heparin is standard of care.

Foetal problems include neonatal lupus syndrome and congenital heart block, which carries a high morbidity. There is no reliable biomarker, so serial foetal echocardiography is recommended from weeks 18 to 28. HCQ treatment is important in pregnancy and withdrawal leads to an increase in flares. There is no increase in foetal malformation and the follow up of children reveals no negative outcomes. Treatment should be continued even in patients with inactive disease.

Successful pregnancies are possible in most young women with SLE, but active disease is associated with poor outcomes. The best prevention of flares and pregnancy complications is delay of conception until SLE is stable for at least 4–6 months.

**Optimal management of hypercoagulability states in SLE: (Roger A Levy, Brazil)**

In antiphospholipid syndrome (APS), it is a balancing act between maintaining a low risk of a clotting event, and not allowing a bleed either. Professor Levy discusses APS, the most serious thrombophilia in systemic lupus erythematosus (SLE), and implications in its management.

Antiphospholipid syndrome (APS) (or Hughes syndrome) is a serious risk in systemic lupus erythematosus (SLE). Like lupus, APS is a systemic autoimmune disease; any vessel in any system can be damaged, causing problems with the CNS, skin, heart, limbs, eyes, ears, plus pulmonary, adrenal, renal and hepatic problems. APS also causes obstetric problems, including late foetal loss, early recurrent foetal losses, pre-eclampsia, venous and arterial events, and microcirculatory problems.

APS was first described by the group led by Graham Hughes in 1983, in SLE patients and later in that decade by the same group and the other group lead by Alarcon-Segovia as an isolated disease. There are overlaps with SLE, but isolated APS is more prevalent in the general population, affecting men as much as women, at any age, and is triggered by infections, invasive procedures or pregnancy. The antibodies used to diagnose the syndrome are predictive, so you can find people with antibodies and no sign of disease, or a trigger event (second hit) may initiate it. Among SLE patients, 30–40% will be antiphospholipid antibody positive (aPL+), but may not have the syndrome; however 50–70% develop APS within 10 years. Recognised risk factors for thrombosis include hypertension, high cholesterol, obesity, estrogen use and smoking. Primary APS patients may have a positive ANA but that does not mean that they also have SLE – APS and SLE can both exist alone, but a proportion of patients have both; 5% of primary APS patients will develop SLE within 10 years.

New tests are available for aPL antibodies, but diagnosis is still difficult (Figure 1). Other clinical features associated with APS may help with diagnosis or predict prognosis. However, a person can have all the symptoms of APS, but be negative to the classic criteria tests (seronegative APS); they are still at high risk of an atherosclerotic event. Possible explanations for these results are wrong diagnosis, aPL+ reverted to aPL-, or different antibodies present that conventional testing fails to identify. These may guide the development of new tests for APS in the future. A study by Conti showed that sera from patients that were negative to the classical tests had a thrombotic triggering action in vitro, showing an increase in phosphorylate IL-1 receptor associated kinase (IRAK-1) expression and increased tissue factor (TF) release – both thrombotic triggers.
There are a number of APS-associated clinical features, which are thrombotic markers indicative of APS even if other tests are negative. They include superficial vein thrombosis, thrombocytopaenia, haemolytic anaemia, livedo reticularis, heart valve lesions, pulmonary hypertension, alveolar haemorrhage, migraine, myelitis, chorea, epilepsy, cognitive disorder and psychiatric disorders.

In the acute phase, thrombosis treatment and prevention in APS should be the same as for other causes: full dose heparin and/or thrombolysis. Achieve INR target before stopping anticoagulation, and start warfarin before heparin is stopped. In an APS patient, there is a high chance (~20%) of a new thrombotic event when anticoagulation is withdrawn, so this is very important. Recurrent events should prompt an increase in the INR range and addition of an antiplatelet agent.

People with aPL triple (+), LA (+), livedo, heart valve disease, and arterial events are at higher thrombotic risk, but classical risk factors must also be controlled, such as hypertension, high BMI, smoking, lipids, elevated homocysteine and vitamin D deficiency. Vitamin K monitoring is important. APS patients should avoid risky situations, use progestagen contraception, and take LMWH if there is serious infection, an invasive procedure, long flight, or immobilisation. Poor adherence to treatment and monitoring exacerbates risks, and compliance must be maximised. Interactions with other drugs, diet, alcohol, smoking and exercise, and clashes with lupus anticoagulant testing, may all reduce compliance.

New oral anticoagulants are not yet approved for APS, and there are reported complications in their use. Trials are ongoing and the results are awaited.
Plenary IV: Treatment in 2014 and beyond

Glucocorticoid-free treatment for lupus nephritis: a paradigm shift in the making? Liz Lightstone (United Kingdom)

Dr Lightstone asks, is it possible to treat LN without (oral) steroids, and outlines the reasons why she thinks the answer is a resounding ‘Yes’.

Kidney involvement in lupus is common and can be severe, especially in children and people of non-European ethnicity. With remission from lupus nephritis (LN), renal and patient survival is 94–95%, but without remission, renal survival is 46% and 31% at 5 and 10 years, and patient survival is 69% and 60% at 5 and 10 years.115 Predicting response is important, and the ALMS study showed that patients do badly if baseline glomerular filtration rate is <30mls/min/, have low complement (C4) or LN for more than 1 year, but do well if complement (C3/C4) is normalised or there is >25% fall in proteinuria by 8 weeks38 or 50% at 6 months.115

Steroids are still part of all treatment regimens for systemic lupus erythematosus (SLE), but are a major cause of long-term damage. There is no good evidence that they are effective on their own, and the only evidence of where to set the dose is that higher doses are associated with more infections.5,116-120 For effective treatment, rational targeted therapy, related to pathophysiology, which induces remission and prevents flares is needed, as are predictors of good/bad response. Minimising treatment-related toxicities, stopping steroids and improving adherence are also important.

A 2012 cohort study only gave oral steroids for systemic manifestations of lupus and showed similar outcomes at 10 years in patients who took low dose prednisolone as high dose, with no increase in frequency of flares.121 The MYLUPUS open label 24-week trial showed no significant differences between outcomes – complete remission (CR), partial remission (PR) or extra renal manifestations – at 24 weeks despite 50% less cumulative prednisolone, and patients had fewer severe infections, in the low dose steroid arm (0.5 mg/kg starting) compared with the high dose arm (1 mg/kg starting).122 The Bilbao Cruces approach showed the likelihood of reaching remission was much higher with less steroid, with better responses, less accrual of damage and fewer adverse events.123

Evidence from St Mary’s Hospital (London) of steroid avoidance in transplantation showed that using anti CD25R and methylprednisolone for induction, just 1 week of steroids and then tacrolimus plus mycophenolate mofetil (MMF) for maintenance reduced rejection, new onset diabetes and post-transplant weight gain over 1 year.124,125 This paradigm of using a biologic to steroid spare, was extrapolated to lupus nephritis and a novel treatment was developed at the Imperial College Lupus centre.

The Imperial College Lupus Centre RITUXILUP protocol is a steroid minimising regimen which has been used since 1st January 2006 in all new/relapsing LN, if the patient is not already on steroids and does not have rapidly progressive glomerulonephritis/cerebral lupus. The first-line treatment protocol is methylprednisolone 500 mg IV + rituximab 1 g – day 1 and day 15, MMF – starting at 500mg bd and titrating to trough levels 1.4–2.4mg/l. And NO oral steroid. Over the time period followed 90% of patients achieved CR or PR, and 72% achieving CR.44 By 52 weeks, 52% were in CR. Of those not in CR, nine of 13 were re-biopsied for persistent proteinuria and were found to be in histological remission, of whom six went on to achieve CR within 6 months without any further change in immunosuppression.44 There were also low rates of adverse events. Only two patients who stayed on RITUXILUP regimen required maintenance oral steroids, five switched to the modified EUROLUPUS protocol and six patients had short courses of oral steroids.44

However, in 2012 the LUNAR trial concluded that rituximab + MMF + steroids was not superior to MMF + Steroids.126 The outcome measures were stringent with an endpoint of 20% improvement in the proportion achieving CR after one year; PR response was good, but the trial was not powered for this. However, by 78 weeks, the proportion of patients with at least a 50% reduction in proteinuria was significantly higher in the in rituximab arm versus placebo arm (70.8% vs 54.2%, p=0.04). Also, significantly fewer patients in the rituximab arm required the addition of cyclophosphamide at 52 or 78
weeks (0% and 2.8%) vs 11% and 15.3% in the control group. Importantly, the addition of the biologic to standard of care showed no new safety signals.

The RITUXILUP investigator led trial is a multidisciplinary, open label, randomised, multicentre controlled of rituximab, and is designed as non-inferiority trial to ask “Is the combination of rituximab, 2 doses of methyl prednisolone, and MMF but no oral steroids is as effective as MMF and prednisolone in inducing renal remission?” The primary endpoint is CR at one year but patients will be followed for a minimum of 2 years to ascertain adverse events.

Optimising outcomes in SLE: best practice: Andrea Doria (Italy)

Disease activity leads to damage in SLE and may lead to death. Professor Doria outlines how to assess disease activity and optimise outcomes

To optimise patient outcomes both the short and long-term prognosis in systemic lupus erythematosus (SLE) should be considered. Relevant risk factors of long-term complications in SLE are persistence of active disease despite standard treatment, and side effects of the standard treatments, which can all lead to damage and ultimately death.7 Disease activity can be divided into clinical and serological activity. Clinical disease activity includes inflammatory and non-inflammatory manifestations, and serological activity includes presence of autoantibodies, decreased serum complement and hypergammaglobulinaemia.119

Reliable biomarkers of active SLE have not been identified, so disease activity indices are used which take into account the symptoms and signs that can be attributed to active SLE.127 Repeating these measurements gives a view of SLE disease activity over time. Historically, there were over 60 disease activity indices and today the two principal indices used in practice are the British Isles Lupus Assessment Group (BILAG) and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). Patterns of SLE disease activity vary according to different definitions/activity indices, and between chronic and relapsing-remitting diseases.127

Disease activity patterns were monitored in a cohort of Italian patients with SLE over a period of 7 years. Of 165 patients diagnosed with SLE before 2004 and seen between 2004 and 2010, those with ≥3 visits per year were included. Clinical parameters were recorded at each visit, and disease activity patterns monitored.128

Annual disease activity patterns were defined using SLEDAI-2K, excluding serology, as follows: clinically quiescent disease (CQD): SLEDAI-2K=0 for 3 annual visits; moderate disease activity (MDA): SLEDAI-2K=1 in ≥1 annual visits; chronic active disease (CAD): SLEDAI-2K ≥2 in at least 2 of 3 annual visits; relapsing/remitting disease (RRD): SLEDAI-2K ≥2 in 1 of 3 annual visits (Figure 1).128 The results showed that patients with CAD and RRD accumulated more damage over time than did those with CQD or MAD.129,12 Cumulative steroid dose in patients with early disease quiescence was lower than in patients with persistent active disease,120 resulting in less risk of organ damage.130
Remission is associated with improved outcomes, and early remission is associated with even better outcomes – lower SLEDAI scores, lower relapse rates, less accrual of damage and a much lower cumulative steroid dosage. Animal models also have a place in lupus, and successful interventions in lupus-prone mice have shown to be most effective when introduced before full-blown clinical disease develops, but the most interesting agents are also effective in mice with established disease. Therefore, a key aim must be early diagnosis and earlier treatment of lupus to minimise damage. Use of biomarkers to identify disease can help in this aim, and there is a range of proposed new diagnostic biomarkers for lupus, including antinucleosome antibodies and anti-ribosomal-P-protein antibodies.

Red flags for early lupus include Raynaud’s phenomenon, constitutional symptoms, arthralgia–arthritis, photosensitivity rash, serositis, urinary abnormalities, leukopenia, thrombocytopenia and hypergammaglobulinaemia, especially in women of child-bearing age.

Strategies for optimising SLE outcomes in clinical practice are to achieve prolonged remission (complete or clinical), withdraw corticosteroids promptly, diagnose and treat early, and use biologics as needed.

**Biologics: The future of SLE treatment? Ronald F. van Vollenhoven (Sweden)**

Professor van Vollenhoven presented current evidence on biologic treatments in SLE, including belimumab, approved for use in SLE, rituximab, epratuzumab, abatacept and others. Noting regulatory/financial constraints, Professor van Vollenhoven gave some guidance on when clinicians might use biologics and what could be available in future for the treatment of SLE.

Belimumab is the first biologic approved for use in systemic lupus erythematosus (SLE). It has a compelling mechanism, proven efficacy and a good safety record. Its use in SLE as second-line treatment is likely to increase, targeting appropriate patients using further studies and clinical experience. Belimumab antagonises BlyS, a cytokine that is involved in regulating the activation of B-lymphocytes, and some believe that autoreactive B-lymphocytes are more sensitive, which potentiates its effect (Figure 1).
Figure 1. BlyS can bind to 3 receptors and most strongly to BLyS-R3, resulting in intracellular signalling leading to B-cell survival and affecting B-cell differentiation.

Belimumab is approved for use in SLE, but when should it be used? The regulatory approval was very broadly worded – for use in active disease, despite standard treatment, and if the patient is seropositive. This could apply to almost all patients, but surely more guidance is needed to identify which patients might most benefit from biologic treatments (ie. belimumab).

The two BLISS trials studied responses to belimumab in SLE. BLISS-52 looked at the % median change from baseline of anti-dsDNA IgG in response to belimumab over 52 weeks and showed that anti-dsDNA decreased more substantially with belimumab, and the biological effect translated into a clinical effect with an increase in the response index. The biological effect came first, then the clinical effect, and there was a dosage variation between 1mg/kg and 10 mg/kg. The BLISS-76 study built on these results and showed that corticosteroid doses could also be lowered.

Looking at the SLE responder index and trying to find predictors of responding favourably to belimumab, pooled data from BLISS-52 and BLISS-76 showed that if patients had disease activity, low complement (C3/4) + anti-dsDNA, their chance of responding well to belimumab was much better, with 51.5% of patients taking belimumab 10 mg/kg + routine therapy compared with 31.7% of patients on placebo + routine therapy. Dooley et al looked at patients in the BLISS trials with moderate nephritis, and saw that patients taking 10mg/kg of belimumab had fewer renal flares, than those on 1 mg/kg, possibly implying that belimumab has an effect on preventing renal flares. In addition, patients reported reduced fatigue and improvements in the vitality domains SF-36 in the belimumab arms compared with placebo.

Rituximab (anti-CD20) is approved for rheumatoid arthritis (RA) and for autoantibody-associated vasculitis (AAV), and it is the most frequently used off-label drug for lupus with about 1% of lupus patients using it across Europe. The LUNAR trial concluded that rituximab may be used – restrictively and appropriately – as an option of last resort for refractory patients.

In terms of where doctors stand with rituximab, it has a compelling mechanism, and shows efficacy in RA and ANCA-associated vasculitis. However, it failed trials in general SLE and in lupus nephritis, but may still be an appropriate option for LN patients who failed cyclophosphamide and/or mycophenolate mofetil. It is also effective for haematologic patients. In addition, there are concerns about safety (infections, progressive multifocal leukoencephalopathy).

Abatacept (CTLA4-Ig) is a T-cell costimulation modulator and is approved treatment for RA, and is used off label in parts of Europe. It has been shown efficacious in animal models of SLE, but trials in
New drugs with different mechanisms of action are now needed to work against different molecular targets, specifically to treat autoimmunity. Each new target has antagonists that are in development, and animal and in vitro experiments are ongoing as are early stage trials. One of these, epratuzumab, is an anti-CD22 antibody (CD22 is a marker on the surface of B-cells, like CD20 which is the target of rituximab). Epratuzumab does not deplete or damage the B-cell, but instead, the CD22 molecule antibody binds to the CD22 marker on the surface of the B-cell and slows the B-cell down until it comes to rest. This is known as a down-regulatory signalling pathway, which is beneficial in patients with a high level of B-cell activation, such as people with lupus.

The phase IIb EMBLEM trial investigated a range of dosages of epratuzumab in SLE, and looked at response rates to epratuzumab, which ranged from 21% for placebo to over 40% for the higher dosages, which is a very good effect size; however, the patient groups in the trial were quite small. In addition, the response rate tailed off at the highest doses — this may be explained by the fact that the down-regulatory signal only occurs when there is cross-linkage, and if there is too much of the active drug, cross-linking does not occur. In addition, early results from the ALLEVIATE trials showed a positive effect with epratuzumab.

Other BlyS antagonists (tabalumab, blisibimod) or BlyS/APRIL antagonists (atacicept) are in development. The atacicept trials had mixed results and some were stopped early due to serious infections; the tabalumab trials in RA were stopped due to lack of effect (but the trials in SLE continue). Development of blisibimod is at an earlier stage.

So are biologics the future of SLE treatment? They are not used first-line at this time but could be the future. Belimumab is used second-line in general lupus for persistently active disease and for glucocorticoid ‘dependence’.

After failure of conventional therapies (‘last resort’), the data modestly support the use of rituximab in lupus nephritis and abatacept in SLE with arthritis. However, the data are less clear, or trials are negative, for rituximab in general SLE and abatacept in lupus nephritis. Multiple biologics are in development, which gives hope for the future.

Conclusions
Following this 3rd Annual Meeting of the Lupus Academy, many delegates provided positive feedback and relevant insights into their research and clinical interests.

The combination of interactive workshops and presentations from world-renowned experts in all aspects of SLE management provided delegates with new insights into this complex and heterogeneous disease. Current advances in the management of neuropsychiatric SLE, lupus nephritis and treat-to-target concepts were reviewed and discussed along with insights into the the latest advances in SLE therapy and best practice for optimising outcomes will have a positive impact on current clinical practice.

The 4th Annual Meeting of the Lupus Academy will take place 27th February to 1st March 2015 in Rome, the programme for which has been based on delegate feedback following both the 3rd Annual Meeting and the Asian Lupus Summit Meeting. The meeting promises to continue the educational values developed over the past three Annual Meetings and bring us closer to the vision of improved patient outcomes in SLE.
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