Lupus Academy Middle East Summit Conference

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Dubai, United Arab Emirates

9–10th December 2016

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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 6 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 Lupus Academy Middle East Summit Conference was held in Dubai in December 2016, with the aim of reviewing and discussing insights in research and clinical practice in lupus and associated diseases. This two day meeting brought together 17 international and regional faculty and >150 clinicians and scientists, with a specialist interest in lupus, from across the Middle East. The meeting was CME accredited and was designated for a maximum of 6 European CME credits.

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

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

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

• Better diagnose and manage lupus through improved understanding of biomarkers in SLE, early lupus characteristics and fundamentals of the SLE treat-to-target approach.
• Implement best practice when using steroids and hydroxychloroquine in SLE.
• Identify clinical challenges and use cutting edge methods to improve the management of APS.
• Improve their clinical practice by better identifying and more effectively managing difficult clinical cases of lupus, including the febrile lupus patient, haematological challenges, pregnant patients and those with CNS manifestations of lupus.
• More readily recognise and effectively evaluate patients with cutaneous manifestations of lupus.
• Develop their clinical practice skills by understanding and implementing the latest techniques for managing lupus nephritis.
• Work to more effectively understand and manage individual patients with lupus, through the principle of identifying the treatment target (eg. remission, low disease activity) and applying treatment goals.
Plenary Session I

Biomarkers in SLE: How useful are they? – David Isenberg (UK)

Professor Isenberg reviewed the diverse roles of biomarkers in the diagnosis and management of systemic lupus erythematosus (SLE) and ongoing attempts to develop a variety of newer and better biomarkers for the future management of SLE.

Professor Isenberg opened his presentation with a summary of the value of biomarkers in SLE, including their role in diagnosis and classification of SLE, identification of disease subsets and activity, understanding end-organ effects and disease prediction, and noting that anti dsDNA antibodies, antiphospholipid antibodies and anti-Sm antibodies are all used in the ACR/SLICC classification criteria. Although >100 autoantibodies have been identified, only a few biomarkers are present in >25% of SLE patients, these are however beneficial in identifying disease subsets (Table).

Table. Biomarkers and disease subtypes.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Disease type</th>
</tr>
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<tbody>
<tr>
<td>anti dsDNA</td>
<td>Renal disease</td>
</tr>
<tr>
<td>Anti-phospholipid</td>
<td>Blood clots / Miscarriages</td>
</tr>
<tr>
<td>anti Ro</td>
<td>Photosensitivity/ Neonatal lupus (also anti-La)</td>
</tr>
<tr>
<td>anti RNP</td>
<td>Overlap features</td>
</tr>
</tbody>
</table>

Professor Isenberg continued with a review of anti-RNP and the history of mixed connective tissue disease (MCTD), highlighting the overlap features leading to what became known as MCTD, as identified by Sharp et al in 1972. In 1980, Nimelstein et al revisited these patients and their observations and found very different results, leading them to conclude that certain features of the patients that had originally been thought to make them clinically distinct had not held true over time. There has been little agreement about MCTD over the past 35 years, as shown by the many conflicting studies about the distinctiveness of MCTD, its serology, its consequences and outcomes. Redefining MCTD as a Muddled Concept To be Discarded appears to be an appropriate response to this short review of MCTD.

Professor Isenberg emphasised that biomarkers can only be useful if they effect disease activity, and be linked to end organ function. In the 1950s to 1980s, 60 disease activity assessment systems were reported, but none were shown to be valid or reliable. In the 1980s, new reliable indices were devised and further developed. The (computerised) classic British Isles Lupus Assessment Group (BILAG) divided lupus into eight different systems or organs, and is based on the physician’s intent-to-treat. This was then changed (removal of damage items; addition of gastrointestinal, ophthalmic sections; redistribution of vasculitis section; change to renal system and changes to allow organ/system score, with improvement to go A→B→C rather A→C) to reflect things learnt during use.
Antibodies are an established biomarker, but there are some new(ish) kids on the block (Table).

**Table. Biomarkers in lupus: New(ish) kids on the block.**

<table>
<thead>
<tr>
<th>Renal</th>
<th>CNS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TWEAK (Tumour necrosis factor-like inducer of apoptosis)</strong></td>
<td>Anti-NMDA receptors</td>
</tr>
<tr>
<td>↑ in urine of SLE with nephritis vs non-renal</td>
<td>↑ CSF IFN α/β</td>
</tr>
<tr>
<td><strong>MCP-1 (chemokine)</strong></td>
<td>IFN inducible chemokines e.g. MIP-3B (CCL 19)</td>
</tr>
<tr>
<td>↑ in urine of SLE with nephritis</td>
<td>(anti-ribosomal P abs)</td>
</tr>
<tr>
<td><strong>Anti-Clq antibodies</strong></td>
<td></td>
</tr>
</tbody>
</table>

A study by Orbai et al (2015), compared 308 SLE patients with 389 patients with other rheumatologic diseases, anti C1q in combination with anti dsDNA and low complement was the strongest serological association with renal involvement.\(^5\) Another study by Morrow et al (1983) looked at 4 patients with SLE; 43 patients with RA, were assayed for C3d, breakdown product of the third component of complement (C3).\(^6\) Although C3d values increased with worsening clinical condition in SLE, it was not sufficiently clear to be useful and was not deemed to provide any advantage over the existing C3 assay.

Focusing on cytokines/chemokine abnormalities linked to SLE, Professor Isenberg highlighted a study noting the discovery of a role for BLYS in patients with autoimmune disease. Zhang et al (2001), found elevated levels of BLYS in patients with SLE (n=40) and RA (n=110), which suggested that BLYS may be a useful marker for early activation of an autoimmune diathesis and likely plays a critical role in triggering activation of self-Ag-driven autoimmune B cells in SLE, making BLYS a viable therapeutic target. A decade later Phase III studies of belimumab showed that the BLYS inhibitor belimumab, plus standard therapy significantly improved SRI response rate, reduced disease activity and severe flares and was well tolerated in patients with SLE. In addition, he described the role of interferon α in the immunopathogenesis of SLE, presenting evidence for increased IFNa in SLE sera and increased gene signature in lesional skin and synovial tissue in SLE patients and highlighting the correlation between type 1 IFN gene signature and several autoantibodies eg,. anti dsDNA, Ro, Sm, and RNP. However, there are conflicting data about correlation between type 1 IFN gene signature score and disease activity, with key clinical data coming from sifalumumab\(^7\) and anifrolumab\(^8\) studies.

Concluding, Professor Isenberg spoke of disease prediction; presenting data on the onset and progression of autoantibody development before clinical diagnosis. Evidence shows that autoantibodies present years before SLE diagnosis and their appearance follows as predictable course, with accumulation of autoantibodies before any SLE symptoms appear. Genome Wide Association Studies have also reported >40 loci associated with an increased risk of SLE development.
SLE is complicated! The ‘classic’ anti dsDNA, anti Sm, ↓ C3 are still good for classification/sub-setting/prediction, but in limited numbers of patients; a host of new potential markers e.g. cytokines/epigenetic markers/genetic loci have been identified. The key problems are to show the relevance of biomarkers to disease and the costs involved to develop affordable assays.

References
Professor Ruiz-Irastorza reviewed the use of hydroxychloroquine and steroids for the management of SLE, highlighting that while they are both effective treatments, their toxicity, damage accrual and effect of survival differ and support a need to change clinical practice.

Professor Ruiz-Irastorza opened his presentation highlighting that antimalarials and glucocorticoids are old, cheap, widely available and effective and, thus, have been long established as the basis for SLE treatment. Whilst both treatments share good efficacy profiles, their safety profiles differ. Professor Ruiz-Irastorza presented several studies demonstrating the effectiveness of hydroxychloroquine (HCQ) in controlling SLE disease activity, reducing damage accrual and improving survival in patients with SLE. A 6 month randomised study of the effect of withdrawing HCQ sulfate in 47 patients with SLE, by The Canadian Hydroxychloroquine Study Group (1991), demonstrated that disease flares were 2.5 times more likely in patients taking placebo versus HCQ, moreover, time to flare-up was shorter in patients receiving placebo. The study concluded that patients with quiescent SLE and taking HCQ are less likely to have a clinical flare-up if they are maintained on the drug. In 2006, Ruiz-Irastorza et al. investigated the effect of antimalarials in protecting against thrombosis and improving survival in 232 SLE patients. The study showed that antimalarials were protective against thrombosis, while aPL-positivity and history of thrombosis increased the risk of thrombosis. HCQ has also been shown to be independently associated with a reduced risk of damage accrual in a study of >500 patients with SLE and no accrued damage when starting treatment. Thus, it is not surprising that studies in Europe, Latin America and the USA have all shown that HCQ has a protective effect on survival. So, HCQ is effective, what about toxicity? Adverse events with antimalarials are usually mild. A systematic review of 95 articles found that antimalarials were not only effective in preventing flares and increasing survival, but their toxicity was infrequent, mild and reversible. Retinal toxicity with HCQ is rare and easy to detect at early stages with regular eye monitoring (annual screening following 5 years of use), which should include high-sensitivity techniques such as optical coherence tomography.

Professor Ruiz-Irastorza, went on to review the guideline-recommended use of glucocorticoids and the dose-dependent (eg. >30 mg/day) damage they cause. In 2004, Buttgereit et al. published an update on the mechanism of action of glucocorticoids in the treatment of rheumatic diseases. This article highlighted that the important anti-inflammatory and immunomodulatory effects of glucocorticoids are mediated predominantly by genomic mechanisms, with membrane-bound glucocorticoids receptors’ (GCRs) saturation occurring in a dose-dependent manner. Thus, intensifying therapeutically relevant genomic actions and that with increasing dosages, the initiation of additional and qualitatively-different nonspecific non-genomic actions of GCs (Table).
Table. Current knowledge on the relationship between clinical dosing and cellular actions of glucocorticoids.

<table>
<thead>
<tr>
<th>Terminology*</th>
<th>Genomic actions (receptor saturation)§</th>
<th>Nongenomic actions§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose (≤7.5 mg/day)</td>
<td>+ (&lt;50%)</td>
<td>–</td>
</tr>
<tr>
<td>Medium dose (&gt;7.5 to ≤30 mg/day)</td>
<td>++ (&gt;50 to &lt;100%)</td>
<td>(+)</td>
</tr>
<tr>
<td>High dose (&gt;30 to ≤100 mg/day)</td>
<td>++(+?) (almost 100%)</td>
<td>+</td>
</tr>
<tr>
<td>Very high dose (&gt;100 mg/day)</td>
<td>+++ (almost 100%)</td>
<td>++</td>
</tr>
<tr>
<td>Pulse therapy (≥250 mg for 1 or a few days)</td>
<td>+++ (100%)</td>
<td>+++</td>
</tr>
</tbody>
</table>

* Values represent mg of prednisone equivalent per day.
§ cGCR = cytosolic glucocorticoid receptor; ? = unknown; – = not relevant; (+) _ perhaps relevant, but of minor importance; + relevant; +(+) + relevant or perhaps even very relevant; +(++) = relevant or perhaps even very or most relevant; ++ = very relevant; +++ = very relevant to most relevant; +++ = most relevant.

This explains whilst steroid doses below 5–7.5 mg/d have a good safety profile, those doses >30 mg/d are associated with a sharp increase in the frequency of side effects and several studies provide evidence of the damage glucocorticoids cause in patients with SLE. Professor Ruiz-Irastorza presented results from the RELES cohort, which showed that first month prednisone dose predicts prednisone burden during the following 11 months. Patients taking medium or high dose prednisolone were more likely to be treated with prednisone >7.5 mg/d compared with patients on no prednisone; conversely, patients receiving low doses in the first month were not. Moreover, there is evidence that low dose prednisone works well, so why start high?

Given this, there is a strong reasoning for considering antimalarials as a main treatment for SLE. Yet, a community-based cohort revealed that HCQ use was suboptimal and recommended that those not using HCQ, those with longer disease duration and those who see non-rheumatologists should be targeted for improvement in treatment. Other studies have shown a marked increase in the number of patients taking antimalarials between 2003 and 2016.

Professor Ruiz-Irastorza concluded his presentation with three principles of action and a short ‘recipe’ for effective management of SLE (Table).

1. Hydroxychloroquine is for the treatment of SLE—glucocorticoids and immunosuppressive drugs are for the treatment of some SLE manifestations.
2. Give steroid pulses and combine drugs to allow lower starting steroid doses and faster steroid tapering.
3. Do not use doses of prednisolone >5 mg/d for maintenance treatment.
Table: Treatment recommendations.

<table>
<thead>
<tr>
<th>Standard treatment</th>
<th>HCQ</th>
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<tbody>
<tr>
<td><strong>Mild-moderate flares</strong></td>
<td></td>
</tr>
<tr>
<td>Prednisone 2.5–7.5 mg/d</td>
<td></td>
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<tr>
<td>Methylprednisolone pulses, 125–250 mg x3</td>
<td></td>
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<tr>
<td><strong>Severe flares</strong></td>
<td></td>
</tr>
<tr>
<td>Methylprednisolone pulses, 250–500 mg x3</td>
<td></td>
</tr>
<tr>
<td>Prednisone up to 20–30 mg/d</td>
<td></td>
</tr>
<tr>
<td>Rapid tapering and maintenance 2.5–5 mg/d</td>
<td></td>
</tr>
<tr>
<td><strong>Severe activity</strong></td>
<td></td>
</tr>
<tr>
<td>Need for long-term prednisone &gt;5 mg/d</td>
<td></td>
</tr>
<tr>
<td>Add immunosuppressive</td>
<td></td>
</tr>
<tr>
<td><strong>Refractory cases</strong></td>
<td></td>
</tr>
<tr>
<td>Biologic</td>
<td></td>
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</tbody>
</table>

References


Plenary Session II
Clinical manifestations and evaluation of cutaneous lupus – Annegret Kuhn (Germany)

Professor Kuhn reviewed the various clinical manifestations of cutaneous lupus erythematosus and provided an update on their assessment and clinical management, as well as the growing importance of identifying biomarkers and using sunscreen for prevention of lesions.

Despite their frequency and high burden of disease, the treatment of cutaneous lupus erythematosus (CLE) is often met with many challenges. Professor Kuhn began her presentation with a case study of a young man with SLE and a bullous eruption along with systemic flares, to highlight the challenges and unmet needs of classifying skin lesions in SLE. There is also a great need to support development of treatment strategies that focus on CLE underpinned by well-designed trials using validated skin scores.

The classification system developed by Gilliam and Sontheimer divided cutaneous manifestations into SLE into LE-specific (CLE) and LE-non-specific cutaneous manifestations. The 2004 Duesseldorf Classification breaks CLE into 4 subtypes (Table).

<table>
<thead>
<tr>
<th>Table. CLE-specific disease subtypes.</th>
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<tbody>
<tr>
<td>1. Acute cutaneous lupus erythematosus (ACLE)</td>
</tr>
<tr>
<td>2. Subacute cutaneous lupus erythematosus (SCLE)</td>
</tr>
<tr>
<td>3. Chronic cutaneous lupus erythematosus (CCLE)</td>
</tr>
<tr>
<td>a. Discoid lupus erythematosus (DLE)</td>
</tr>
<tr>
<td>b. Chilblain lupus erythematosus (CHLE)</td>
</tr>
<tr>
<td>c. Lupus erythematosus profundus/panniculitis (LEP)</td>
</tr>
<tr>
<td>4. Intermittent cutaneous lupus erythematosus (ICLE)</td>
</tr>
<tr>
<td>Lupus erythematosus tumidus (LET)</td>
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</table>

1. ACLE is associated with 20–60% of SLE cases. The localised form of ACLE is characterised by a malar rash on the central portion of the face and the generalized form is more widespread on other areas of the face and body. These rashes are frequently accompanied by oral mucosal lesions and LE-non-specific manifestations. Diffuse thinning of the hair (“lupus hair” or “wooly hair”) is also evident in ACLE. Approximately 40–90% of ACLE patients have anti-dsDNA antibodies and 10–30% have anti-Sm antibodies.

2. SCLE presents in annular and/or papulosquamous forms with polycyclic confluence of lesions. It is non-scarring, with vitiligo-like depigmentation. Patients have high photosensitivity, with 70–90% having anti-Ro/SSA antibodies and 30–50% having anti-La/SSB antibodies. There can be a genetic predisposition for SCLE: HLA-A1, -B8, -DR3. More than 50% present with ≥ 4 ACR criteria for the classification of SLE (Table), yet severe disease is only present in 10–15% (less renal and CNS disease).

3. CCLE manifests as discoid LE (DLE), chilblain LE (CHLE) and LE panniculitis/profunus (LEP). DLE presents mainly as a localised (80%) but also as a disseminated (20%) form and with discoid erytematosus plaques with follicular hyperkeratosis, central scarring with hypopigmentation and active erythematosus border. There is frequent involvement of the scalp (scarring
alopecia) and mucous membranes moreover, DLE can be provoked by irritative stimuli (“Köbner” or isomorphic phenomenon). High ANA titre is only evident in <5%.

4. ICLE is characterised by erythematous, urticaria-like, succulent plaques without epidermal involvement. It is fairly localised, affecting sun-exposed areas like the face, upper trunk, extensor aspects of the arms. High photosensitivity, with positive photoprovocation test, is evident in >70% of patients and ANA is present in 10–30% of patients and anti-Ro/SSA and/or anti-La/SSB antibodies in 5–10% of patients with variable good prognosis and in some cases spontaneous remission.

If any combination of 4 or more of the 11 ACR criteria for the classification of SLE (Table) is present (at the same time or serially) the diagnosis of SLE is considered likely.

Table. SLE: ACR criteria (1982)

| 1. Malar rash | 2. Renal disorder |
| 3. Discoid lesions | 4. Neurological disorder |
| 5. Photosensitivity | 6. Haematological disorder |
| 7. Oral ulcers | 8. Immunological disorder |
| 9. Arthritis | 10. Antinuclear antibody |
| 11. Serositis |

The ACR criteria for the classification of SLE defines photosensitivity as ‘Skin rash as a result of an unusual reaction to sunlight, by patient history or physician observation’. However, since this definition there have been several calls for these criteria to be updated to include recent diagnostic tests; moreover, the criteria were not developed with input from dermatologists and attribute too much focus on skin as an expression of a multiorgan disease. The consequence of this being that patients with skin diseases are classified as SLE based mostly on skin symptoms. Albrecht et al, highlighted that the criterion ‘photosensitivity’ is not specific for lupus erythematosus and that patients with only skin lesions can fulfill the ACR criteria for SLE without presenting systemic organ manifestations.

Professor Kuhn highlighted the role of sunscreens in preventing skin lesions of CLE. A study by Kuhn et al (2011) found that standardised photoprovocation is a reproducible method to assess photosensitivity in subjects with CLE and is therefore used as a diagnostic test for CLE. In a more recent photoprovocation study testing ultraviolet (UV) A and UVB irradiation has helped identify peptidome as a rich source of biomarkers predictive of photosensitivity in CLE, namely elevated beta 2-microglobulin levels being predictive of skin lesion formation. The use of sunscreen in patients with SLE has been shown to prevent interferon-driven inflammation as demonstrated by the complete eradication of MxA expression and significant reduction in the number of CD11c and CD123 dendritic cells and prevention of increased levels of CD68-positive macrophages.

A multicentre study by the European Society of Cutaneous Lupus Erythematosus (EUSCLE) investigated different therapeutic strategies in 1002 CLE patients across Europe. Sunscreens were shown to be highly effective in preventing skin lesions in all CLE disease subtypes in the 70% of patients with high photosensitivity and correlated with a lowered CLASI activity score.
In 2005, the first validated score with specific evaluation of skin lesions was published as “Cutaneous Lupus Erythematosus Disease Area and Severity Index” (CLASI). This score evaluates “activity” and “damage” of the heterogeneous skin lesions of CLE by taking into account both anatomical regions and morphological aspects. In 2010, the CLASI score was revised and modified by including additional aspects of the mucocutaneous spectrum of the disease. Reliability analysis supported the validity and applicability of the “revised CLASI” (RCLASI). Due to its detailed and comprehensive structure, the RCLASI may be applied to support the diagnosis of the various CLE subtypes and to evaluate the efficacy of treatment (Figure). Moreover, it is a valuable instrument for monitoring the disease on different sites of involvement, not only in routine clinical practice but also in long-term clinical trials.

Figure. RCLASI.

References


Decreasing morbidity and mortality and improving outcomes in SLE – Ian Bruce (UK)

Professor Bruce presented the role of SDI scoring in the assessment and management of organ damage. Highlighting that pre-existing damage is an important predictor of damage accrual and mortality, Professor Bruce presented fixed risk factors (ie. age, race/ethnicity and male gender) factors that increase risk (ie. steroids, hypertension, high disease activity) of damage accrual and also strategies to reduce this risk (ie. antimalarials, targeted therapies).

Professor Bruce began his presentation by highlighting that mortality associated with systemic lupus erythematosus (SLE) has improved dramatically over the past 60 years, with the 1950s seeing a 50% 5-year mortality rate compared with a 10-year survival rate of >90% seen in more recent decades. In addition, a meta-analysis of 12 studies by Yurkovich et al has also shown that mortality in SLE is improving compared with the general population with the standardised mortality ratio falling from >10.0 in the 1970s to 2.5–3.5 in the first decade of the new millennium.

Professor Bruce highlighted data from long-term studies around the world, which identified the leading causes of death in SLE to include cardiovascular disease, infections and SLE complications. All the same, with improvement in survival over the past 60 years, there is now increased focus on outcomes, including irreversible SLE-associated organ damage. It is essential to understand damage in SLE as higher levels of damage are associated with greater accumulation of damage in the future as well as increased mortality. The development of the ACR/SLICC Damage Index (SDI) includes 12 organ systems and allows the assessment of overall long-term morbidity associated with SLE; it has proved to be a consistent and reliable measure of damage over time allowing the prediction of both further damage and also mortality. Professor Bruce reviewed several studies that assessed organ damage in patients with SLE. A study by Nived et al highlighted the clinical relevance of the SDI for survival in SLE. Nived found that SDI scores after 5 years have a high predictive value for survival during the following median observation time of 7 years. Cardoso et al also found that baseline and accrued organ damage, as measured by SDI, was useful in predicting increased risk of mortality over a 6.3 year follow-up in Brazilian SLE patients. Similar results have also been found in Nordic patients with SLE, with linear damage accrual occurring in 54% over a 10 year period. A systematic literature review of 50 articles by Sutton et al shows a clear pattern of damage increase overtime and that this is a predictor of mortality.

Having presented clear evidence of the association between damage accrual and mortality, Professor Bruce reviewed the factors associated with damage accrual and poor prognosis in SLE, including older age, race/ethnicity (including African ancestry), male gender, low socioeconomic status, active disease/flares, renal involvement and steroids. In 1996 Stoll et al proved the validity of the SDI as a predictor of severe outcome and indicator of morbidity in different ethnic groups, which showed that Afro-Caribbeans and Asians had higher damage scores than Caucasians. A more recent study by Alarcon et al (2004) found that key predictors of damage accrual in Hispanic, African-Americans and Caucasians, included previous damage, age, disease activity and use of corticosteroids. It is clear damage in SLE begets damage in SLE, and this is exactly what the SLICC inception cohort confirmed, showing that patients with damage at baseline were more likely to have worsening SDI than those without damage at baseline (Figure).
Figure. Time to SDI Worsening in SLICC Cohort.

Whole group

Patients with and without initial damage


Disease flares also result in future damage. A study of Chinese patients by Mok et al 2003, showed SDI scores (notably, renal, musculoskeletal and gonadal) to significantly increase over a 3 year period, with severe disease flares and cyclophosphamide being key predictors of new damage.\(^18\) Similarly, a Latin American cohort demonstrated that the greater the number of flares, regardless of severity and other risk factors, the higher the risk of damage accrual.\(^19\) Conversely, a study of Caucasian patients found that 37% of patients achieved a prolonged remission, which was associated with a better outcome in terms of damage accrual.\(^20\)

As mentioned, steroids also beget damage.\(^17\) In a study of 73 patients, a significant proportion of damage (58%) was attributed to steroid use and this damage accumulated over time with 80% of damage being caused by steroids at Year 10.\(^21\) Steroid dose is also a significantly predictive factor for the rate of damage accrual, according to a study by Petri et al (2012).\(^22\) Conversely, hydroxychloroquine (HCQ) is associated with a reduced risk of damage accrual over time in patients who have not yet accrued damage at the time of treatment initiation.\(^23\)

Reviewing the SLICC inception cohort, Professor Bruce highlighted the SDI transition rates before presenting new approaches to reducing damage accrual in SLE.\(^3\) Presenting pooled data from the BLISS-52 and BLISS-76 studies, Professor Bruce highlighted that long-term treatment with belimumab (and standard of care) resulted in a low incidence of organ damage accrual, with the majority of patients (85.1%) having no change in SDI at 5–6 years versus baseline.\(^24\) Moreover, the median time to first worsening was 679 days in patients with no organ damage at baseline and 677 days in patients with organ damage at baseline.

Concluding, Professor Bruce reiterated the main strategies for damage prevention and improving outcomes, including better disease control and managing individual risk factors such as hypertension.
and hyperlipidaemia, introducing antimalarials, minimising steroid use, and recommending vaccinations, cancer screening, and smoking cessation programmes.

References


Lupus Nephritis: Update on modern management – Liz Lightstone (UK)

Professor Lightstone reviewed the evolving management of lupus nephritis, presenting both the standard of care and importance of focusing on steroid-sparing regimens when treating and developing new treatments for lupus nephritis.

Lupus nephritis is one of the most serious complications of systemic lupus erythematosus (SLE), with overt kidney disease present in 40-60% of patients at the time of diagnosis. Lupus nephritis affects those from non-Caucasian backgrounds more severely than those from Caucasian backgrounds. Induction of remission improves patient survival, with ≥50% reduction in proteinuria at 6 months being linked to a significant improvement in 15 year survival in this group.¹

Professor Lightstone presented a case study to asking the question when is biopsy is necessary and when is it not? She highlighted the importance of preserving renal function and life, quality of life (QoL) and fertility requires (1) rational targeted therapy related to pathophysiology, which induces remission and prevents flares; (2) minimising treatment-related toxicities and improving QoL and survival by getting rid of steroids, improving adherence and facilitating healthy pregnancies.

Lupus Nephritis Standard of Care

Focusing on treatment, the only current licenced medications for the treatment of lupus nephritis are aspirin, steroids and hydroxychloroquine. None of the other treatments (cyclophosphamide [CyP], mycophenolate mofetil [MMF], azathioprine, tacrolimus, rituximab—any biologic) regularly used are licensed for treating SLE. Standard of care for induction is defined by the Euro-Lupus²,³ and ALMS⁴,⁵ trials, yet the unmet needs present themselves as low rates of complete remission as shown by the ALMS,⁶ LUNAR,⁷ BELONG⁸ and ACCESS⁹ trials, while an analysis of studies in developed countries between 2000–2006 by Tektonidou MG et al (2016) shows that a high percentage of patients still reach end stage renal failure (ESRF) within 15 years of diagnosis.¹⁰ Although complete remission is judged at 6/12 months in most trials, what matters to patients is long-term outcomes (ie. will my kidneys still work in 10–20 years?). Recent studies looking at predictors of long-term outcomes may change our notion of what we are trying to achieve in the short term. The Euro-Lupus trial found that low-dose CyP was as effective as and less toxic than high-dose CyP and at 10 years there was no difference between two groups for death, doubling serum creatinine/ESRF. Moreover, a significant fall in proteinuria at 3 and 6 months predicted good renal outcome.³ Dall’Era M et al (2015) also showed that proteinuria levels of <0.8g/day at 12 months was the best predictor of good long-term renal function in the Euro-Lupus Nephritis Trial.¹¹ In addition, Professor Lightstone highlighted that long-term ALMS outcomes suggest CyP induction is associated with less failure, with non-Hispanic patients more likely to achieve complete remission. Factors associated with treatment failure included lack of treatment with hydroxychloroquine, failure to reduce anti-dsDNA during the first 8 weeks of induction, failure to reduce UP/C during the first 8 weeks of induction and anti-dsDNA positivity at the end of induction.¹² There is also growing evidence demonstrating that multitarget therapy provides superior efficacy compared with intravenous CyP as induction therapy for lupus nephritis. In a 26-centre TCT by Liu Z et al (2015), more patients in the multitarget group (45.9%) achieved complete remission than in the intravenous cyclophosphamide group (25.6%). Moreover, the multitarget group also achieved higher overall response rates and a shorter time to overall response compared with CyP.¹³ Professor Lightstone highlighted the situations when CyP should be used, these included:

- Severe extra renal disease (cerebral, myocarditis).
- RPGN picture – with steroids, ± PEX, ± rituximab.
- Commonest – 2nd line; when MMF has failed.
- When adherence is a predictable issue.
Steroids and Steroid Avoidance

Professor Lightstone then highlighted toxicity issues with steroids. Having been introduced in 1951, their inclusion in the lupus nephritis treatment paradigm was considered level 1a evidence. Most current treatment protocols for LN involve oral steroids and often high dose. However, there has been no systematic attempt to define correct dose of steroids, duration of steroids and how to wean steroids. The general consensus being steroids on their own are not efficacious but contribute to infectious complications and cause damage; moreover relapsing/remitting lupus nephritis means long-term treatment with oral steroids is often necessary, with such chronic exposure leading to significant morbidity and mortality.\textsuperscript{14-18} In addition there is a dose-response relationship with steroids and the adverse effects they produce.\textsuperscript{19} There is a clear need to improve response rates with new treatments and reduce toxicity through steroid sparing regimens. Rovin BH et al (2012) assessed the efficacy and safety of rituximab in patients with lupus nephritis treated with concomitant MMF and steroids (LUNAR).\textsuperscript{7} Although rituximab therapy led to more responders and greater reductions in anti-dsDNA and C3/C4 levels, it did not improve clinical outcomes after 1 year of treatment. This said, the primary endpoint aimed to prove a 20% delta in complete and partial remission with major weighting towards complete remission. Moreover, in addition to the positive secondary endpoints, several exploratory endpoints at Week 78 favoured the rituximab regimen, including steroid sparing. It appears less is more when it comes to improving outcomes with steroid sparing regimens. Zeher M et al (2011) found that enteric-coated mycophenolate sodium may facilitate steroid reduction without loss of efficacy and fewer infections.\textsuperscript{20} In addition, Ruiz-Irastorza G et al (2014) found that a combination of medium-dose prednisone, methylprednisolone pulses, cyclophosphamide and hydroxychloroquine was at least as effective as regimes containing high-dose prednisone in inducing remission and caused less toxicity.\textsuperscript{21} Despite rituximab and steroid sparing, there are currently no positive trials for the use of any biologic for lupus nephritis. Experience from renal transplantation does however show that steroid avoidance and introduction of an anti-IL-2R antibody and methyl prednisolone induction, one week of steroids and then tacrolimus plus MMF resulted in a 20% reduction in rejection, >35% reduction in new onset diabetes and 5 kg reduction in post-transplant weight gain over one year.\textsuperscript{22-24}

Changing the Paradigm

Having presented the evidence for steroid sparing, Professor Lightstone focused on presenting the rationale for changing the current treatment paradigm to steroid avoidance by replacing with biologic monotherapy. The Rituxilup protocol is a single centre cohort study that evaluated the effectiveness of treating lupus nephritis with rituximab and mycophenolate mofetil but no oral steroids.\textsuperscript{25} Of the 50 patients enrolled, 42 have reached 5 years follow-up, the majority of whom (88%) achieved complete or partial remission and the majority of whom (77%) are steroid free. Relapses were only in patients with Class IV or V disease, the majority responded to retreatment, again with no oral steroids. Given these results, the open label, randomised, multi-centre, controlled Rituxilup trial (NCT01773616) will now aim to demonstrate the combination of rituximab and no oral steroids to be as effective as MMF and prednisolone in inducing renal remission.

Sustained disease remission and steroid remission in lupus nephritis has also been demonstrated in the RituxiRescue cohort with the RituxiRescue regimen (2 x 1g rituximab ± 125-500mg methylprednisolone on Days 1 and 15, maintenance mycophenolate mofetil + no increase in b/line steroid dose).\textsuperscript{26} At 1 year 62% of patients were in remission, with this increasing to 91% by Year 5 (Figure). Over 50% of patients were completely weaned off steroids by Year 5 with average steroid doses falling from 14.9 mg/day at baseline to 5.8 mg/day by Year 5, with low rates of relapse.
The calcineurin inhibitor, voclosporin (23.7 mg or 39.5 mg), in combination with MMF and steroids improves rates of remission patients with active lupus nephritis, as demonstrated in the global multicenter AURA trial. At Week 24 both low and high dose voclosporin were statistically superior to placebo in partial remission and time to complete and partial remission. Voclosporin continues to be studied in Phase III trials of lupus nephritis (NCT03021499).

Summarising, Professor Lightstone reinforced that it is time to change the treatment paradigm in lupus nephritis and that there are potentially more effective and less toxic alternatives to steroids. Trials like AURA are setting new benchmarks for steroid dosing. Steroid sparing regimens should be implemented from the start of treatment and steroid minimisation a primary goal of all lupus trials.

References


Treat-to-target in SLE – Andrea Doria (Italy)

Professor Doria presented the concepts of T2T and LLDAS in SLE, highlighting the importance of achieving remission and low disease activity state in minimising damage accrual and improving patient outcomes in SLE.

Professor Doria began his presentation with a reminder of the poor long-term prognoses in SLE, highlighting that key risk factors for long term complications in SLE include persistence of active disease despite standard of care and side effects of treatments such as corticosteroids and immunosuppressants. In 1976 a long-term systematic analysis of 81 SLE patients over 5 years at the University of Toronto Rheumatic Disease Unit revealed that 11 patients died, 6 of these within the first year following diagnosis and 5 patients an average of 8.6 years after diagnosis. It was found that those who died early in the disease with active lupus were taking high doses of steroids, and that those who died late in the disease had been taking steroids long-term and there was a high incidence of myocardial infarction. Thirty year later, Doria et al (2006) demonstrated an improvement in survival in patients with SLE, however he noted that long-term prognosis is still poor in patients with severe SLE manifestations. Treating-to-target (T2T) involves defined treatment goals in order to improve the patient’s prognosis by addressing important unmet needs, such as treating persistent disease activity manifesting and chronic active disease and relapsing-remitting disease and avoiding drug-related side effects, especially those resulting from corticosteroid use. The principle of T2T is targeting a specific value, not the symptoms, with the aim being to improve long-term outcomes such as organ damage. T2T has already proven successful in the management of diabetes, hyperlipidaemia and hypertension. T2T involves identifying a target for the individual patient, making a therapeutic intervention, reassessing the patient after an established period of time and, if the target is not met, modifying the intervention. Recently published recommendations for SLE suggest looking at clinical remission or low disease activity (LDA) due the detrimental effects of persistent disease activity and protracted corticosteroid therapy on patient outcomes.

T2T: Remission

Professor Doria focused on the application of T2T principles in SLE, highlighting that the treatment target in SLE should be disease remission, or when this cannot be achieved, low disease activity should be the therapeutic goals. There are however a number of different ad hoc definitions of remission that have been used in clinical trials and observational studies. Such existence of so many definitions highlights the need for amalgamation of SLE research whereby we can better understand the treatment and outcomes for SLE patients. A recent publication by van Vollenhoven et al (2016) outlines consensus (DORIS) findings on definitions of remission in SLE. The definitions of remission in SLE would be worded as follows: “remission in SLE is a durable state characterized by ... (reference to symptoms, signs, routine labs). To define remission, a validated index must be used, e.g., clinical-SLEDAI = 0, BILAG 2004 D/E only, clinical ECLAM =0; with routine laboratory assessments included, and supplemented with Physician Global Assessment. Moreover, there must be distinction between remission off therapy and remission on therapy, where remission-off-therapy requires the patient to be on no other treatment for SLE than maintenance antimalarials; and remission-on-therapy allows patients to be treated with maintenance antimalarials, stable low-dose glucocorticoids (prednisone ≤5 mg/d), stable maintenance immunosuppressives and/or stable maintenance biologics. The task force also agreed that the most appropriate outcomes (dependent variables) for testing the prognostic value (construct validity) of potential remission definitions are: Death, Damage, Flares, and measures
of Health-related quality of life.”

Professor Doria also presented work by Zen et al (2015), which assess the prevalence effect of prolonged remission (≥5 consecutive years) on outcomes in Caucasian patients with SLE (DORIA). The study defined three levels of remission using the SLE Disease Activity Index (SLEDAI-2K):

1. Complete remission: no disease activity in steroid-free and immunosuppressant-free patients
2. Clinical remission off steroids
3. Clinical remission on steroids

Damage accrual was measured using the SLICC/American College of Rheumatology Damage Index (SDI).

There are some notable similarities between the DORIS and DORIA definitions of remission (Table). There are some notable similarities between the DORIS and DORIA definitions of remission (Table).

**Table. Comparison of DORIA and DORIS definitions of remission.**

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<th>DORIA</th>
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<tr>
<td></td>
<td>Clinical</td>
<td>Complete</td>
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<tr>
<td></td>
<td>on Cs</td>
<td>off CS</td>
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<tr>
<td>cSLEDAI=0</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>PGA&lt;0.5</td>
<td>✓</td>
<td>-</td>
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<tr>
<td>Anti-dsDNA/low C3/C4</td>
<td>✓</td>
<td>-</td>
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<tr>
<td>HCC/CQ</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Prednisone ≤5 mg/d</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Immunosuppressants</td>
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<td>Biologics</td>
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Of the 224 patients included in the study, at 5 years 7.1% achieved complete remission, 14.7% achieved clinical remission of steroids and 15.6% achieved prolonged remission on steroids. Key predictors of organ damage included patients with unremittent disease and those taking corticosteroids.

Professor Doria then considered what the shortest duration of remission was that would yield a decrease in damage progression, presenting data from a 7-year follow-up study by Zen et al (2017), using the same classification criteria and the aforementioned study by Zen et al (2015). Prevalence of remission ≥5 years was achieved in >38% of the cohort (n=293) (Figure).
Damage was similar, irrespective of the level of remission achieved in those achieving <4 years remission, however damage was higher in patients in clinical remission for ≥5 years and taking steroids. The study concluded that two consecutive years is the shortest duration of remission associated with decrease in damage progression. Another study by Wilhelm et al (2016) used DORIS to estimate rates and predictors of remission in a cohort of 2307 patients with SLE and found that high baseline treatment was the major predictor of a longer time to remission, followed by high baseline activity.  

T2T: LLDAS

When remission cannot be achieved we look towards a lupus low disease activity state (LLDAS). Low disease activity has been defined and validated using LLDAS attainment, in a single-centre SLE cohort, to predict non-accrual of irreversible organ damage, measured using the SDI (Table).  

Table. LLDAS definition.

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<tbody>
<tr>
<td>1.</td>
<td>SLEDAI-2K ≤4, with no activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, fever) and no haemolytic anaemia or gastrointestinal activity</td>
</tr>
<tr>
<td>2.</td>
<td>No new features of lupus disease activity compared with the previous assessment</td>
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<tr>
<td>3.</td>
<td>SELENA-SLEDAI physician global assessment (PGA, scale 0–3) ≤1</td>
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<tr>
<td>4.</td>
<td>Current prednisolone (or equivalent) dose ≤7.5 mg daily</td>
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<tr>
<td>5.</td>
<td>Well tolerated standard maintenance doses of immunosuppressive drugs and approved biological agents, excluding investigational drugs</td>
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Achievement of LLDAS was determined in 191 patients over a mean of 3.9 years. Patients spending >50% in LLDAS had significantly reduced organ damage accrual compared with patients spending <50% (p=0.0007); they were also significantly less likely to have an increase in SDI of ≥1 (p=0.005) during the follow-up period or have severe flares at subsequent visits (p<0.0001). Another study by Tsang et al (2016) sought to identify predictors of organ damage and specifically the relationship
between prolonged disease remission or low disease activity and damage accrual in a longitudinal cohort of 183 SLE patients followed up over a mean of 5 years. They found that the most significant predictors of damage included one major flare, mean daily prednisone dose during follow-up and nephrological manifestations at baseline. Both prolonged remission and LLDAS were associated with improved outcomes.

Professor Doria concluded by highlighting that, in everyday practice, patients should be brought to the lowest level of disease activity, ensuring a significant benefit over a persistently active disease, this being either clinical remission or LDA. However, complete remission, clinical remission or LDA should not be seen as different treatment goals, rather they should be read as different scores of the same lupus target, aiming to the highest degree of disease quiescence that can be applied to any patient.

References