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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 four 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 4th Annual Meeting of the Lupus Academy was held in Rome, Italy, in February 2015, 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 >250 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 11 European CME credits.

The scientific programme, developed by a Steering Committee of 12 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.

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.
- Have a greater understanding of managing various clinical manifestations of lupus, through new trends in managing lupus nephritis, renal transplantation and early diagnosis/prevention of osteonecrosis and osteoporosis.
- Consider the course of and approach to SLE management from conception, through pregnancy and transitioning from childhood onset SLE to adulthood.
- Understand cutting edge management of APS and SLE and how this will influence the future management of these diseases.
- Reflect on their own clinical cases following participation in interactive workshops designed to bring to life the management of various lupus manifestations seen in clinical practice.*

*workshop content is not covered in this report
### Programme

#### Friday 27th February

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<th>Event</th>
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<td>18:00</td>
<td>Opening Address</td>
<td>Andrea Doria (Italy)</td>
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<td><strong>Keynote Lecture</strong></td>
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<td></td>
<td><strong>Moderators:</strong> Andrea Doria (Italy) &amp; Roger A. Levy (Brazil)</td>
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<td>18:20</td>
<td>My ten commandments in the management of lupus</td>
<td>Murray B. Urowitz (Canada)</td>
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<td><strong>Discussion Forum: Issues and Answers</strong></td>
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<td><strong>Moderators:</strong> Munther A. Khamashta (UK) &amp; Ricard Cervera (Spain)</td>
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<tr>
<td>19:00-20:30</td>
<td>Vitamin D and SLE: To D or not to D? The matter of the debate (15 minutes)</td>
<td>Ricard Cervera (Spain)</td>
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<td></td>
<td>Pros: (20 minutes + 10 minutes rebuttal)</td>
<td>Yehuda Shoenfeld (Israel)</td>
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<tr>
<td></td>
<td>Cons: Ian Bruce (UK) (20 minutes + 10 minutes rebuttal)</td>
<td>Ian Bruce (UK)</td>
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<td>Discussion (15 minutes)</td>
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<tr>
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<td><strong>Plenary I: New Aspects in the Diagnosis and Management of SLE</strong></td>
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<td><strong>Moderators:</strong> Bevra H. Hahn (USA) &amp; Zahir Amoura (France)</td>
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<td>08:30</td>
<td>Early lupus: how early is early?</td>
<td>Andrea Doria (Italy)</td>
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<td>09:00</td>
<td>Treat-to-target: issues and answers</td>
<td>Ronald F. van Vollenhoven (Sweden)</td>
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<td>09:30</td>
<td>Biomarkers in SLE: how useful are they?</td>
<td>David A. Isenberg (UK)</td>
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<td></td>
<td><strong>Case Study Workshops (AM)</strong></td>
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<tr>
<td>11:00</td>
<td><strong>Moderator:</strong> Zahir Amoura (France) Investigating the febrile lupus patient</td>
<td>Sandra V. Navarra (Philippines) &amp; Fabrizio Conti (Italy)</td>
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<td>11:00</td>
<td><strong>Moderator:</strong> Ricard Cervera (Spain) Haematologic challenges: cytopaenias</td>
<td>Michelle Petri (USA) &amp; David A. Isenberg (UK)</td>
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<td>11:00</td>
<td><strong>Moderator:</strong> Roger A. Levy (Brazil) CNS lupus</td>
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<td>11:00</td>
<td><strong>Moderator:</strong> Murray B. Urowitz (Canada) Difficult skin disease</td>
<td>Annegret Kuhn (Germany) &amp; Marta Mosca (Italy)</td>
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<td>11:00</td>
<td><strong>Moderator:</strong> Bevra H. Hahn (USA) Lupus nephritis</td>
<td>Richard A. Furie (USA) &amp; Gabriella Moroni (Italy)</td>
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#### Case Study Workshops (PM)

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<td>Renal transplantation in SLE: outcomes and prognostic factors</td>
<td>GB</td>
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<td>Osteonecrosis and osteoporosis in SLE: early diagnosis and prevention</td>
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### Sunday 1st March

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<td>Breakfast with the Professor</td>
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<td>Planning and managing pregnancy in SLE</td>
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<td>Outcomes in children from mothers with SLE and APS</td>
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<td>09:00</td>
<td>Transition of childhood onset SLE into adulthood</td>
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<td>Alberto Martini (Italy)</td>
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#### Plenary IV: Management of SLE and APS: Today and Tomorrow

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<td>10:45</td>
<td>Plasma exchange and IVIG in SLE and APS</td>
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<td>Ricard Cervera (Spain)</td>
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<td>11:15</td>
<td>Managing SLE today and in 2025</td>
<td>GB</td>
<td>Richard A. Furie (USA)</td>
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<td>11:45</td>
<td>Discussion</td>
<td>GB</td>
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</tr>
<tr>
<td>12:15</td>
<td>Summary and close</td>
<td>GB</td>
<td>Roger A. Levy (Brazil) &amp; Andrea Doria (Italy)</td>
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Keynote Lecture

My ten commandments in the management of lupus: Murray B. Urowitz

Professor Urowitz outlined his ten commandments for identifying and treating lupus, beginning with the question: Is the woman with psychosis and a rash the same as a man with arthritis and kidney disease, or the adolescent with thrombocytopenia and antiphospholipid syndrome? And showing how his commandments might help physicians to diagnose and treat these patients appropriately.

Systemic lupus erythematosus is not one disease – it is multiple diseases, and specific goals for management are difficult to define. However, general principles of management both ‘thou shalt’ and ‘thou shalt not’ can be developed.

Professor Urowitz’s ten commandments in the management of lupus include:

1. **Classify/diagnose the patient properly, using ACR or SLICC criteria.** ACR 1997 consists of 11 criteria, and if four are not attributable to something else, there is a 90% accuracy for diagnosis; but ACR only lists malar and discoid rashes, not all skin manifestations. The newer SLICC criteria include a large number of skin manifestations, which really describe the symptoms of lupus: acute, sub-acute and chronic cutaneous lupus, ulcers and non-scarring alopecia. In SLICC too, four criteria are needed, but at least one each of clinical and laboratory findings is required.

2. **Phenotype the disease:** all lupus is not the same – there are many disease variants and manifestations.¹

3. **Treat-to-target**, which first means choosing a target to aim at, from disease activity, clinical phenotype, pathogenic mechanism, or preventing damage and eliminating steroid use.

4. **Prescribe an antimalarial for all:** this is backed up by good evidence, including a systematic review of literature in English from 1982–2007 showing high levels of evidence that antimalarials prevent flares and increase long-term survival; and moderate evidence of protection against organ damage, thrombosis and bone loss.

5. **Manage corticosteroids:** use them to ‘put out the fire’. Choose small doses (0–20 mg; for arthritis and skin), medium doses (20–40 mg; for serositis) or large doses (>40 mg); don’t use mg/kg as there is no evidence for effectiveness being based on drug given per kg of body weight. Steroids cause damage accrual – musculoskeletal, ocular, neuropsychiatric damage is caused by the primary drug used to treat SLE! Duration and dose increase damage,³ so reduce after 6 weeks, then plan to wean to zero.

6. **Manage cytotoxic therapies,** which can be used if corticosteroids are not successful in mild-to-moderate SLE, and alongside corticosteroids in severe SLE (severe renal or CNS disease may be treated from the beginning). Methotrexate, azathioprine, mycophenolate mofetil and tacrolimus can be used; azathioprine and tacrolimus are considered safe in pregnancy.

Multi-target cytotoxic therapy is a new innovation,⁴ allowing the benefits of more than one drug to target the disease. Tacrolimus and mycophenolate mofetil were shown to be superior to cyclophosphamide as an induction treatment for lupus nephritis.⁴ Very slow withdrawal (>2 years) reduces likelihood of flares; and patients on prednisone during withdrawal flared more often.⁵

7. **Consider the newer biologics** for patients who have not responded to more traditional drugs. Belimumab is available now, with other drugs (epratuzumab) coming on line.

8. **Monitoring for and treating comorbidities** is essential to discover unmet needs.⁶ These include atherosclerotic vascular disease, neurocognitive dysfunction and bone disease (osteoporosis and osteonecrosis). Monitoring is important to identify those patients who are below the surface for having an actual event, but for whom the risk factors are increasing, and the threshold for a cardiovascular event approaching. Early dementia is increasing in lupus and may become as important and
cardiovascular disease in SLE in the future. Cognitive dysfunction is more than twice as likely in SLE patients versus controls.\(^7\)

9. **Don’t forget patient-related outcomes**, which can be measured with SF-36\(^8\) (8 domains, both physical and mental components, used for many different diseases) and LUPUSQoL\(^9\) (a lupus-specific QoL measure). Both reflect that lupus patients are less well and have a lower general quality of life than controls with other common chronic diseases (AIDS, Sjogren’s, rheumatoid arthritis, etc). Patients with pain all over may have fibromyalgia, which does not contribute to lupus disease activity and is not treated with lupus primary therapies – but can have a big effect on QoL. But the LupusQoL does not change if the patient is in remission.

10. **Monitor patients every 3–4 months** using clinical and laboratory criteria.\(^10\) At this frequency, variables of interest that are not yet recognised by the patient can be identified – and therefore treated sooner than they would have been with a longer monitoring frequency.

These ten commandments are a basis for diagnosis and treatment of SLE – they may be superseded, but many of them may continue to be foundations for management of SLE in the future.

**References**


6. Urowitz M. University of Toronto Lupus Clinic Data.


Discussion Forum: Issues and Answers

Vitamin D and SLE – to Do or not to D? Yehuda Shoenfeld & Ian Bruce

Ricard Cervera introduced the topic and moderated the discussion as Yehuda Shoenfeld (Pros) and Ian Bruce (Cons) debate the use of vitamin D in lupus.

Vitamin D is essential for life, mainly provided by the sun, with a small amount coming from oily fish, other foods, and supplements. However, systemic lupus erythematosus (SLE) patients are advised to stay out of the sun, and may have vitamin D deficiency because of this. Deficiency may lead to lung disease, infection, cancer, and autoimmune diseases. There is a debate about the importance of vitamin D in lupus, which begins with whether vitamin D levels should be monitored in lupus patients at all, and extends to whether lupus patients should be given vitamin D supplements as a matter of course.

Professor Cervera asked the audience to answer three questions using their tablets, these questions were then asked again at the end of debate following presentation of the pros and the cons of using vitamin D in the management of SLE:

Figure. Questions to the audience: Before the debate

![Pie charts showing audience responses to questions: Do you think that Vitamin D plays a role in the pathogenesis of SLE? (n=199) 42% Yes, 58% No. Do you agree that the levels of Vitamin D should be monitored in all SLE patients? (n=202) 69% Yes, 31% No. Do you think it is necessary to supplement all SLE patients with Vitamin D? (n=205) 57% Yes, 43% No.]

Vitamin D and SLE – to Do or not to D? Pros: Yehuda Shoenfeld

Professor Shoenfeld began the debate by presenting the pros for the monitoring and use of vitamin D in SLE patients. Referring to Murray Urowitz’s ten commandments, he added an 11th commandment: TAKE VITAMIN D, and entreated every person in the room to take 2000 units of vitamin D daily forever to reduce mortality, sickness, infection, autoimmune diseases, and cardiovascular diseases.

He reviewed recent papers describing the benefits of vitamin D in SLE and other diseases, and in healthy people. Al Saleem showed an inverse correlation with the levels of vitamin D and autoantibodies, and treatment with vitamin D led to an improvement in the SLEDAI score. Vitamin-D deficiency is common in paediatric lupus and is independently associated with elevated high-sensitivity C-reactive protein (hsCRP), a marker of inflammation that predicts cardiovascular disease risk. Vitamin D is involved with 400 different genes in humans. It has shown suppression of TGF-β-SMAD signal transduction by vitamin D, which prevented renal fibrosis in mouse models of tissue fibrosis. In China, SLE disease activity was inversely correlated with vitamin D levels. Even Ian Bruce, his opponent in the debate, published a paper showing that vitamin D reduce vascular damage in SLE and is a novel agent to improve myeloid angiogenic cell function.

Vitamin D has a receptor in almost every tissue and organ in the body, so it is not surprising that a lack of vitamin D contributes with many diseases. Even in Israel (with 350 days of sun a year), only 20% of healthy people have vitamin D levels within the recommended range, due to lifestyle, less active lives, and indoor hobbies and interests. This is underlined by the finding that autoimmune...
diseases are much more common further away from the equator where people get less sun and its intensity is weaker. The overall prevalence of SLE in Norway was 51.8 per 100,000 population (95% CI 45.2-58.4). The findings also indicated a higher prevalence in Norwegians compared to Caucasians in Denmark and England. The higher prevalence of SLE in foreign adopted individuals warrants further examination.

Vitamin D is an antibiotic – and deficiency is implicated in the increase in colds and respiratory disease in the winter when there is less sun, as higher levels vitamin D are important in preventing infections. The mechanism for this was described in a paper by Hewison in 2008. In vitro studies have proven the antibiotic-like mechanism of vitamin D. Several epidemiological studies suggest a correlation between low levels of vitamin D and infections, but there are few data about the effects of vitamin D supplementation on infections, which remains to be fully investigated. Vitamin D levels in patients with SLE are around half those of controls, and those in systemic sclerosis and rheumatoid arthritis are lower still.

Figure. Immune aberrations of SLE: opposite to vitamin D actions

Serum concentrations of 25-OH vitamin D in patients with SLE are inversely related to disease activity: is it time to routinely supplement patients with SLE with vitamin D? Lower levels of vitamin D were also seen in patients with APS in comparison with healthy controls matched for age and sex. Vitamin D correlated with thrombogenic effects, so perhaps it might influence thrombosis in APS, mediated by anti-β2GPI.

Vitamin-D inhibits tissue factor expression induced by anti- β2GPI antibodies on endothelial cells, which is the main pathogenic mechanism for thromboembolic events. Professor Shoenfeld’s presentation in favour of vitamin-D supplementation in SLE concluded by saying that for patients with autoimmune-rheumatic diseases further randomized controlled studies are needed regarding efficacy, required dose etc. But, in the meantime, vitamin-D supplementation is harmless, inexpensive, reduces overall mortality and should be considered for patients with SLE.
**Vitamin D and SLE – to Do or not to D? Cons: Ian Bruce**

Professor Bruce then presented the cons to using vitamin D in SLE stating that although he is not against vitamin D in general, he is sceptical of its widely claimed clinical benefit in SLE. There are lots of questions surrounding the use of vitamin D, and these questions should prompt caution. Professor Bruce set out to discuss four points:

1. We’ve been here before in debating use of vitamins and supplements. Association is not causation
2. Interventions require unbiased assessments
3. The use of guidelines and misguided-lines.

**We’ve been here before:**

He reviewed the papers looking at vitamin D and health highlighting a recent meta-analysis that found 137 different adverse health outcomes related to vitamin D deficiency. These included cancer, heart disease, bone disorders, and metabolic disorder outcomes. But deficiencies in other vitamins have also been implicated in a wide range of adverse health outcomes, including vitamins A, B6, B12, C, and E, β carotene, folic acid, and selenium. Clinical trials of these other supplements have however been largely negative and some actually suggested harms.

**Association is not causation:**

One study showed low vitamin D in early SLE, but the primary results were not statistically significant. The authors found an association of low vitamin D with photosensitivity and renal disease in EARLY SLE however we know that Bengtsson et al. previously showed that a number of environmental risk factors are implicated in SLE, including alcohol, smoking, hypertension, and pale skin types (the type that tends to avoid sun long before getting SLE).

Some research that showed a significant association between vitamin D and SLE disease activity nevertheless also showed that vitamin D accounted for only 1.4% of variance in disease activity. Another observational study showed that patients with higher vitamin D had lower disease activity measured as a 0.22 reduction in SELENA-SLEDAI score and a 4% reduction in urine protein-creatinine ratio. A number of confounders were unaccounted for in these studies and residual confounding may well explain these small effects.

Vitamin D is also a reverse acute phase reactant – it is lower in active rheumatoid arthritis (RA) than in inactive RA; lower in acute sepsis; and also lower post-knee replacement surgery, as part of the post-op systemic reaction. Vitamin D is also influenced by steroids, antimalarials, body mass index and body fat distribution, and renal disease; and low vitamin D levels are a marker of an unhealthy lifestyle. All of these factors may confound any associations seen in observational studies and can be examples of reverse causation.

A clinical study on cardiovascular risk showed that endothelial function improved with vitamin-D supplementation, indicating that there might be advantages in reducing cardiovascular risk. Patients in the highest quartile for vitamin D tended to have less hypertension and less likely to be hyperlipidaemia. However we still need to be cautious as a meta-analysis of population-based clinical cardiovascular disease outcome trials showed no evidence of long-term prevention of cardiovascular disease.

**Interventions require unbiased assessments:**

One previous study had examined interferon signature responses and found that dendritic cells in patients with lupus have a much higher production of interferon, the authors hypothesised that if vitamin D was supplemented, there would be a dramatic reduction in the interferon signature; the subsequent trial did not bear that out.
Another vitamin D in SLE trial had a primary outcome of change in pro-inflammatory and haemostatic biomarkers \((n = 6-10)\), and a secondary outcome of SLEDAI 2K score.\(^{18}\) All 10 biomarkers significantly improved at 12 months, including complement and anti-dsDNA. SLEDAI2K was a secondary and exploratory analysis, the whole group assigned to therapy was not analysed, the clinical SLEDAI changes vs dsDNA, low complement were not reported, and the tolerance of variations in background therapy were not reported in detail. Finally, self-management with steroids was not mentioned, and would have occurred in at least some of the participants.

Figure. Low Vitamin D in early SLE\(^{13}\)

- 123 SLE vs 240 controls
- Lower 25-OHD levels in SLE
  - \(\beta\)-coeff = 2.25, \(p = 0.15\)
  - Mean (SD) vitamin D
  - Cases: 21.6 ng/ml (12.9)
  - Controls: 27.4 ng/ml (15.7)
  - Caucasians (\(p = 0.04\))
  - A-Americans (\(p = 0.36\))

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Guidelines and misguided-lines:

There is no international consensus around vitamin D population guidelines, and they target assessment to those ‘at risk’ of vitamin-D deficiency. The optimal level varies by country, and 20–30 ng/ml may be ‘optimal’ (IOM and others). The daily dose for maintenance is unclear, and specific to different contexts, including where people live and the colour of their skin. And finally, the guidelines make no recommendations beyond maintenance of bone health, which would be premature, perhaps misleading to patients, promotes polypharmacy, and would over claim benefits of vitamin D.

When it comes to recommending vitamin D in all SLE patients, there are a huge range of suggested doses, from 600–800 IU/day to 1500–2000 IU/day to 4000 IU/day or even more. Preparations available are mainly as supplements with less stringent manufacture regulations. Also, because of the lack of randomised controlled trials, our understanding of vitamin D in SLE remains limited. There may be a threshold effect, individual variation questions on safety and a need for full monitoring. All these questions need answers before setting guidelines beyond what is known for bone health.

**Vitamin D and SLE – to Do or not to D? Yehuda Shoenfeld’s Rebuttal (Pros)**

Professor Shoenfeld responded to the case against vitamin D. He said the side effects of vitamin D are very rare and may be overstated. He reported a reduction in total morbidity and mortality in elderly people taking vitamin D – which contradicted Professor Bruce’s suggestion that falls may become more common. Vitamin is cheap, freely available, and does not need a prescription. Sometimes you have to wait for further evidence, but at other times, as in vitamin D where the risks are potentially low and the benefits high, it is worth taking a risk!

**Vitamin D and SLE – to Do or not to D? Ian Bruce’s Rebuttal (Cons)**

Professor Bruce clarified his use of the term ‘suggestion of harm’ saying that it did not mean that he believed that there was harm, but that one should be cautious. Cellular studies do not always correlate with what is observed in actual patients, so mechanisms of action need to be ascertained.
Supplementation of all SLE patients with vitamin D would be premature, is not supported by the evidence.

A short discussion was then opened with the audience, before the debaters summed up their positions. To conclude, the questions asked at the start of the debate were repeated, to see whether hearing the use of vitamin D being debate had altered listeners’ opinions on its importance, or their practice.

Figure. Questions to the audience: After the debate

Professor Cervera concluded that there are still questions to be answered and many things to discuss in the use of vitamin D in SLE and related diseases.

References


Plenary I: New Aspects in the Diagnosis and Management of SLE

Early lupus: How early is early? Andrea Doria

Professor Doria discussed the importance of early diagnosis of systemic lupus erythematosus (SLE) in improving outcomes. He outlined methods to increase the chances of a correct and timely diagnosis, using the constantly evolving criteria for disease classification and the latest methods of monitoring clinical and immunological features consistent with SLE.

Professor Doria began by reviewing the classification criteria and the introduction of antinuclear antibody testing in 1980. This reduced the lag time between onset of SLE and diagnosis, from around 60 months before 1980 to around 9 months after 2000. From 1990 until now, however, nothing new has been introduced to improve diagnostic process in SLE.

When does SLE start? Autoantibodies have been shown to appear many years before clinical disease. The accumulation of autoantibodies leads to antibody-mediated renal damage in SLE, silent lupus nephritis, and an inflammatory response in the cells. Immune onset, leads to pathology onset, sub-clinical SLE and undifferentiated connective tissue disease; this becomes lupus after diagnosis.

How can we identify patients with early SLE? Using a multistep process, evidence for lupus can be built up as the disease progresses and the various specific and non-specific manifestations start to show. Advances in technology could lead to the identification of new biomarkers, defined as a measurement, including but not limited to a genetic, biological, biochemical, molecular, or imaging event whose alterations correlate with disease pathogenesis, and/or manifestations, and can be evaluated qualitatively and/or quantitatively in laboratories.

What is the importance of early diagnosis? In lupus-prone mice, successful interventions are most effective when they are introduced before the development of the disease. Only the newer more complex drugs have an effect once the disease has developed. The impact of delay in renal biopsy on renal outcomes is a risk factor for an adverse renal event. In all studies the effect on renal outcome was attributed to the delay in treatment. There is a window of opportunity of 3–5 months to initiate treatment for lupus, in which long term complications may be minimised.

How should we manage patients with early SLE? No randomised controlled trails (RCTs) address this question, but the most promising drugs for early treatment are vitamin D3, antimalarials, immunosuppressants and, finally, biologics. The earlier the diagnosis, the earlier the stage of lupus seen, and the fewer complications have already occurred. So can glomerulonephritis be prevented in patients who do not show symptoms at diagnosis? There is a correlation between pentraxin-3 antibodies and glomerulonephritis. The binding of C1q to pentraxin 3 in apoptotic cells can induce tissue inflammation. The binding of antipentraxin-3 antibodies to pentraxin 3 can result in inhibition of complement activation.

Professor Doria concluded that early diagnosis of SLE is crucial for an early therapeutic intervention, which can increase the probability of disease remission and improve patient prognosis. Biomarkers are urgently needed to help identify patients in an early stage of the disease. Some candidates for early therapeutic intervention in SLE have been identified; however, no RCTs are available to date. Reducing disease activity and achieving remission in SLE leads to an improvement in disease prognosis and a decrease in direct medical costs.
References


Treat-to-target – Issues and answers: Ronald F. van Vollenhoven

Professor van Vollenhoven presented the principle of treating-to-target, identifying appropriate therapeutic targets and pursuing these systematically, which has led to improved care for patients with several diseases and useful guidance for healthcare providers and administrators.¹²

Professor van Vollenhoven began by reviewing the Euro-Lupus trial,³ which showed that virtually 100% of patients were free of renal disease after 14 years and that long-term outcomes with low- and high-dose intravenous cyclophosphamide followed by azathioprine were as good as in NIH cyclophosphamide patients. This was not reflected in all trials, however. A patient survey in Sweden showed low patient-reported quality of life (EQ-5D) and high cost of treatment in lupus patients, for both direct and indirect medical costs.⁴

Long-term problems in lupus are not only caused by the disease but also by the treatment. Corticosteroids in particular cause many problems and a goal of treatment is to minimise their use while still managing the disease adequately. A trial showed that treating lupus nephritis with cyclophosphamide was as effective as steroids – but with fewer side effects.⁵

Professor van Vollenhoven then gave an overview of the use of biologics in SLE. Only one biologic is approved for use in SLE, but several are used off label, and still more are in development. There are regulatory and financial constraints in their use, however, as well as uncertainty about when they should be used. Data from the BLISS trials failed to provide evidence of the glucocorticoid-sparing effects of belimumab, and highlighted how difficult it was to get patients off steroids.⁶ Rituximab, anti-CD20 monoclonal antibody, is not yet approved for use in SLE, though it is approved in other diseases and is starting to be used off label in lupus, with good results. The first patient treated had a reduction in disease activity, and a repeated biopsy 3 years after treatment showed inactive histopathology and remission (WHO class I B, activity index 1, chronicity index 8). However, trials in both renal and non-renal lupus were negative.⁷,⁸

Participants at the meeting were invited to put patients in to the RING trial, a multicentre trial in lupus nephritis; Rituximab for lupus Nephritis with remission as a Goal.

Epratuzumab has also delivered good results, with a positive British Isles Lupus Assessment Group (BILAG)-based Combined Lupus Assessment response rate at week 12 for all patient groups.⁹

Figure. EMBLEM: BICLA response rate at Week 12 (ITT population).
2 patients randomized but never received drug; p values were not adjusted for multiple comparisons and are based on an exploratory post-hoc analysis;
p value for all 6 treatment arms for overall treatment effect assessed in primary analysis = 0.148
Other new drugs are in development, though some promising drugs have been stopped due to poor initial results.

At any point in time, many patients have moderate or high disease activity, the risk of flare remains high, HR-QOL is significantly reduced, and long-term prognosis may be poor. New treatment strategies are needed, and treating-to-target is important.

The principle of treating-to-target in systemic lupus erythematosus (SLE) involves identifying a target for each patient; intervening; agreeing on when to re-assess; and, most importantly, if the target is not met: modify the intervention. An international initiative was launched to develop treat-to-target guidance for SLE, and 34 specialists in rheumatology, nephrology, dermatology and/or clinical immunology, and a patient representative contributed. Topics of critical importance were identified and a systematic literature review (SLR) performed. The results of the SLR were condensed and reformulated as recommendations, discussed, modified, and voted upon. The finalised bullet points were analysed for degree of agreement among the panel and the Oxford Centre level of evidence (LoE) and grade of recommendation (GoR) were determined for each recommendation.

The systematic literature searches led to eleven recommendations, of which the most prominent are: targeting remission, preventing flares, preventing damage, minimizing glucocorticoid exposure, and improving quality of life. A generally applicable definition of remission in SLE is urgently needed, and an initiative has now been started by a large international task force (DORIS), and has led to the formulation of a number of principles to guide future trials.

Treating-to-target is essential to the care of patients with SLE. Long-term outcomes are still poor, biologics are contributing more but need further development, and active strategies may offer better long-term hopes for patients with lupus.

References


**Biomarkers in SLE. How useful are they? David A. Isenberg**

Professor Isenberg questioned what biomarkers are good for, and outlined their use and potential in lupus, concluding that the key problems are to show relevance to disease, and the costs involved to develop affordable assays.

Over 100 antibodies have been identified in lupus, but most are present in a very small number of patients. Only a few are present in >25% of lupus patients, notably anti dsDNA, anti-histone, anti ssDNA, anti-RNP, anti Ro, anti-poly (ADP-ribase) and antiphospholipid antibodies. The presence or absence of these may reflect the different manifestations seen in lupus, and biomarkers can be used to identify different disease subsets.

Overlap features leading to what became known as mixed connective tissue disease, were identified by Sharp et al in 1972. Nimelstein et al 1980 revisited these patients and their observations and found very different results. Nimelstein et al concluded that certain features of the patients that had originally been thought to make them clinically distinct had not held true over time.

In order to be effective, biomarkers must reflect disease activity, and be linked to end organ function. In the 1950s to 1980s, several disease activity assessment systems were tried, but none were shown to be valid or reliable. In the 1980s, new reliable scores were devised and further developed. The British Isles Lupus Assessment Group (BILAG) divided lupus into eight different systems or organs, and is based on the physicians intent-to-treat. This was then changed (removal of damage items; adding gastrointestinal scores, etc.) to reflect things learnt during use.

Antibodies are an established biomarker, but there are some new(ish) kids on the block:

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

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

In a study of 308 SLE patients compared to 389 patients with other rheumatologic diseases, anti C1q in combination with anti dsDNA and low complement was the strongest serological association with renal involvement.

Biomarkers might include antibodies, complement activation products, interleukins, interferons, epigenic alterations (which may lead to changes in, for example, CD11a expression, B-cell costimulation, etc.), nitration as a surrogate marker for endothelial activation (or dysfunction),
antinucleosome antibodies. Both nucleosomes and anti-nucleosome antibodies have been found in serum of patients with SLE and levels correlate with disease activity. So, if both nitration and nucleosomes are important in SLE then levels of nitrated nucleosomes (NN) could be important.

Disease prediction can be seen and used ahead of formal diagnosis – antibody changes occur before clinical disease as seen in Professor Doria’s presentation, and can be used to predict disease progression. In addition, there are genetic predictors for SLE, and about 40 loci are associated with risk of developing SLE.

There is significant correlation between type 1 IFN gene signature and several autoantibodies e.g. anti-dsDNA, Ro, Sm, RNP, but there are conflicting data about correlation between type 1 IFN gene signature score and disease activity.

SLE – it’s 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


New trends in the treatment of nephritis. Gabriella Moroni

Professor Moroni presented details of the “NIH regimen” (intravenous cyclophosphamide and oral steroids) which, from the 1980s until 10 years ago, represented the standard of care for induction and maintenance treatment of lupus nephritis (LN). She went on to discuss alternative therapies prompted by an incomplete response in some patients and the treatment-related toxicity observed with this approach.1

Professor Moroni began her presentation by saying that there are a number of unmet needs in LN treated with the NIH schedule: the response to therapy is slow and incomplete (50–60% at 6 months); relapses are frequent (45%); many progress to end stage renal disease (25%); and adverse events are frequent and severe.2–4

The Euro-Lupus Nephritis trial demonstrated that, in Caucasian patients at least, outcomes equivalent to the NIH regimen could be obtained with a smaller dosage of cyclophosphamide (CYC) plus methylprednisolone pulses and azathioprine (AZA) for maintenance.5 The results of this trial also suggest that the intensity of the immunosuppression can be tailored to the severity of the disease among patients with proliferative lupus nephritis.1

Multi-targeted therapy provides superior efficacy compared to IV CYC for induction treatment of LN. Both groups had similar incidence of adverse events, and there were significantly fewer gastrointestinal disorders and leukopenia in multi-target therapy, but more tremors. More patients in the multi-target than in CYC group dropped out as a result of side effects. These results need to be confirmed, and it must be remembered that chronic renal failure, high chronicity index at renal biopsy and uncontrolled arterial hypertension are contraindications to calcineurin inhibitors.

Efficacy of rituximab (RTX) has been shown in refractory lupus nephritis. An overall response was shown in 74% of patients. Rituximab seems to be at least as effective as mycophenolate mofetil (MMF) and CYC pulses in inducing remission. Rituximab should be considered a viable alternative for the treatment of active LN.6 Rituximab was seen to be an effective treatment for lupus nephritis and allows a reduction in maintenance steroids.7 A prospective observational single-centre cohort study was performed to evaluate the effectiveness of treating lupus nephritis with RTX and MMF, but without oral steroids.8

In the MAINTAIN Nephritis Trial, 52 patients were given AZA, and 50 patients MMF, and followed up for 48 months. Renal flares were observed in 25% of the azathioprine group and 19% of the MMF group.9

Mycophenolate mofetil was superior vs AZA was compared as maintenance therapy in LN, in 227 patients who had initial renal response, for 3 years. There was a composite end point. Failure of treatment was seen in 32% of the AZA group and 16% of the MMF group. Serious adverse events were similar in the two groups, but more patients in AZA withdrew because of adverse events.10

A randomized pilot trial was conducted comparing cyclosporine and azathioprine for maintenance therapy in diffuse lupus nephritis over 4 years.11 The primary outcome was prevention of renal flares. The results showed in the cyclosporine group, seven flares/36 patients (19%) (10.6 flares/100 pts/year); and in the azathioprine group: eight flares/33 patients (24%) (13.4 flares/100 patients /year).
All flares responded to a new course of therapy with the exception of one nephritic and one protein flare in AZA and one protein flare in cyclosporine group. No patients died or developed end stage renal disease. The reduction of proteinuria occurred earlier in the cyclosporine group. At the end of follow-up, 41.7% of patients in cyclosporine and 15.1% in AZA had undetectable proteinuria (P = 0.045).12

Until recently, steroids and cyclophosphamide represented the mainstay treatment of lupus nephritis. These drugs allowed us to obtain good but not completely satisfying results and at a price of disquieting side effects. In the last few years, a number of immunosuppressive drugs and biological agents have been introduced in the therapeutic armamentarium of SLE, which allow us to minimize the use of cyclophosphamide and the doses of corticosteroids both in induction and maintenance therapy.

The possibility of alternating old and new agents may help in tailoring treatment according to the characteristics of the patient, so improving both the efficacy and the safety of the chosen treatment.

References
Renal transplantation in SLE. Outcomes and prognostic factors. Frederico Oppenheimer

Professor Oppenheimer presented an overview of the use of renal transplantation, showing that it is the best option for patients with end stage renal disease (ESRD) in systemic lupus erythematosus (SLE).

Renal transplantation represents the final solution for patients with lupus nephritis, and is the best option to treat chronic renal failure because it restores all kidney capabilities, has lower morbidity and mortality than dialysis, leads to a better quality of life and has a lower overall cost. Although the risk of death after transplantation is immediately higher due to the operation, it soon decreases, and within 4 months of transplant the patient shows less morbidity and mortality than the patient on dialysis.¹

Principal factors affecting the results of kidney transplantation include living versus deceased donor, HLA matching and type of immunosuppression, donor and recipient age, cardiovascular events, infections, malignancies, and recurrence of original disease.

In the USA from 1982–2004, ESRD due to lupus went up from one case per million to five cases per million, but the numbers are still very low.² In Catalonia in 2005, systemic diseases were the lowest category of disease aetiology for patients starting renal replacement therapy. Reasons for loss of renal transplant range from chronic rejection, through death, to recurrence, acute rejection, and non-compliance.

Transplantation is a good treatment for a number of other reasons. Disease activity usually declines in ESRD in lupus patients after transplantation. The immunosuppressants used in kidney transplantation may protect the patient from SLE recurrence, and many are the same as the drugs used to treat lupus itself. The risk of graft loss due to recurrence is very low, and there are comparable rates of patient and graft survival to other nephropathies.

In patients receiving a kidney from a deceased donor, there was a measurable but not clinically significant difference in graft survival in lupus patients and patients without lupus.³ This difference was much less in patients receiving a kidney from a living donor.⁴

In addition, the use of mycophenolate mofetil has dramatically changed the outcome of transplantation in lupus patients, and survival rates have been increased.⁵ Pre-emptive, early transplant (before dialysis has become necessary) has a positive impact on the long term survival rates in SLE. The activity of the lupus is lowered, and the chance of graft loss is reduced.⁶ These data were confirmed in Caucasians in the American Registry, which also showed a better prognosis and lower graft rejection rates.⁷ However, recurrence remains a problem causing graft loss in some patients, but not in patients with lupus nephritis at all.⁸ Recurrence of lupus nephritis significantly increases the risk for graft failure, but contributes far less than rejection.⁹ Recurrent lupus nephritis can occur as early as the first week to as late as 16 years after transplantation, with most events occurring during the first 10 years.⁹

A review of 50 cases of renal transplantation in SLE from a single centre from 1986–2013¹⁰ showed that in 50 transplants in 40 patients (some patients had more than one transplant), only one recurrence was detected. Disease activity was not always recorded, but deceased donor grafts were more often lost than tissue from living donors, MMF and tacrolimus improved outcomes (although
the time span was long so these have now been replaced by more modern drugs), and antiphospholipid antibodies were not found to be a concern in graft loss.\textsuperscript{10}

In conclusion, renal transplantation is the best therapeutic option for patients with ESRD resulting from lupus nephritis. Outcomes of patient and graft survival from deceased or living donor transplants are comparable to recipients with other causes of ESRD. Recurrence of lupus nephritis after transplantation has been reported with very variable rates, but the risk of graft failure due to recurrence is very low. Maintenance therapy must be adequately adjusted using an individualised approach and with the continuous collaboration between transplant and autoimmune disease physicians caring for the patients.

References
Osteonecrosis and osteoporosis in SLE. Early diagnosis and prevention.
Bevra H. Hahn

Professor Hahn presented bone disease in lupus, beginning with ischemic necrosis of bone for which little can be done, apart from diagnosing early and getting an orthopaedic surgeon involved at the start. Early identification, treatment and prevention of progressive osteoporosis raises challenges, but also brighter for the patient outcomes.

Ischemic necrosis of bone (INB) occurs in 5–30% of systemic lupus erythematosus (SLE) (though Professor Hahn’s own experience shows a narrower range of 5–10%); femoral head is most common, but many other sites can be involved, including knees, shoulders, wrists, ankles. Multiple sites are common in SLE, and if necrosis is present in one femoral head, the chance for involvement of the other femoral head is 50%.¹

There are a number of factors increasing risk: high doses of glucocorticoids (GC); first year of treatment; young age (<40 years old); long duration of treatment; and others not related to SLE (e.g., alcohol, trauma, sickle cell disease).¹

Clinical clues to diagnosis of INB include a patient complaining of one or a few joints hurting most of the time (the same joints), but in whom SLE is quiescent in other systems. This is especially in the hip and shoulder; if there is any suspicion, order an MRI for symptomatic joints (X-ray and CT are less effective for diagnosis of INB).¹

Treatment for INB depends on location and extent of disease.¹,² These can be assessed using the ARCO, Ficat and Arlet scales, which range from zero to Class IV.

- Zero: High risk for INB; No symptoms
- Class I: Symptoms, normal routine X-rays
- Class II: Symptoms, X-rays cystic or osteosclerotic lesions, no subchondral fractures

Surgical intervention may make a difference in Class I and Class II INB. Conservative management includes minimizing weight bearing, and doing physical therapy for strengthening muscles. Surgical management involves core decompression (“drilling”), structural bone grafting, vascularized fibula grafting, osteotomy, resurfacing arthroplasty, insertion of stem cells, insertion of bone morphogenetic proteins, or combinations.¹,²

- Class III: Symptoms, crescent sign (structural collapse of a necrotic segment of subchondral trabecular bone), intact joint space
- Class IV: Symptoms, end stage X-rays with osteoarthritic changes in joint in addition to routine evidence of INB

In late stage disease (Class III or IV), the only surgical management that has any effect is total joint replacement.¹,²

Surgical interventions for early INB with or without stem cells, bone morphogenetic proteins, or bone grafts are controversial and it is unclear that any prevent progression to joint collapse. Progression rate is approximately 60%.

The evidence for total hip joint replacements is better. In one series of SLE patients, n=24 (28 replacements), follow-up 5.5 years (mean), all better patients improved in terms of pain reduction.
and joint function (p<0.001 on evaluation instruments) The complication rate was 1% (two incisional infections and one UTI).³

The outlook for osteoporosis is better – bone remodelling continues in health and disease.⁴ Anabolic treatment can increase WNT protein, which is a major stimulating growth factor for bone development and turnover.⁴ There are several promising new treatments coming online soon: increasing the effect of WNT by using an antibody to sclerostin which then does not remove excess WNT; managing the effect of osteoclast control over osteoblast production by inhibiting Cathepsin K (which is secreted by osteoclasts and depletes bone) using a small molecule, which renders the osteoclast unable to turn down osteoblast function.

Prevalence of bone loss in SLE varies widely between centres and patients: osteopenia: 10–70%; osteoporosis: 5–50%; fractures: 5–20% (in order, leg, foot, arm; vertebrae; hip). There are many mechanisms for bone loss in SLE: active disease/chronic inflammation; reduced physical activity; vitamin D deficiency; ovarian failure; undertreated hypothyroidism; renal failure; and drug treatments.

Patients who flare have more bone loss.⁵ SLE patients fracture at a higher bone density than healthy individuals, and risks are increased by increasing age, lower hip bone mineral density (BMD), cumulative glucocorticoid dose, and premature menopause.⁶

There are various ways to assess risk, including the FRAX score⁷ (which calculates a risk for osteoporotic fracture over 10 years) and the ACR 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis.⁸

The targets of current anti-osteoporosis treatment mostly reduce osteoclast function and drive the osteoclasts into apoptosis, inhibit resorption, and increase bone mineral density. These targets include calcitonin, rank ligand, bisphosphonates, and oestrogen receptors. Most reduce fractures, but all are coupled to osteoblasts, so after a couple of years, bone production decreases again.

Figure. NICE guidelines for the treatment of osteoporosis⁹
Bisphosphonates are very popular in the USA for reducing fracture risk: reduce Vertebral Fractures by 60–70%; non-vertebral fractures by 20–40%; and hip fractures by 20–40%. Zoledronic acid, denosumab and teriparatide are the most successful at reducing fracture risk.

Glucocorticosteroid related bone loss causes decrease bone formation (decreased OB, GNT, DHEA), enhances osteocyte apoptosis, decreases intestinal Ca++ absorption and renal tubular Ca++ reabsorption producing increased PTH, and increases RANK-L*, which activates osteoclasts and prolongs their survival (in the first 6-12 months). It ultimately reduces both bone turnover and trabecular connectivity.

Vitamin D is important for healthy turnover of bone and remineralisation of bone.

The ACR have produced Guidelines for Management of GC Bone Loss including doses in 2010, and these give different treatment recommendations for low, medium and moderate risk of joint fracture. These guidelines are currently being rewritten with, hopefully, denosumab included as a component of treatment.

Treatment to maintain bone density in SLE should be given from a baseline BMD intervention T score of −1.5. Aims are to control disease activity, optimize 25OH Vitamin D levels (30–60 ng/mL) and calcium intake: 1200–1500 mg qd, prevent falls and encourage physical activity. In addition, give anti-resorptive, anti-osteoclastic therapy: bisphosphonates or denosumab (anti-RANK-L), increase bone formation with Teriparatide for 18–24 months followed by bisphosphonate in patients with low bone mass, and if ovarian function is inadequate, consider HRT (which although it prevents osteoporotic fractures, may cause flares in some women). Zoledronic acid is superior to daily risedronate in improving BMD in glucocorticoid-induced osteoporosis. Zolendronate (i.v. 5 mg annually; $900.00) and denosumab (S.C. once every 6 months; $2100) were best at reducing risk of vertebral fractures (48–50% more effective than other interventions). All bisphosphonates tested were significantly better than placebo ($760/year alendronate weekly; $2400/year risedronate monthly). The differences in effectiveness are most likely because compliance is increased by parenteral dosing.

There are several serious adverse effects of anti-osteoclast treatment, especially in long-term use. Bisphosphonates are stored for years in bone; safety in premenopausal women, especially for foetus, are not clear. Bone gain declines rapidly after discontinuing denosumab and declines slowly after discontinuing teriparatide. Combinations of drugs may help: bisphosphonates or selective oestrogen receptor modulators before parathyroid hormone (PTH) decreases response; PTH followed by bisphosphonates increases bone gain.

The major bone effects in SLE, especially with glucocorticoid treatment are ischemic necrosis of bone, and osteoporosis and fractures. Early diagnosis for INB – persistent joint pain one or a few joints improves outcome, and prevention of fractures is effective in SLE even in patients taking glucocorticoids. Watch for results of Cathepsin inhibitors and anti-sclerostin, which should increase bone without increasing resorption.

References


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9. Available at: www.nice.org.uk.


Plenary III: From Conception through Adolescence: Issues in SLE and APS

Planning and managing pregnancy in SLE: Munther A. Khamashta

Professor Khamashta presented details of his clinic for lupus and antiphospholipid syndrome (APS) patients who are or want to become pregnant. He talked about the multidisciplinary nature of the clinic (obstetric physician [who is an obstetric medical specialist], neonatologist, haematologist and an obstetrician) and reflected on what he has learned and the best way to ensure that mother and baby remain healthy.

Pregnancy in systemic lupus erythematosus (SLE) requires a multidisciplinary team of consultants, which makes for very expensive babies. Pre-pregnancy counselling is important, because although most lupus patients have normal fertility, there are some things which should be considered before conception. It is best to conceive during SLE remission, to ensure that all drugs are safe for use during pregnancy, and to stratify patients by their level of risk; low risk patients can often be delivered in the community. Patients who get pregnant without consultation are at higher risk than those who have pre-pregnancy consultation.

A pregnancy is considered as high risk if there is renal involvement, antiphospholipid syndrome, previous poor obstetric history, or cardiac involvement. Restrictive lung disease (FVC <1 litre), active disease, and extractable nuclear antigens (Ro, La) are also risk factors in pregnancy. Pulmonary hypertension is a strong contraindication for pregnancy as it carries a 50% risk of maternal death.


Active disease at conception increases risk of PET/IUGR/preterm delivery. Flares are difficult to diagnose, as many of the symptoms of a lupus flare are also seen in normal pregnancies, including musculoskeletal pain (lower back pain), hair loss, facial erythema, fatigue, oedema, anaemia, and raised ESR. But there is controversy over whether pregnancy increases flares or not!

Lupus flares occur in 40% of patients during pregnancy or postpartum. Most are mild and easy to control with steroids. Renal involvement leads to an increased risk of preterm delivery, and even quiescent lupus nephritis increases risk of foetal loss, especially if the mother is hypertensive or proteinuric. The risk of deterioration is higher with higher serum creatinine, and is lower with higher serum creatinine. After a renal flare, delay pregnancy for 6 months.

A systematic review of pregnancies in patients with SLE and lupus nephritis, showed much worse outcomes in mothers with active nephritis than those with a history or nephritis but no nephritis during the pregnancy, and a premature birth rate and hypertension rate approaching twice as high.

Distinguishing between physiological reasons for increased proteinuria, pre-eclampsia, and nephritic flare is extremely difficult. There are key features which help to distinguish, but rely on the obstetrician to decide on the cause. Many lupus drugs are considered safe for use in pregnancy and during breastfeeding, though some are not compatible and should be stopped at least 3 months before pregnancy.

EULAR and the BSR have given approval to a list of drugs that are considered safe in pregnancy and breastfeeding that will be able to be used to support decisions on drug use, and will be a legal safeguard for lupus doctors.
High risk pregnancies may have 15 visits to the lupus pregnancy multidisciplinary care clinic. Women get a baseline assessment, judicious monitoring of maternal disease and foetal wellbeing, screening for pre-eclampsia, serial ultrasound scans (uterine and umbilical artery Doppler growth; liquor), and are offered timely delivery. Mid-trimester uterine artery Doppler screening is a very effective predictor of pre-eclampsia.

Neonatal lupus is a passively acquired autoimmunity; cutaneous symptoms appear around 6 weeks after birth, and many babies with congenital heart block require a pacemaker to be fitted, either in infancy or in early teens. There is a recurrence rate of 1 in 5, and there is currently no treatment to prevent recurrence. Trials of intravenous immunoglobulin (IVIG) failed to show prevention of congenital heart block.³ However, further trials showed that there was no recurrence of cardiac neonatal lupus in foetuses exposed to hydroxychloroquine.⁴

Major clinical features of APS include recurrent arterial/venous thrombosis, recurrent pregnancy loss, and thrombocytopenia. Livedo reticularis is a prominent marker. For mothers who have had screening and treatment for APLS, there is a success rate for a healthy pregnancy outcome of 85%.⁵

Recommendations for management of pregnancy in aPL-positive women³

- No thrombosis/miscarriage – no treatment – careful monitoring; low-dose aspirin (no evidence)
- Previous thrombosis – heparin + low-dose aspirin
- Recurrent early miscarriage – low-dose aspirin; heparin + low-dose aspirin
- Late foetal loss/severe pre-eclampsia/IUGR – heparin + low-dose aspirin

If aspirin/heparin fails, try again with aspirin/heparin. Then try adding low dose steroids, IVIG, hydroxychloroquine, or azathioprine and see which gives the best effect. Thromboprophylaxis post-partum is essential, as the risk of thrombosis in these patients is 4-5% compared with just 0.1-0.3% in the normal population.⁶

After pre-pregnancy counselling and with careful multidisciplinary management throughout the pregnancy, the outlook is good for women with SLE and their babies.

References


Outcomes in children from mothers with SLE and APS. Angela Tincani

Professor Tincani discussed the points to consider about health in babies with systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS), and how to ensure that the mother and baby are as healthy as possible. The issues include preterm births, drugs during pregnancy, anti Ro/SS-A antibodies, and anti-phospholipid antibodies.

Systemic lupus erythematosus and APS are autoimmune disorders that primarily affect women of childbearing age, and their first question when starting to think about pregnancy is ‘Will my baby be healthy?’ rather than ‘How will pregnancy affect my lupus?’

The rate of preterm birth (before 37 weeks) is increased in SLE patients. The reported incidence is 23–28%. Preterm birth may be spontaneous, because of premature rupture of membranes (PPROM), or induced to protect the health of the mother and/or of the baby (onset of foetal distress, intrauterine growth restriction or pre-eclampsia). The risk factors for preterm delivery include disease activity (clinical and serological activity, i.e. high titre anti-DNA antibodies, low serum complement levels), antiphospholipid antibodies, high prednisone dose, hypertension, and thyroid disease. Very preterm babies are at highest risk for neonatal death and for both long-term medical complications and cognitive impairment.1–4

Mothers treated with prednisone, hydroxychloroquine, azathioprine (AZA), or cyclosporin A in different combinations does not impair the development of either the immune system or the response to vaccination, or the rate of infection in the first year of life.5,6 There were a few transient short-lived problems.

A recent trial of azathioprine use in pregnancy in 15 children born to 11 mothers taking AZA (median 150 mg/d) for inflammatory bowel disease during pregnancy and a median 6 months lactation (mean age 3.3 years).7 Fifteen children born to 12 patients without using any immunosuppressive therapy for inflammatory bowel disease breastfed for 8 months (mean age 4.7 years). There was no difference in mental and physical development, infection rate, and hospitalizations, although common cold and conjunctivitis were more common in the group NOT exposed to AZA.7

Another trial concluded that after adjustment for several confounding factors including antiphospholipid antibody syndrome, AZA was significantly associated with Special Educational Services utilization occurring from age 2 years onward (odds ratio 6.6, 95% confidence interval 1.0–43.3), and bordered on significance for utilization at any age or age <2 years.8

She reviewed the use of fluorinated corticosteroids to encourage premature development of internal organs in very preterm births where incomplete heart block was present. There are many papers citing problems with this treatment, but some children have grown to maturity with no adverse effects.

Blind assessment was undertaken of the cognitive functioning of three cohorts of children ages 6–16 years with in utero exposure to maternal anti-Ro antibodies in the following groups: No complete atrioventricular block (CAVB) and no prenatal dexamethasone treatment (n=14); CAVB without prenatal treatment (n = 10); CAVB with prenatal dexamethasone treatment (n=16).9 There was no significant difference in intelligence scores, verbal comprehension, perceptual reasoning, working memory, or processing speed.
Antiphospholipid antibodies (aPL) are present in up to 50% of patients with SLE. The foetus is exposed to maternal IgG aPL, and about 30% of infants passively acquire maternal IgG aPL. In vitro, aPL have been shown to react with neuronal cells; in vivo, IgG maternal antibodies crossing the placenta could potentially react with foetal cerebral tissue, because the blood–brain barrier is incomplete. In children born to mothers with aPL, intelligence levels have been found to be normal, however language delay, learning disabilities (LD) and autism have been described.

To conclude, SLE and APS patients can be reassured about their children’s health with:

- An interdisciplinary team including obstetrics and neonatologists for the possible pregnancy and neonatal complications
- Good counselling about drugs suitable in pregnancy
- Adequate monitoring for anti Ro/SS-A positive patients and (when indicated) fluorinated corticosteroid treatment
- Paediatric neurologist evaluation: in fact most of the neuropsychiatric problems described in these children are mild and easily resolved by the appropriate treatment.

References
Professor Martini discussed the way that young patients should be managed, particularly socially and psychologically, and how to effect a smooth transfer and transition to the adult lupus service.

Juvenile systemic lupus erythematosus (SLE) is exactly the same as lupus in adults. Patients with juvenile SLE have renal involvement and encephalopathy more often than patients with adult-onset SLE.\(^1\) 60–80\% of children with SLE have urinary or renal function abnormalities early in the disease course.\(^2\) Lymphadenopathy, nephropathy, neuropsychiatric disease and haemolytic anaemia are all more common in paediatric onset SLE than in adult onset SLE, and early-onset SLE should raise a high suspicion of a monogenic disease, caused by a single gene mutation.\(^3\)

There has been a proposal for a paediatric version of the SLICC/ACR Damage Index (SDI). A cross-sectional study in 1015 patients with juvenile SLE from 39 countries showed 405 patients (39.9\%) had an SDI score of \(\geq 1\) (mean +/- SD score 0.8 +/- 1.4). The paediatric version of the SDI included growth failure and delayed puberty as new domains.\(^4\)

Management of SLE in adolescents includes managing growth (keep corticosteroids low); bearing in mind a long-term life expectancy when prescribing; treating an adolescent who is going through all the usual adolescent issues as well as trying to manage a chronic illness, such as the need to establish a well-balanced personality, the struggle to assert independence, development of self-esteem, issues with body image, relationships with peers, career expectations, and, as in adults, compliance with drug regimens.

Adolescents are in a unique time of change, with different priorities: to develop and consolidate self-identity and self-esteem, develop their sexual identity, establish relationships with peers, acquire independence, and develop and realize their vocation. SLE may heavily interfere with the attainment of these objectives. This may come out as rebellion, denial or depression: rebellion is a normal part of adolescence and a rebellious teenager may be less diligent in proper lupus self-care (leading to bad compliance); denial is a mechanism that adolescents may use similarly to adults, particularly when the disease goes into remission; and depression, which is anger that turns inward (“why me”) is common in the early stages of understanding what lupus is about.

Careful steroid management is needed – adolescents hate steroids. It is important to explain the therapeutic relevance of steroids as well as their side effects (when they are reversible, preventable etc.), and to manage hunger with appropriate diet.

The move to adulthood involves significant changes including moving from school to higher education, training or employment, from living with family to independent living, etc., and if a patient suffers from a chronic disease he has also to move from child- to adult-centred healthcare.

Paediatric care is family focused with strong involvement of parents; paternalistic; considers social, developmental and disease aspects; and is provided in a relaxed, informal atmosphere. Adult care is patient focused, with treatment decisions shared with the patient; is focussed treatment; and is provided in a more formal atmosphere.

There are two aspects of moving from paediatric rheumatology to the adult service – transfer and transition. Transfer is an event that happens on one occasion when information and people move from one place to another. It is very important that clinical responsibilities at this time are clearly
defined so that it is clear to the patients and their families who have the responsibility for the young person’s healthcare. This is particularly important for situations when urgent advice is needed.

Transition is an active process that takes care of the medical, psychosocial, educational and vocational needs of adolescents as they move from child-orientated to adult-orientated medicine. Transition has to promote skills in communication, decision-making, and self-care so that the patient can achieve control and independence with respect to their healthcare. An individualised approach is needed to prepare each patient and family for the transition. The close relationship and trust with the paediatric team, which usually develops over many years, can make the move from child to adult care very disheartening. Several studies have noted that while paediatricians tend to discuss family and social life or school progress, adult physicians tend to stress the risk of long-term complications, and the need to maintain strict disease control. Many patients found the move to adult care particularly stressful, and felt abandoned by their pediatric health providers.

Transition is a process not a date. Chronological age should not be used as the main criterion. Ideally SLE should be as stable as possible around the time when transfer is occurring. Adherence may be a problem: the adult patient is of course free to refuse treatment, but it is essential that the patient fully understands the potential implications of their decision. Young people may not be mature enough to fully appreciate the implications of their decision.

Adolescents have to move from a situation of dependency to being independent, and the presence of a chronic disease such as SLE can keep them tied to their families for physical, emotional and financial reasons. The need to be accepted by their peer group may lead to problems with adherence.

Goals of a paediatric rheumatology transition programme comprise knowledge about disease, medications, and roles of health care providers; skills in communication with health care providers; assistance with separation from parents with respect to medical issues; encouraging adherence to medical recommendations; assistance/guidance with issues of education, jobs/career, independent living, and relationships outside the family; and implementing final transfer to adult healthcare providers (rheumatologist and others as necessary), providing adequate records to new care providers.5

References
Plenary IV: Management of SLE and APS: Today and Tomorrow

Future treatments for APS: Roger A. Levy

Professor Levy reviewed current treatment recommendations for antiphospholipid syndrome (APS), and introduced the rationale and preliminary results of the use of new and innovative approaches for APS.

In the future, the focus for treatment in APS will switch from anticoagulation to immunosuppression to new targeted therapies. Diagnosis of APS is difficult – some patients have thrombotic events, others obstetric issues. Other probable criteria include heart valve disease, renal microangiopathy, thrombocytopenia, livedo, myelitis/chorea, and superficial vein thrombosis (SVT).

There are many treatment recommendations for APS: for patients with venous events, aim for INR 2-3; for arterial events, aim for INR 3–4. The problem comes with recurrent events in spite of full anticoagulation. The recommendation is to aim for INR 3–4, which is slightly higher than ideal but may be more easily achievable. In refractory cases and catastrophic APS: aim for INR 3–4 + low-dose aspirin (and possible addition of hydroxychloroquine [HCQ], statins, rituximab, intravenous immunoglobulin, eculizumab, etc.).

Guidelines for the treatment of APS were published in 2013 and disease pathogenesis in APS was outlined.

A recent systematic review outlined potential future treatment strategies for aPL/APS based on in vitro and/or animal studies, and listed completed and ongoing clinical interventional studies.

New generation oral anticoagulants (NGOA; rivaroxaban, apixaban, edoxaban and dabigatran) show no food/alcohol interactions, reduced drug interactions, and can be used in a fixed dose with predictable anticoagulant effect. No need for routine anticoagulation monitoring. They are licensed for a range of uses. Adherence is essential, and missing a couple of doses may cause a thrombotic event as they have a short half-life, so there is a risk of bleeding, which is hard to revert.

The rivaroxaban in APS (RAPS) trial is an open-label, non-inferiority randomised controlled trial in patients with venous thrombotic (VTE) APS, with or without SLE. Participants must have had a single episode of VTE, while not on anticoagulation or recurrent episode(s) of VTE, which occurred whilst off anticoagulation or on sub-therapeutic anticoagulant therapy + at least 3 months of anticoagulation on warfarin since last VTE (warfarin (target INR 2.5) vs rivaroxaban 20 mg/d).

Hydroxychloroquine reduces thrombosis in SLE and is also useful in APS. Its effects are anti-inflammatory and immunomodulatory, it acts on glucose and lipid metabolism, and has an anti-thrombotic effect. Clinical data is limited and there have not been any prospective studies. Hydroxychloroquine has been used for primary prevention of: postoperative thrombosis in the general population (1970s-early 1980s); thrombosis in SLE patients with or without aPL (1980s to present); and thrombosis in aPL(+) individuals. Also used for the secondary prevention of thrombosis in primary antiphospholipid syndrome (PAPS) (30% thrombosis in warfarin group vs none in warfarin + HCQ group).

Patients are being enrolled for a prospective, randomized controlled trial comparing HCQ vs. placebo in the primary thrombosis prevention of persistently aPL-positive but thrombosis-free patients without other systemic autoimmune diseases. Current recommendations are to use HCQ in all aPL-positive SLE patients, that it may be considered as an adjunctive treatment in refractory PAPS cases.
(multiple-targeted effects, good safety profile), and that adherence to HCQ is essential, though is only 7–51% in SLE.\textsuperscript{11}

Some clinical studies have been carried out on use of statins in aPL(+) patients: Fluvastatin 20 mg/d for one month: decreased expression of tissue factor (TF), protein activator receptor (PAR) 1 \& 2, vascular endothelial factor, annexin II;\textsuperscript{14} fluvastatin 40 mg/d for 3 months: reduced 6/12 pro-inflammatory and prothrombotic biomarkers (aPL, IL1\textbeta, IFN\alpha, IL6, IL8, IP10, TNF\alpha, sCD40L, sTF, VCAM1, ICAM1, E-selectin).\textsuperscript{9} Based on the available data, statins cannot be recommended in APS in the absence of hyperlipidaemia.\textsuperscript{11}

B-cell inhibition may have a role in difficult APS cases, possibly in those with hematologic and microthrombotic/microangiopathic manifestations. Belimumab: not studied (yet) for preventing aPL manifestations.\textsuperscript{11}

Complement is implicated in APS via generation of C5a, which contributes to vascular inflammation. Complement 5a-C5aR ligation up-regulates neutrophil-derived TF expression. In animal studies, an absence of complement regulatory proteins associated with microangiopathy and pregnancy loss. Treatment with anti-C5 MoAb or C5aRA peptides attenuates thrombosis. Eculizumab (rhMoAb) binds to C5, inhibiting cleavage to C5a and C5b, and has been reported in clinical studies in patients with aPL.\textsuperscript{15,16}

Peptide therapy is a potential important future target for aPL(+) patients. However, none of the peptides is ready for trials. Chemical modification is needed, to improve half-life and minimize immunogenicity. Different peptides may be needed for different aPL manifestations.\textsuperscript{11}

Future targets for APS include molecules and receptors for intracellular signalling. Defibrotide derived from porcine intestinal mucosal DNA reduces inflammation and vascular permeability, has antithrombotic and thrombolytic effects, regulated HLA molecules, and improves vascular tone.\textsuperscript{17}

The role of TLR 2 and 4 is important in mediating endothelial dysfunction and arterial remodelling in PAPS.\textsuperscript{18} The relaxation response of aPL to acetylcholine in mesenteric arteries obtained from WT and TLR2-4 KO mice mRNA expression of TLR2-4 and protein in PAPS monocytes is promising, and an aPL injection was shown to decrease endothelial cell relaxation in WT but not in TLR2 and TLR4 KO mice.\textsuperscript{18}

Sirolimus, which inhibits the activation of the mammalian target of rapamycin complex 1 and 2 (mTORC) pathway, has been used to combat transplant rejection and may be a treatment solution in the future.\textsuperscript{19}

Tolerogenic dendritic cells (tDC) as an autoimmune disease treatment accelerates deregulatory cell phenotype, increases the anti-inflammatory cytokine, and decreases proinflammation.\textsuperscript{20}
Table. Future APS targets.20

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>In vitro / In vivo Assays</th>
<th>Clinical Studies</th>
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<tbody>
<tr>
<td>Defibrotide</td>
<td>Adenosine Receptor Agonist NT TF expression</td>
<td>Levels of endothelin, IL-2, TNF and PAI</td>
<td>Case Reports in Refractory CAPS</td>
</tr>
<tr>
<td>NF-κB inhibitor (MG 132)</td>
<td>TLR4</td>
<td>↓ aPL pro-inflammatory and pro-thrombotic effects in models</td>
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<tr>
<td>P38 MAPK inhibition</td>
<td>P38 MAPK</td>
<td>Blocked NFκB signalling &amp; TF expression in aPL stimulated THP-1 cells</td>
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<tr>
<td>TLR4 inhibitor (TAK 242)</td>
<td>TLR4</td>
<td>In vitro study with aPL isolated and tested in WT and TLR4 KO</td>
<td>Clinical study (APS pts) - EC dysfunction</td>
</tr>
<tr>
<td>mTORC inhibitor (sirolimus)</td>
<td>mTORC 1 &amp; 2</td>
<td>Inhibition of Intimal thickening in porcine coronary arteries</td>
<td>Prospective trial: Suppression of intimal proliferation after Sirolimus eluting stent. Kidney Tx Trial</td>
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<tr>
<td>Tolerogenic dendritic cells</td>
<td>b2-GPI DI</td>
<td>D1-tDC &amp; β2GPI tDC attenuate APS; induce Treg in β2GPI mice</td>
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References


Plasma exchange and IVIG in SLE and APS: Ricard Cervera

Professor Cervera presented new information on the use of plasma exchange and intravenous immunoglobulins (IVIG) in the treatment of SLE and APS.

Extracorporeal blood purification technique is designed for the removal from the plasma of large molecular weight substances. There are differences between plasma exchange and plasmapheresis. Plasma exchange involves the removal of large quantities of plasma (usually 2–5 L) from a patient and replacement by either fresh-frozen or stored plasma or another solution (i.e., albumin). Plasmapheresis is the removal of plasma (usually, 600 mL) without replacement.

Plasma exchange is designed to remove large molecular weight substances. They should be sufficiently large, so that they cannot be easily removed by less-expensive purification techniques (hemofiltration, high-flux haemodialysis), with a sufficiently long half-life, so that extracorporeal removal is much more rapid than endogenous clearance pathways. They are often acutely toxic and resistant to conventional therapy, so that the rapid elimination from the extracellular fluid is indicated.

Large molecular weight substances that can be removed include auto-antibodies, immune complexes, cryoglobulins, myeloma light chains, endotoxins, cholesterol containing lipoproteins, thrombotic factors, complement products, and even cytokines. Levels of each type of substance that can be removed in each session differs between substances, even if 100% of the plasma is exchanged. There may also be rebound in some substances, such as immunoglobulin, so that a number of sessions are needed to reduce the levels sufficiently. The plasma volume must then be replaced with normal plasma, which also replaces any deficient components of plasma.

However, there are some side effects of plasma exchange: infections, central line complications, pneumothorax, haemorrhage, hypersensitivity reactions (plasma), metabolic disturbances, hypocalcaemia, hypopotassemia, metabolic acidosis, hypomagnesaemia, and hypogammaglobulinaemia.

Table. American Society of Plasmapheresis (ASA) guidelines on the use of therapeutic apheresis.

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>Plasma exchange is accepted as first line therapy</td>
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<tr>
<td>II</td>
<td>Plasma exchange is accepted as second line therapy</td>
</tr>
<tr>
<td>III</td>
<td>The optimal role of plasma exchange is not well established. Decision must be individualized</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence indicates that there is no benefit. Their use is not recommended</td>
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The ASA recommend use of plasma exchange in the following indications: pulmonary haemorrhage, transverse myelitis, hyperviscosity syndrome, cryoglobulinaemia, thrombotic thrombocytopenic purpura, and even congenital heart block (anti-Ro/La). It is also recommended in catastrophic antiphospholipid syndrome (CAPS), which represents less than 1% of APS patients. The CAPS Registry is an international register of patients with catastrophic APS, which now contains over 500 patients and allows sharing of information and outcomes. Those with CAPS have a 50% chance of...
recovery, but in patients treated with plasma exchange, this rose to 65%. In those treated with plasma exchange (with or without IVIG) + steroids + anticoagulation (triple therapy) this recovery rate rose further to 70%. This led to the creation of the algorithm below, which appears to have reduced mortality by 20% in patients treated using this algorithm:

**Figure. Algorithm for the management of CAPS**

This information has now been incorporated into the ASA APS guidelines.

Intravenous immunoglobulin is a highly purified IgG preparation made from pooled human plasma from 3,000 to 10,000 healthy blood donors. It typically contains more than 95% unmodified IgG, which has functionally intact Fc-dependent effector functions and only trace amounts of IgA, IgM, soluble CD4, CD8, HLA molecules and certain cytokines. It was initially used for the treatment of primary immunodeficiency syndromes, but soon started to be used in autoimmune diseases. These now include multiple sclerosis, chronic inflammatory demyelinating polyradiculoneuropathy, Guillain-Barré syndrome, myasthenia gravis, autoimmune thrombocytopenic purpura, Kawasaki syndrome, systemic vasculitis, inflammatory myopathies, systemic lupus erythematosus, and antiphospholipid syndrome. They have many mechanisms of action, but are very expensive and also have many side effects, including headache, nausea, vomiting, chills, myalgias, flushing, fever, hypertension/ hypotension, anaphylactic reactions (if IgA deficiency), and more uncommonly thromboembolic complications, acute renal failure, and aseptic meningitis.

In SLE, IVIG is indicated in proliferative lupus nephritis, haemolytic anaemia, autoimmune thrombocytopenia, transverse myelitis, pulmonary haemorrhage, and even by some in congenital heart block, although IVIG failed to prevent congenital heart block in a randomised controlled trial.

In APS, IVIG is indicated in catastrophic APS, severe thrombocytopenia, and after recurrent pregnancy losses.
Rituximab inhibits antibody production and interferes with B cell-mediated mechanisms. After 24 hours, start daily plasma exchange to remove already released antibodies. Then after 2 days of plasma exchange, start treatment with IVIG, to replace protective antibodies removed by plasma exchange, inhibit positive feedback mechanisms, and accelerate pathogenic antibodies clearance. Recent trials have shown the efficacy of such treatments.

To conclude, plasma exchange and IVIG are effective therapeutic options in SLE and APS patients with some severe and refractory manifestations. The combined therapy of plasma exchange, IVIG, and rituximab may be an innovative option in the most severe cases.

References
5. Available at: www.med.ub.es/MIMMUN/FORUM/CAPS.HTM.
Managing SLE today and in 2025: Richard A. Furie

Professor Furie set out to predict the future of treatments for systemic lupus erythematosus (SLE) and outlined his thoughts on disease activity assessments, clinical trial endpoints, and the novel therapies that are currently in development.

The use of mycophenolate mofetil has revolutionised treatment of lupus, and the approval of belimumab by the FDA was a significant step forward, but there are many questions still to ask.

Will the patient-physician encounter change? Development of a laboratory panel (analogous to Vectra® disease activity testing in rheumatoid arthritis) would improve diagnosis, but not at the expense of taking a proper history, and physical and laboratory testing.

Cell-bound complement activation products (CB-CAPS) are present at higher levels in SLE patients. Levels of CB-CAPS incorporated into the Avise® test as a diagnostic; but perhaps it can be used as a prognostic test as well. The mean SLE disease activity index (SLEDAI) fell from 6.8 to 2.8, and the BILAG from 15.7 to 8.5. CB-CAPS is a marker for disease activity and quality of life measure. Decreases in EC3d and increases in C4 were associated with reductions in modified (m)SLEDAI 2K and British Isles Lupus Assessment Group (BILAG) scores. Increases in C3 levels were associated with reductions in mSLEDAI 2K only. Decreases in EC3d and EC4d were associated with favourable changes in SF36 (each 6/8 domains), whereas C3, C4, and DNA were associated with changes in 2/8, 0/8, and 0/8, respectively.

Clinical trial endpoints are important, but there has been a poor record in lupus clinical trials to date. The drugs probably work, there is a multiplicity of active pathways, and trial design is important, but often the trials do not prove efficacy. There is a range of clinical trial endpoints, including SLEDAI, BILAG, SRI (SLE Responder Index), BICLA (BILAG-based Composite Lupus Assessment), and the modified SRI. SRI was developed post-hoc belimumab phase II, then later the FDA Guidance for Industry SLE – Developing Drugs for Treatment (2005). The novel responder (SRI) index was composed of a >4 point improvement in SS score, no BILAG worsening (new A or 2 B flares), and no worsening in physician global assessment (PGA) (<0.3 point increase).

BILAG-based Combined Lupus Assessment (BICLA) is based on BILAG rather than the SLEDAI index. A standard endpoint would be nice (lupus doctors are jealous of ACR 20). Some criteria can be easily measured (such as renal function), but the difficulty of translating trial results to everyday practice will likely remain, particularly for extra-renal studies.

There is still a range of unmet needs in lupus: lupus nephritis, severe extra-renal disease, damage prevention, flare prevention, steroid- and immunosuppressive drug-sparing, and remission induction. To do this we need to understand the immune system. The innate immune system is evolutionarily ancient, works on non-specific responses, provides immediate defence, includes complement, neutrophils, macrophages, toll-like receptors, and is the activator of the adaptive immune system.

Conversely, the adaptive immune system is evolutionarily advanced, found in vertebrates only, consists of antigen-specific responses, includes the memory to mount stronger attacks (somatic mutations), as well as B lymphocytes, antibodies, and T lymphocytes. It is activated by the innate immune system.
Extracellular targets include interleukin (IL)-6 and interferon (IFN); trials in IL-6 have not given good results. Interferon α levels are elevated in lupus. SLE sera induce IFN gene signatures, and 60% of patients have IFN gene signatures in peripheral blood mononuclear cell (PBMC). SLEDAI correlates with IFN gene expression, and anti-IFN α Ab reduces IFN gene expression. The question is can IFN inhibitors reduce SLE activity?

There are a number of type I IFN antagonists, including antibodies to IFN alpha: three antibodies (sifalimumab, rontalizumab, AGS-009); 2 diseases (myositis,¹ SLE²); and antibodies to type I IFN receptor (IFNAR): 1 antibody (anifrolumab); 2 diseases (scleroderma,⁶ SLE⁷).

Disease pathogenesis can be linked to SLE drug development strategies: cellular targets include B cells (cellular targets CD 20 and CD 22; extracellular targets BLyS [BAFF], APRIL); T cells (cellular targets, CD28-CD80/86 pathway).

Is anti-CD20 B cell depletion therapy dead? Clinicians still believe in rituximab, even though the LUNAR trial failed. But at week 78 LUNAR showed a reduction in proteinuria.⁸ Rituximab is still used for refractory nephritis, autoimmune cytopenias, and CNS disease.

There is a question about whether companies will pursue an indication in SLE, and a new third generation antibody is being explored (obinutuzumab).

Epratuzumab is a new anti CD22 drug. CH22 is a co-receptor of B cell receptor, which modulates B cell adhesion. Epratuzumab (mAb binds CD22), promotes natural inhibitory function of CD22 on BCR, inhibits BCR-driven signalling, and modulates adhesion molecule expression and migration. Results are eagerly awaited from the phase III trial (EMBODY) and should be out by summer 2015.

B cell-directed therapies are looking hopeful. They all reduce levels of BLyS and APRIL. Of these, Belimumab received FDA approval 2011. Tabalumab: ILLUMINATE 1: both doses failed; ILLUMINATE 2: high dose effective. Blisibimod is currently in phase III trials. Atacicept in lupus nephritis: Study terminated; extra-renal SLE (n=461): 150 mg arm terminated (2 deaths), and 75 mg dosing arm ineffective.

The problem is that there are more studies than there are patients, and this is a major issue in developing new drugs. However, there are a number of new drugs under development, and this will be good for SLE patients and their outcomes.

References

