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

The 9th Annual Meeting of the Lupus Academy was held in online in September 2020, 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 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 14 AMA PRA category 1 Credits™.

The scientific programme, developed by a Steering Committee of 12 international experts, 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:

- Describe current and future treatment options for optimising the management of SLE
- Explain and debate the role of IFN signature as a reliable biomarker and IFN inhibition as a viable treatment approach in SLE
- Discuss novel approaches in the management of SLE, including measurement of disease activity, self-care for patients with lupus, and biologics and pregnancy
- Demonstrate optimal assessment and monitoring of patients with SLE
- Discuss cases of different lupus manifestations, their comorbidities and management of these in clinical practice, including dermatological, cardiovascular, kidney disease in pregnancy and rare disease manifestations
- Demonstrate understanding of targeting novel treatment pathways and their effect on clinical outcomes, including low-dose interleukin 2, 12 and 23, plasma cells and novel intracellular pathways
- Describe treat-to-target and low disease activity and their application in clinical practice with available novel therapies
- Discuss the definition and treatment approaches for refractory lupus manifestations, including nephritis, cytopenias, musculoskeletal involvement and APS in SLE
Keynote Lecture

Understanding and treating SLE: A new era is dawning: Ronald van Vollenhoven (Netherlands)

Professor van Vollenhoven shared some observations lupus therapies and reasons to be optimistic about these in the near future.

Professor van Vollenhoven began his presentation highlighting the heterogenous nature of lupus as well as its numerous clinical manifestations and how the disease and treatment used to manage the disease can have a negative effect on patients. It is therefore imperative that better treatments are created and that patients are better managed.

A study based on UK data looked at the mortality associated with systemic lupus erythematosus (SLE) versus matched controls and found that overall mortality is increased 1.8 fold in patients with SLE, with younger patients having the biggest relative risk of mortality. Although this study does not state that the mortality is the result of the disease or treatments, both factors contribute to it. Similarly, health-related quality of life for patients with lupus has been shown to be just 0.64 of that of matched controls, a figure not dissimilar to advanced chronic lung disease, advanced HIV disease, or stage three Hodgkin’s disease.

B Cells

When understanding and treating SLE, it is important to focus on the disease pathophysiology and decide where to best target treatments. In recent years, many treatments have the B-cells, the B-cell compartment of the immune response, where the antibodies are produced. Given autoantibodies are the hallmarks of SLE, targeting them makes sense. Today, belimumab is the only approved treatment targeting the B-cell activator BLISS. Since its approval several years ago, there have been some refinements to belimumab. Other B-cell inhibitors under investigation have failed to yield the same results. Over a number of years, atacicept has had some success targeting the BLIS/APRIL pathways and more recently telitacicept has shown promise. Another B-cell focused treatment approach involves the concept of not just inhibiting the B-cells, but instead destroying/depleting them. Intravenous belimumab, originally tested in two Phase 2 trials was not only found to be more effective than placebo, but more so in patients with anti-DNA or low complement. This served as the foundation for belimumab’s regulatory approval and use in tens of thousands of patients in clinical practice. Other studies of subcutaneous belimumab have shown similar results, with significant improvements across SRI domains. Importantly, studies have also shown that belimumab is corticosteroid sparing. A more recent study, BLISS-LN, showed that if belimumab was added to MMF it would yield significantly better results for patient with SLE and lupus nephritis (LN) compared with MMF alone.

Other BLISS-blocking drugs in development include atacicept, for which the Address II trial showed promising results and also a Chinese study of telitacicept, which has been given fast track designation by the FDA and an expedited clinical trial programme. The anti-CD20
drug, rituximab, has been used off label in SLE patients for some time, by some as a last resort treatment. More recently another anti-CD20 agent, obinutuzumab, has shown some success in patients with LN, where it was added to standard of care treatment (MMF) in much the same design as the BLISS-LN trial. Despite the role of B cells in the pathogenesis of SLE and LN, and the success of several agents against these, it has become apparent that B-cells may not be central to the pathogenesis of all SLE and that other mechanisms, such as the interferon (IFN) pathway, are at play in the pathogenesis of SLE.

Interferon
Lars Rönnblom, a pioneer of the role of IFN in SLE, with over 2 decades of research in the area, has shown us that IFN is important for host defence and is also a central player in autoimmune disease. A few years ago, Phase 2 trials of anifrolumab showed much promise in patients with SLE, remarkably so in patients with severe cutaneous SLE. Two Phase 3 trials were subsequently undertaken, TULIP 1 and 2. TULIP 1 did not meet its primary endpoint, but secondary outcomes were met, and the second trial TULIP 2 was successful. Clearly, IFN blockade will need to be matched with the SLE patient subtype most likely to achieved best outcomes with this treatment. Yet it is not yet precisely clear how IFN works and who it works best for; future research is needed to shape our understanding of IFN blockade in lupus. Research by Lars Rönnblom et al, has shown that plasma dendritic cells produce high amounts of IFN. Focusing on this cell in a trial of BIIB059 antibody, an antibody that recognizes the BDCA2 marker present on plasmacytoid dendritic cells, IFN inhibition looks promising for patients with SLE and CSLE.

Other Cytokines
IL-12 and IL-23 blockade with ustekinumab has been effective in patients with psoriatic arthritis and Crohn’s disease and it was suggested years ago that patients with lupus may also benefit from this treatment approach. Although, phase 2 trials of the IL-12 and IL-23 blocker ustekinumab provided promising results, results from an interim analysis of the recent Phase 3 LOTUS trial did not follow suit and the trial was stopped. It is not known if the trial design or the drug led to failure. However, blocking other cytokines may yield better results, particularly downstream blockade of JaK, which results in the blockade of several cytokines. Baricitinib, a JaK inhibitor approved for rheumatoid arthritis (RA), has already shown efficacy in SLE at a dose of 4 mg, with 2 mg under Phase 3 investigation.

Conclusion
Professor van Vollenhoven summarised his presentation by highlighting our increasing understanding of the immunology of SLE has resulted in improvements in treatment developments and clinical management of lupus. Not least the success of belimumab in LN and anifrolumab ‘waiting in the wings’ for its place in the treatment paradigm, when determined by the regulatory authorities. Future treatments targeting plasmacytoid dendritic cells and JaK continue to generate data, which will eventually inform us of their
role in clinical practice. Professor van Vollenhoven concluded, stating that in a few years’
time, treatment scenarios for SLE and related diseases are going to look dramatically
different and dramatically better. A new era is dawning for the management of SLE.

Debate

New Developments in Basic Science and Clinical Research: Defining SLE: The Matter of the Debate: Ricard Cervera (Spain)

Professor Ricard Cervera opened the Lupus Academy’s first virtual debate on new
development in SLE science and clinical research and the current place for biologics in the
management of SLE.

Professor Cervera set the scene for the debate by highlighting the myriad of manifestations
clinicians face when diagnosing and treating SLE. Recent years have seen an increase in
understanding of basic science and clinical of lupus, including DNA, RNA, proteins,
metabolites, metabolomics, proteomics, transcriptomics and genomics. Use of these in
everyday practice has broadened our understanding of the pathophysiology of SLE,
including the roles of B-cells, T-cells, cytokines and proteins. Subsequent development of
many biologic therapies to target these molecules has led to important advances in the
management of SLE. However, Professor Cervera highlighted that there is a very big
difference between the use and market value of these drugs in SLE, with few patients
receiving biologics because of cost. Therefore, the question posed for debate was how many
patients will need a biologic therapy?

Professor Isenberg was tasked with arguing a majority of SLE patients will need a biologic,
whereas Professor Urowitz was tasked with arguing a minority of SLE patients will need a
biologic. An initial poll of the audience saw a 50:50 split opinion on these arguments.

A majority of lupus patients (will) need a biologic! David Isenberg (UK)

Professor David Isenberg was tasked with arguing that biologic drugs are the future of lupus
treatment. Using work of two artists to illustrate his case for biologics.

Using the work of Kathe Strenitz (1924–2017), Professor Isenberg depicted the dark alley of
lupus, highlighting the bridges between old and new treatment. Following this, he
presented work by Maurits Cornelis Escher, illustrating that we don’t know what is around
the corner, much like lupus.

With this foundation, Professor Isenberg presented a case history of an 18-year-old Indian
with arthritis and hair loss and cold blue fingers that developed into a catastrophic
antiphospholipid syndrome (CAPS) complication of SLE, which was treated with intense
vasodilation, steroids and cyclophosphamide (CYC). Six years later she developed lupus
nephritis (WHO Grade IV) treated for five years with prednisolone and CYC then
azathioprine (AZA). She had several infections and stopped treatment. Three years later, she
had recurrence of nephritis, (second biopsy confirmed active nephritis) went back on
prednisolone and AZA for 2 years, stopped them again led to a further flare. She was given more prednisolone and AZA. After 2 years her proteinuria was <50 mg/mmol. Following a trip to the Democratic Republic of the Congo she returned with increased proteinuria, a fever and felt unwell. She had her third renal biopsy, which revealed tuberculosis. She responded to treatment, but developed a widespread rash, requiring treatment with cyclophosphamide and steroids. She remained in remission on low-dose steroids for 2 years.

Case Against Conventional Therapy
Given this, Professor Isenberg presented work from Professor Urowitz’s group, highlighting all cause, cause specific and age specific standardised mortality ratios (SMR), which have hardly changed over the past 30 years. The study concludes that mortality in SLE has improved over the past 50 years but the SMR is still ≈3 (i.e. SLE patients are still 3 x more likely to die compared to patients without lupus). Also, SMR (all-cause and cause specific) was particularly higher in those <40 years. Therefore, there is a need to optimise the management of SLE (and its co-morbidities). Similar results were found in a UK general practice study, where death rates were double in SLE patients compared with controls. Moreover, a large study has shown that persistent disease activity in SLE patients on treatment increased with time, with 30%, 44% and 54% increases at 1, 3 and 5 years respectively.

Professor Isenberg continued to highlight the link between early damage and mortality, with a study by Rahman et al, which showed 25% of patients with damage at their first SDI assessment died within 10 years. Much of this damage was caused by steroids used to treat active disease, with more disease activity leading to more damage and more damage leading to more death; thus inadequate management with conventional drugs is the ultimate cause of mortality. Professor Isenberg, then continued to highlight morbidity issues, which are also not well controlled with conventional drugs. Unfortunately, despite its clear association with damage, steroids have remained the cornerstone of SLE treatment for the past 50 years, with variable use dependent on patient factors. Given this Professor Isenberg likened conventional lupus treatment to ‘Esher’s Roundabout’ where patients cycle through the same treatments in order to try and manage their disease.
In summary, Professor Isenberg argued that while mortality rates in SLE have clearly fallen encouragingly in the past 50 years, SLE patients are still about 3 x more likely to die and up to 12 x for those under 40 years. Clearly, morbidity linked to the disease, concomitant diseases and the side-effects of treatment remain a big problem. Therefore there is a need to improve both longevity and quality of life, with new treatment paradigms (i.e. biologics, small molecules etc).

The Need for Biologics
There are several biologics that lupus patients may benefit from, including anti-CD20, anti-interferon, two-factor B-cell blockers as well as others. Professor Isenberg presented work from UCL carried out over the past 20 years, showing that 74% of patients taking biologics had a ≥5 point reduction in BILAG, 67% lost all BILAG A and B scores and only 20% failed to decrease BILAG scores. Indeed, B-cell depletion is very effective in patients with cutaneous lupus and renal lupus. Herein rests the argument for using B-cell depletion therapy at the beginning of treatment as opposed to the end, not least because of steroid sparing and low toxicity associated with such therapy for patients with renal lupus. Similar data have been found for patients with non-renal lupus, where 50% of those receiving B-cell depletion therapy experienced flare, while 70% of those on conventional therapy experienced flare. This result converted into less steroid use in patients taking B-cell therapy.

Professor Isenberg concluded his argument by highlighting that in 1950 lupus patients had a 50% 4-year survival rate compared with 85% for 15 years today. However, the data are still not good enough as a 20-year-old with lupus still has a 1 in 7 chance of dying by the age of 35 years. Therefore, mortality and morbidity require a shift from conventional to precision medicine with biologics.
A minority of lupus patients (will) need a biologic! Murray Urowitz (Canada)

Professor Urowitz was tasked with arguing that only a minority of patients will need a biologic to manage their lupus. He presented evidence of conventional therapies in improving survival, SMRs, disease activity, remission as well as decreasing incidence of major comorbidities.

Survival and SMRs
Presenting evidence for improved survival in SLE, Professor Urowitz highlighted that 5-year survival in the 1950s was approximately 50%, whereas between 2008 and 2016 this had risen to 95% in developed counties alongside >80% for 10- and 15-year survival;28, 29 similar results were seen in the Toronto clinic. Professor Urowitz argued that these results were obtained in the era before biologic therapy. In addition, SMR for lupus patients have seen a huge decrease between 1971 and 2013, again in the pre-biologic era. Moreover, only 19% of patients who died, did so due to SLE, the main causes of death were infection (34.6%) or atherosclerotic disease (21.5%), neither of which would require biologic treatment. Likewise, when looking at cause of death by disease duration it appears that the highest number of patients (37%) die from SLE in the first 5 years, with this rate dropping to <16% beyond 5 years.

Disease Activity
Professor Urowitz presented the adjusted mean SLEDAI (AMS), showing average disease activity overtime. The results again showed that patients in the 1970s had worst disease activity, with figures improving significantly over the next 40 years. The need for steroid use also decreased over the same time period.

### Follow-up (Calendar) Period

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Remission
A follow-up study of inception patients (n=222) over >10 years, with visits <18 months apart, found that patients followed one of three courses:
(1) Monophasics (M): 11.6% of patients achieved clinical remission (clinical SLEDAI-2K=0) within the first 5 years and sustained for ≥10 years.

(2) Relapsing-remitting (RR): 77.6% of patients had ≥2 remission periods (period=2 consecutive visits of clinical SLEDAI-2K=0) and

(3) Persistently active (PA): 10.8% of patients had no remission.

Therefore, M and RR spend the majority of their time in disease remission.

Professor Urowitz continued to highlight that a majority of patients also experience a dramatic decreased in major comorbidities. In the 1970s 16% of patients presented with atherosclerotic vascular disease (AVE) in their first 8–9 years of disease, decreasing to 6–7% in recent decades; however, overtime these patients continue to develop AVE, thus AVE still represents a major comorbidity today, in the biologic era. The SLICC-Registry for AVE in SLE, revealed low levels of AVE (4.5–4.5%) in recent years, a surprising result given 8–13% was expected. The lower prevalence, in recent years, was the result of better control of AVE risk factors in recent years compared to the 1970s. In addition, there is better early control of disease today than in the 1970s, irrespective of biologics. Thus, the combination or more patients being treated for classic CV risk factors, better control of these risk factors and better early control of lupus disease activity have resulted in the four-fold reduction in AVE we see today.

David Isenberg (UK): Rebuttal

Professor Isenberg began his rebuttal with a grim reminder that patients with lupus are more likely to die from lupus and experience more morbidity than others. This is illustrated by the UCL cohort, in which 15% of patients died over a 20-year period, with the main causes of death being infection, AVE, cancer and active disease—the mean age of death being 47 years. Clearly there is a need to progress to better treatment. Professor Isenberg looked at some recent trials of new treatments for SLE. The TULIP-2 of anifrolumab found BICLA responses in IFN gene signature (IFNGS)-high patients to be about twice that in IFNGS patients.\(^{15}\) Also, a greater number patients taking anifrolumab achieved sustained steroid reduction compared with placebo. The renal cohort at UCL has also shown that there was no improvement in outcomes prior to the use of biologics. Recently, patients treated with rituximab have achieved superior and sustained BILAG response to treatment at 3 and 6 months, along with reductions in steroid use.\(^{30}\) Rituximab has also been proven effective in membranous nephritis, with greater time to treatment failure compared with cyclosporine.\(^{31}\) Furthermore, even though some patients develop allergic responses to rituximab, other fully humanised anti-CD20 like obinutuzumab have offered promising results in Phase 2 trials.

Concluding, Professor Isenberg that there few, if any, Eureka moments to be had with conventional immunosuppression and there is a need for new therapy. Instead, there are, and there will be, more such moments with biologics as we increase our capacity in the individual patient to provide the precision medicine approach that we are all seeking.
Murray Urowitz (Canada): Rebuttal
Professor Urowitz began his rebuttal with some lessons from drug trials, quantifying response to placebo (not other drugs) for different trial endpoints. Presenting details of a systematic review of 403 abstracts and 51 articles, 12 of which were included in the analysis, Professor Urowitz highlighted the analysis included 7940 patients, of whom 2631 were treated with placebo plus standard of care (SOC) (ie. steroids, hydroxychloroquine [HCQ], AZA, methotrexate [MTX] or mycophenolate mofetil [MMF]). Of these patients one third responded to treatment with placebo + SOC. Moreover, these patients were able to reduce steroid intake to <7.5 mg/day, saw normalisation of anti-dsDNA antibodies and complement (C3 & C4). Professor Urowitz also highlighted that key trials of lupus biologics (BLISS-52/76 and TULIP 1/2) had many sites with few participants eligible for biologic treatment, bringing into question the demand for biologic therapy. Moreover, given SOC has shown to improve survival, SMRs, disease activity score (DAS), remission and co-morbidities, Professor Urowitz questioned how great the need for biologic therapy actually is.

A final poll of the audience saw the 50:50 split on these arguments, a draw at the end of the debate.
Plenary I: New Aspects in the Management of SLE

Measuring SLE disease activity in 2020: Perspectives from clinical research: Luís Inês (Portugal)

Professor Ines’ presentation focused on measuring lupus disease activity with current perspectives from clinical research case studies.

Professor Ines began his presentation by highlighting the current challenges when trying to measure lupus disease activity, including the wide variety of lupus manifestations across many organs, the variability in severity of these manifestations and subjectivity of scoring damage and comorbidities.

Physician Global Assessment
Beginning with Physician Global Assessment (PGA), Professor Ines highlighted its strengths including its simplicity, ability to measure a combination of disease activity features and sensitivity to change. He also noted several weaknesses such as non-standardised scoring, interrater reliability is dependent on physician training, that it has limited reproducibility and does not capture details of specific organ manifestations. PGA is currently a component included in definitions of treat-to-target (T2T) DORIS remission (with SLEDAI) and lupus low disease activity (LLDAS) with SLEDAI. PGA is also used in responder composite indicines (SRI and BICLA) used as a primary outcomes measure in RCTs.

British Isles Lupus Assessment Group
BILAG strengths include its ability to show disease activity in individual systems, as well as being a comprehensive measure of most disease activity features, grading severity for single manifestations and showing change in disease state from previous assessments. Weaknesses of BILAG include its time-consuming assessment, complicated scoring and need for computer software, limitation to highest scoring feature within an organ system and impractical utilisation in a clinical setting.

SLEDAI-2K
SLEDAI-2k is a very quick and user-friendly scoring tool and is widely used in clinical practice. However, it is dichotomous in nature and does not assess severity of manifestations, weighting of several items is not appropriate, there is low sensitivity for improvement, and worsening and severe manifestations are not included.

Addressing the Unmet Needs
The lack of a user-friendly, sensitive to change, and accurate tool to measure lupus disease activity, is a major unmet need in several settings including: As outcome measure for clinical trials; To guide management of individual patients in clinical practice; Moreover, a primary
outcome measure in RCT should be practical for assessment of patients in clinical practice.  

43, 44

Addressing these unmet needs, included the development of SLE-DAS, which was derived from a real patient cohort with multivariate linear regression, and PGA as dependent variable. SLEDAS includes severe disease activity features absent in SLEDAI, its development was externally validated, with a high correlation with SLEDAI-2K and PGA and higher performance than SLEDAI to predict damage accrual.  

40 Continuous monitoring of SLEDAS has shown that it is very responsive to changes in leucocyte count, thrombocytopenia, swollen joints and complement as compared with SLEDAI, which only scores absence and presence of these factors, rather than severity. Therefore, SLEDAS is highly sensitive to change for lupus disease activity, highlighting both clinical improvement and worsening in patients with lupus.

Professor Ines concluded by highlighting the strengths of SLEDAS in that it is user friendly, freely available online, and offers improved accuracy, including weighting of manifestations, continuous severity scoring, severe features absent in SLEDAI, exclusion of items with low specificity and its high discriminative power to detect clinically meaningful changes in disease severity. SLEDAS is undergoing continuous validation for both remission and disease activity. Professor Ines shared case-based examples measuring disease activity in clinical practice in 2020 using these tools.

Lifestyle for lupus patients: Exercise, diet, and well-being: Perspectives from clinical practice: Chiara Tani (Italy)

Professor Tani’s presentation reviewed the link between lifestyle, disease onset and disease expression in lupus as well as the optimisation of lifestyle and non-pharmacological interventions in the clinical management of lupus.

Multiple environmental, genetic and epigenetic factors have been implicated in the course of SLE pathogenesis.  

45 Professor Tani highlighted that the development of SLE is a multi-step process comprising: (1) Preclinical (Disease Onset Trigger), (2) Clinical (Disease Activity and Damage Accrual) and (3) Comorbidities.
Disease Onset Trigger
Environmental triggers of SLE disease onset include chemical, physical and biologic agents,\textsuperscript{46-49} much evidence coming from silica and tobacco use, and infection, namely Epstein-Barr virus. A metanalysis found an increased risk of lupus among former and current smokers compared with those who had never smoked.\textsuperscript{47} Ultraviolet light has also been studied as a trigger of lupus, with phototesting with UVB and long-wave UVA irradiation being shown to cause characteristic skin lesions clinically and histologically resembling lupus. A potentially crucial mechanism in the initiation of the autoimmune cascade has been attributed to UV-induced keratinocyte apoptosis and nuclear antigens redistributions to the cells surface.\textsuperscript{50-53}

Disease Activity and Damage Accrual
There is an association between tobacco consumption with overall disease activity. Moreover, higher intensity and longer duration of smoking are associated with a higher risk of discoid rash, photosensitivity and an overall SLE activity for every year of smoking. There is also an association between being an active smoker and skin damage, and also causes a reduction of therapeutic effectiveness of hydroxychloroquine in cutaneous lesions and belimumab in systemic manifestations.\textsuperscript{54 55-57}

Although there have been concerns of an association between exercise and lupus disease activity, exercise is proven to be safe and well tolerated in the vast majority of patients with SLE.\textsuperscript{58} Conversely, exercise has actually been shown to have a beneficial effect on SLE, resulting in reduced fatigue, depression, anxiety and pain, with improved sleep and health-related quality of life (HRQoL).\textsuperscript{54} Moreover, aerobic exercise programs are safe and effective in improving aerobic and functional capacity, in addition to tolerance to exercise. Physical activity also contributes to body weight and waist circumference reduction, and improvements in maximum oxygen consumption, endothelial function and insulin sensitivity.
Diet is also an important lifestyle intervention. Omega-3 has been found to have beneficial anti-inflammatory properties.\textsuperscript{59, 60} Dietary patterns low in omega-3 and high in carbohydrates have correlated with disease activity, adverse serum lipids, and the presence of subclinical atherosclerosis. Conversely, a Mediterranean diet has been associated with lower disease activity and damage accrual in observational studies.\textsuperscript{61-64} In addition, the Michigan Lupus Epidemiology and Surveillance Program found lower ratios of n-6 (pro-inflammatory) to n-3 (anti-inflammatory) fatty acids and higher levels of n-3 fatty acid intake are favourably associated with improved self-reported lupus disease activity and sleep quality, with depression, fibromyalgia, pain, and HRQoL not statistically associated.\textsuperscript{65} Preclinical data show effectiveness of dietary intervention with Omega-3, Vitamin D and Curcumin supplementation, however there are few controlled trials on dietary intervention in SLE. One study showed low glycaemic index diet and low calories diets are safe, well tolerated and effective in weight loss and in improving fatigue.\textsuperscript{66} Several studies on Omega 3 and Vitamin D have, however, provided inconsistent results.

**Comorbidities**
About 28–35\% of SLE patients are overweight and about 27–38\% are obese. These patients have increased gene and protein expression of several pro-inflammatory molecules (i.e. cytokines IL-23 and TNF-\alpha). Obesity has been shown to be an independent predictor of lupus disease activity and severity (particularly LN), organ damage, worse patient reported outcomes (PRO), depression, pain and fatigue.\textsuperscript{67-69} 

**Tips for Healthy Lifestyle for Patients with SLE**
Patients with SLE should follow a Mediterranean diet and one with a low glycaemic index. They should avoid high protein intake, particularly if they have LN, and stay active with supervised exercise. Patients should also avoid tobacco and alcohol, use sun protection and cardiovascular disease (CVD) prevention strategies should be recommended for all patients with stable SLE. Patients should be educated and empowered to achieve these goals.

Cardiovascular disease prevention is important and should include the following:

**Initial Consultation**
- Assessment of CV risk factors, lifestyle habits (diet and exercise), aPL-profile, and medications
- Education, including detailed discussion of risk factors as well as CVD and thrombosis prevention strategies
- Tailored lifestyle recommendations and a written summary report
- Referral to a registered dietitian as needed based on pre-set criteria or smoking cessation programmes

**Follow-up Consultations**
• CVD risk factor re-assessment and questions about diet/exercise habits were repeated every 3–6 months
• Continued education by trained personnel
• Newsletters, pamphlets, and brochures about CVD risk factors and prevention strategies

A survey revealed only 22% of patients are aware of their SLE-associated CVD risk. The 3-year CVD prevention counselling program that was offered as part of standard lupus care demonstrated that selected CVD risk factors can be modified with continuous counselling in lupus patients.70

Professor Tani concluded her talk by reiterating, SLE is a chronic condition with a significant impact on physical and mental health, all potential interventions to improve quality of life are relevant for SLE patients. Among the possible non-pharmacological interventions, exercise and diet have a pivotal role. Alongside clinical advantages, evidence-based activities promoting healthy lifestyles could contribute both to patient empowerment in disease self-management and to the sustainability of public health services.

**Microangiopathy in SLE: A diagnostic and therapeutic challenge: Ricard Cervera (Spain)**

Professor Cervera’s presentation set out to highlight the main challenges in the differential diagnosis of microangiopathy in SLE, describe treatment options and discuss research into new markers for microangiopathy in SLE.

The challenge of microangiopathy in SLE widely encountered in clinical practice, particularly those patients with the most severe forms of lupus in intensive care units. The differential diagnosis must consider several other complex manifestations, including CAPS, HIT, HELLP, TTP and DIC.

**Differential Diagnosis**

Perhaps most frequently reported and importantly is CAPS,71 in which no large vessel occlusions are manifested represent approximately 70% of cases and presents as a microangiopathic storm. Yet it is not easy to diagnose because the aPL markers are not clear or constant in these patients. Occasionally, aPL may not be detected during CAPS because of consumption at the thrombi and lupus anticoagulant is difficult to assess during anticoagulation. Moreover, most patients in ICU are on heparin and thus heparin induced thrombocytopenia (HIT) must be ruled out before a CAPS diagnosis is made.72, 73

Similarly HELLP, an endothelium-based disease, predominantly affects small vessels in hepatic circulation, and has been traditionally included in the differential diagnosis of CAPS. However, in pregnancy clinical signs of CAPS are similar to HELLP with 50% of patients presenting clinical characteristics.74, 75
Thrombotic thrombocytopenic purpura (TTP) was first described by Douglas Symmers in 1952 to describe a “unique histological picture of widely disseminated thrombosis of the smallest-caliber blood vessels with endothelial hyperplasia, dilatation of many affected vessels and no inflammation reaction.” Registry data from the Oklahoma Registry show that 40% and 28% of patients present with IgG and IGM anticardiolipin antibodies, respectively. Thus, many patients with TTP also present with APS. Another condition to consider in differential diagnosis is disseminated intravascular coagulation (DIC), the first case which was identified in 1965 and occurred alongside CAPS. In addition, like the aforementioned conditions, it is important to note that sepsis can also appear alongside other haemostatic abnormalities and can indeed also be the trigger for these conditions as shown by Booth et al 2011, where 7% of microangiopathy cases were caused by sepsis.

Treatment
According to the CAPS registry 2001, the majority of patients with CAPS are treated with anticoagulation (IV heparin followed by coumadin) (84%), IV steroids (80%) CYC (35%), plasma exchange (20%) and IV gammaglobulin (19%). Of the patients who received treatment (50%) 65% had received plasma exchange, 63% anticoagulants, 54% steroids, 50% IV gammaglobulin, 41% CYC and 70% combination treatment. Given this, a triple therapy regimen with plasma exchange, steroids and anticoagulation was created, not just for CAPS but for other microangiopathic conditions.

In 2007, eculizumab, a humanized monoclonal antibody that binds to the C5 component of complement and inhibit terminal complement activation was approved for paroxysmal nocturnal hemoglobinuria (PNH) and in 2011 for atypical hemolytic uremic syndrome (aHUS). Although the trial for CAPS was discontinued eculizumab is used for different types of microangiopathy. However, better markers for microangiopathy are needed. In the past 10 years markers like ferritin have appeared in certain microangiopathic conditions, with high levels been identified in patients with CAPS. Recently, we learned that one of the most serious complications of Covid-19 is microangiopathy, haemostatic activation and complement activation.

Professor Cervera concluded by highlighting that thrombotic microangiopathy is a syndrome that comprises several disorders, including CAPS, TTP, HUS, DIC, HIT, HELLP, and even COVID-19. Its differential diagnosis can be very difficult in real world and a comprehensive diagnostic work-up should be carried out. Treatment usually includes antithrombotic therapies, plasma exchange and immunoglobulins as well as new anticomplement biologic therapies. Finally, he noted, new markers for microangiopathy in SLE/APS are still pending.
Plenary II: Novel Therapeutic Developments in 2020

Plasma-cell directed therapies: Reinhard Voll (Germany)

Professor Voll’s presentation highlighted the potential importance of plasma cells as a potential treatment target in SLE.

Professor Voll began his presentation by highlighting the importance of autoantibody mediated mechanisms in the pathogenesis of SLE. With cytotoxic antibodies in autoimmune hemolytic anemia, immunocomplex formation, antibody depositions with organs and complement activation in LN and vasculitis, and the involvement of function modulating antibodies causing antiphospholipid antibodies and antibodies to clotting factors.

Professor Voll noted that refractory disease courses are often associated with high autoantibody titres against dsDNA and/or other autoantibodies in spite of treatment and asked why autoantibody titres are sometimes resistant to treatment? This is largely due to plasma cells.

Until 1997, immunologists believed plasma cells were all short-lived and constantly replenished by B-cells; however in 1997 Manz et al revealed that some are long-lived, offering life-long protection from infection. But if these plasma cells produce pathogenic autoantibodies, antibody-mediated disease can take hold and treatment with MTX, AZA, CYC, steroids and even rituximab are ineffective against long-lived plasma cells, which don’t present a CD20 antigen and are therefore resistant to rituximab.

Treatment: Targeting the Plasma Cell

Today there are more options to target plasma cells, including autologous high-dose chemotherapy + ATG, TACI-Ig, daratumumab and proteasome inhibitors. Treatment with high-dose chemotherapy + ATG gives a good chance for drug free remission, often all autoantibodies disappear (but also protective antibodies); however, there is treatment-related mortality, especially in patients who have acquired substantial organ damage. Those who survive the procedure have a low risk of relapse. BAFF and APRIL Neutralisation with atacicept has shown promise in patients with moderate to severe SLE and may also decrease the flare rate; however, in patients with MS flare rate increased.

Anti-CD38 with daratumumab has been shown to reduce autoantibody levels in patients with multiple myeloma.

Proteasome Inhibition and Lupus

Professor Voll then introduced the targeting of plasma cells with proteasome inhibitors, which may offer more hope for patients with SLE. Plasma cells produce up to 10,000 antibody molecules per cell per second, about 30% of which are unfolded proteins which need degrading by the proteosome pathway. This unfolded protein response is a critical regulator of plasma cell survival and inhibition of the proteosome is key to regulating plasma cell survival. Bortezomib is currently approved for the treatment of multiple myeloma and mantle cell lymphoma. It specifically, reversibly and potently inhibits the chymotrypsin-like activity of the 26S proteasome and, thereby, inhibits the degradation of...
misfolded, defective, supernumerous, and regulatory proteins. It blocks IκB degradation and consequently, NF-κB activation and is cytotoxic to a variety of cancer types in vitro and in vivo. Importantly, inhibition of the proteosome pathway leads to plasma cell apoptosis.

Proteosome inhibition with bortezomib has been shown to eliminate normal plasma cells in mice with lupus with short and long-term treatment,\(^8\) with all mice surviving over one year. Bortezomib has also shown therapeutic efficacy in patients with lupus.\(^8\) Refractory SLE patients were shown to have an immediate and sustained response to treatment with bortezomib, with an 80% decrease in anti-dsDNA antibodies, sometimes to normal levels, whereas vaccine antibodies remained stable.\(^8\) This was likely due to plasma cells having a high IgG rate, almost five times greater than bone marrow and spleen antibodies, which means lupus antibodies are hypersensitive to proteasome inhibition.

In conclusion, Professor Voll summarised that proteasome inhibitors, atacicept and anti-CD38 can eliminate plasma cells and that plasma cells residing within inflamed tissues appear to be hypersensitive towards proteasome inhibition. Marginal zone B cell-derived plasma cells are resistant to proteasome inhibition. Plasma cells differ dramatically in their sensitivity to plasma cell-targeted therapies, yet the mechanisms for this remain unclear. Proteasome inhibition may represent a new treatment strategy for antibody-mediated diseases such as SLE, with clinical trials of treatments ongoing.

**Blocking IL-12 and IL-23: A New Strategy in SLE: Bevra Hahn (USA)**

Professor Hahn's presentation briefly introduced the basic science providing the foundation for clinical studies for IL-12 and IL-23 therapies for SLE.

Professor Hahn began her presentation by highlighting some of the pro-inflammatory biology behind IL-12 and IL-23. These cytokines are made by antigen presenting cells and combine to activate receptors on T cells.\(^8\) Naïve T cells can be driven by interleukin (IL)-12 to Th1 subsets (which secrete interferon gamma [IFNγ]) and activate macrophages, and by IL-23 to expand and maintain Th17 subsets (which secrete IL-17A and F and induce chemotaxis). IFNγ-secreting cells and IL-17-secreting cells are found in skin and kidney tissue in patients with active SLE, although not as prominently as cells secreting type 1 IFNs. IL-12 and IL-23 are heterodimers and share p40, a common unit that binds to the receptor for each cytokine. Ustekinumab is a humanised monoclonal antibody, administered subcutaneously, that binds p40 and thus reduces cell activation by IL-12 and IL-23 and has shown efficacy in other diseases. In a Phase 2 study of lupus, ustekinumab was shown to block the effects of IL-12/23 and produce an SRI-4 response, with no flares, at 24 weeks similar to that seen in the trials of belimumab.\(^17\) In the responders to there appeared to be a more prominent IL-12 effect than IL-24 effect. However, the Phase 3 trial of ustekinumab did not yield similar results and was stopped.
Professor Hahn presentation went on to outline the theory behind IL-12/23 inhibition, other diseases in which it works and cytokines that are present in target tissue. In theory, blocking IL-12 and 23 should reduce autoantibody production of B-cells driven by Th1 and inflammation driven by natural killer cells and TH17. The inhibitors of the IL12/23 and IL-17 pathways work in several other rheumatic diseases and are FDA-approved.

<table>
<thead>
<tr>
<th>Target</th>
<th>Anti-p40 IL12/23</th>
<th>Anti IL-23p19</th>
<th>Anti-IL-17A</th>
<th>Anti-IL17RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease</td>
<td>Ustekinumab</td>
<td>Tildrakizumab</td>
<td>Guselkumab</td>
<td>Risankizumab</td>
</tr>
<tr>
<td>PsO</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>PsA</td>
<td>x</td>
<td></td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>CD</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AS</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>RA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lupus</td>
<td>In Clinical Trials until 2020</td>
<td>In Clinical Trials</td>
<td>In Clinical Trials</td>
<td>In Clinical Trials</td>
</tr>
</tbody>
</table>

PsO, psoriasis; PsA, psoriatic arthritis; CD, Crohn’s disease; AS, ankylosing spondylitis; RA, rheumatoid arthritis.

Inhibition of IL-12/23, IL-23 and IL-17 has proven to be effective in psoriasis and psoriatic arthritis, resulting in impressive improvements in PASI-75 scores compared with placebo and etanercept. IL-12 is present in LN lesions, more so in Class IV and V nephritis, providing a strong rationale for its inhibition in patients with renal disease. Biopsies have also shown that IL-23 is also prolific in the infiltrate in biopsies taken from patients with LN. Professor Hahn introduced the inhibition JaK/STAT downstream of cytokines IL-12 and 23. JaK inhibition has proven effective for the treatment of other immune-mediated inflammatory diseases. Recently JaK inhibition was shown to reduce arthritis flares, tender joint count (TJC) and swollen joint count (SJC) in a Phase 2 trial of patients with SLE.

Summarising, Professor Hahn highlighted that IL-12, IL-23 (maybe IL-17) are promising targets for new therapies for SLE and that these cytokines are critical for development/function/survival of Th1 and Th17 cells, which drive autoantibodies and tissue inflammation – and natural killer and cytotoxic T cells. She noted that ustekinumab, which suppresses both IL-12 and IL-23 binding to some receptors, was effective in a Phase II trial in...
SLE but Phase III trial has been stopped, noting the mechanism may have been via IL-12, Th1 and IFNγ. Finally, inhibition of IL12/23/17 axis is now being studied in clinical trials with JαK inhibitors baricitinib (Phase 3 with 1,100 patients planned), upadacitinib (Phase 2) and tofacitinib (DLE, Phase 1).

**Novel intracellular pathways: Thomas Dörner (Germany)**

Professor Dörner’s presentation reviewed the novel intercellular pathways in SLE, discussing the potential for novel therapeutic targets as well as explaining the significance of JαK and Bruton’s Kinase BTK pathways and current treatments in development for SLE.

Professor Dörner began his presentation by highlighting the key cytokines in the pathogenesis of SLE across two groups, including JαK/STAT inhibition and the second group including cytokines that are independent of JαK/STAT. By inhibiting JαK/STAT it may be that the activity of associated subset of cytokines in the same group can be blocked (ie. IL-6,7,10,12,15,21 and 23). This multitargeting therapeutic strategy has already been used in patients with RA. Most JαK inhibitors in clinical development are in Phase 2.

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Type: JαKI or JαK3 inhibitor</th>
<th>Sponsor</th>
<th>Phase</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tofacitinib</td>
<td>Selective JαKI and JαK3 inhibitor</td>
<td>Tufts Medical Center Pfizer</td>
<td>I/II</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Baricitinib</td>
<td>Selective JαKI and JαK2 inhibitor</td>
<td>Eli Lilly and Company</td>
<td>III</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Filgotinib</td>
<td>Highly selective JαKI inhibitor</td>
<td>Gilead Sciences</td>
<td>II</td>
<td>Recruiting vs. GS-9876 in NCT03134222</td>
</tr>
<tr>
<td>BMS-986165</td>
<td>TYk2 inhibitor</td>
<td>Bristol Myers Squibb</td>
<td>II</td>
<td>Recruiting</td>
</tr>
<tr>
<td>GSK2586184</td>
<td>Janus kinase 1 (JαK1) inhibitor</td>
<td>GlaxoSmithKline</td>
<td>II</td>
<td>Terminated</td>
</tr>
<tr>
<td>Solcitinib (Solco)</td>
<td>JaK-1 inhibitor/BTK</td>
<td>AbbVie</td>
<td>II</td>
<td>Recruiting NCT03978520</td>
</tr>
</tbody>
</table>

Further downstream from JAK is increased STAT1, which is proven to be characteristic in SLE lymphocytes and correlates with SLE disease activity (SLEDAI). Further evidence for JAK/STAT involvement in lupus comes from a Bayesian gene network by Li et al in 2019. Clinical trials of JαKs in patients with SLE first assessed the JαK 1 inhibitor, solcitinib, which was terminated due to lack of efficacy, and tofacitinib, which although well tolerated it was not powered for efficacy. Baricitinib was the first molecule to be studied in a 24 week Phase 2 trial of SLE. The study found that that baricitinib 4 mg resulted in significant improvements in arthritis or rash as compared with placebo and safety in line with that already seen in studies in RA patients.
Baricitinib’s mechanism of action is highlighted by the changes in gene expression it induces through inhibition of multiple immune pathways,\textsuperscript{102} including down-regulation of STAT1 and STAT2, and reduction in IFN signature particularly with the 4 mg baricitinib dose. However, this reduction in IFN expression did not correlate with the clinical response in SLEDAI-2K or SRI-4 at Weeks 12 or 24. Unlike IFN, however, changes in STAT-related genes did correlate with clinical improvement measured using SLEDAI-2K. These data are awaiting further validation in Phase 3 trials. Baricitinib 4mg also correlated well with reduction in IL-12/23p40 and IL-6 at Week 12 compared with baseline.\textsuperscript{103}

Switching focus to BTK inhibition, Professor Dörner highlighted these kinases are involved in T-cell/macrophage pathways as well as B cell pathways. Several BTK inhibitors are in Phase 1/2 development. These can be divided into covalently binding and not covalently binding approaches, a topic of much debate.

<table>
<thead>
<tr>
<th>Evobrutinib (M2951)</th>
<th>Brutons tyrosine kinase inhibitor (BTKi)</th>
<th>EMD Merck Serono</th>
<th>Phase II</th>
<th>Recruiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenebrutinib (GDC-0853)</td>
<td>BTKi</td>
<td>Genentech</td>
<td>Phase II</td>
<td>Active, not recruiting</td>
</tr>
<tr>
<td>LOU064</td>
<td>BTKi</td>
<td>Novartis</td>
<td>Phase I</td>
<td>Active</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>BTKi</td>
<td>J&amp;J/Abbvie</td>
<td></td>
<td>Approved for CLL and mantle cell lymphoma</td>
</tr>
<tr>
<td>Acalbrutinib</td>
<td>BTKi</td>
<td>Acerta/Astra Zeneca</td>
<td></td>
<td>Approved for mantle cell lymphoma</td>
</tr>
<tr>
<td>Tirabrutinib</td>
<td>BTKi</td>
<td>Ono/Gilead</td>
<td></td>
<td>CLL and Sjögren’s early stage</td>
</tr>
<tr>
<td>Poseltinib (LY3337641)</td>
<td>BTKi</td>
<td>Hanmi/Eli Lilly</td>
<td>Phase I</td>
<td>Phase I completed</td>
</tr>
<tr>
<td>BMS-986142</td>
<td>BTKi</td>
<td>BMS</td>
<td>Phase II</td>
<td>In RA and Sjögren’s</td>
</tr>
</tbody>
</table>

Upon BCR stimulation there is a reduced Syk and BTK tyrosine phosphorylation autoimmunity: anergic/post-activated (APA) B cells. Therefore, anergic post-activated B-cells had enhanced CD22 expression but decreased CD21 and CD19 expression and intracellularly there was reduced BTK, SyK, PLC-g2 and increased STAT, PD-1/L1, SHP2, PTPN22 and PTEN activity.\textsuperscript{104} Given this there is a possibility to reach beyond B cells and block BTK in macrophages. A Phase 2 study of the BTK inhibitor fenebrutinib in moderate-to-severe SLE...
found no significant difference between high or low dose fenebrutinib or placebo during the 48-week study.\textsuperscript{105}

In conclusion, Professor Dörner reiterated that targeting intracellular pathways in SLE holds promise to address unmet needs by inhibiting various cell types in this heterogeneous entity according to multitarget treatment principles. Indeed, a number of JaK inhibitors are in clinical development for SLE. Baricitinib (JaK1/2) achieved the primary endpoint in a Phase 2 study with known safety profile. Mechanistically, a statistically significant reduction in a series of genes downstream from STAT1, STAT2, and STAT4 and reduced IL-6, p40IL-12/23 expression correlated with lupus activity under baricitinib. In addition, various BTK inhibitors are promising by targeting monocyte, basophil and B cell activities: A first Phase 2 study of fenebrutinib, however, did not achieve the primary endpoint, so it will be of interest whether other BTK-inhibitors in development can overcome the recently identified status of APA B cells.

**Molecules in early development: Richard Furie (USA)**

Professor Furie presentation reviewed the strategies for IFN inhibition as well as targeting B and T cells and reviewing approaches to downregulate proinflammatory cytokines. There are several molecules in early development, which carry hope for the future management of SLE.

Professor Furie began his presentation by defining the word Eclectic: “*Denoting or belonging to a class of ancient philosophers who did not belong to or found any recognized school of thought but selected doctrines from various schools of thought*” or applied to the case of lupus “*Denoting or belonging to a class of persevering drug developers who did not belong to or found any recognized SLE pathogenetic mechanisms but selected drug targets from various immune system elements.*” The pathogenesis of lupus begins with a basic understanding of the innate and adaptive immune system, the environment and the interplay between. Several immune targets have been identified and targeted in Phase 1/2 studies including the interferons, B-cells, T cells and cytokines.

**Inhibiting Interferons**

Patients with SLE have elevated IFN\(\alpha\) levels and sera induce IFN gene signatures (GS) in normal peripheral blood mononuclear cells. About 60–75\% of SLE patient are IFNGS+ and clinical and serologic activity correlate with IFN gene expression. Therefore, a key question is can IFN inhibitors reduce SLE clinical activity? There are several direct and indirect ways of targeting interferons. Focusing on the plasma dendritic cells, Professor Furie highlighted the different ways of targeting this including via IL-3R\(\alpha\), ILT7 and BDCA2. BDCA2 is a uniquely expressed lectin on pDCs, the ligation of which suppresses IFN production in PDC. The anti-BDCA2, BIIBO59, has a dual mechanism of action with the front end binding to BDCA2 and the Fc portion will bind the FC receptor to block immune complexes from activating the pDC, result in FC-dependent and FC-independent inhibition and blocked production of chemokines and cytokines, including IFN1.\textsuperscript{106} Several years ago a small study showed that
the majority of patients with skin lupus who underwent single treatment with anti-BDCA2 had both a clinical and pharmacodynamic response to treatment compared with placebo.\textsuperscript{107}

This molecule then went on to two Phase 2 studies. One of these (LILAC) was a 4-arm study comparing BIIB059 50 mg, 150 mg, 450 mg and placebo over 12 Weeks. Significant improvements (39–48%; \textless 0.001) in CLASI-A score were shown in patients receiving BIIB059. Data are forthcoming from the second study in patients with SLE.\textsuperscript{16}

**B Cell-Directed Therapies**

There are many lupus targets on B cells, most of which have been identified and targeted including CD20 but also intracellular targets. Clinicians still believe in the anti-CD20 therapies, despite several failures. Obinutuzumab is a third generation antibody, approved for CLL in 2013 and with success in a Phase 2 study of LN.\textsuperscript{108} Obinutuzumab is a more potent antibody than rituximab, with a 100-fold greater ADCC effect, greater direct cell death and has been superior to rituximab in H2H trials in B cell malignancies.\textsuperscript{109-113} The Phase 2 Nobility LN study showed obinutuxumab + MMF produced greater completer and overall renal response rates than placebo.\textsuperscript{108} Moreover, patients with sustained B-cell depletion, at Week 76, had better outcomes.\textsuperscript{12}

**Cytokine Directed Therapies**

Low dose IL-2 restores hemostasis by increasing T-regs in patients with SLE. A 40 patient study resulted in a 90% SRI response at Week 12,\textsuperscript{114} however, the study did not have a
control group. In a follow-up study of 60 patients, 55% of patients responded at Week 12 and 65.5% at Week 24. More recent evidence comes from a Phase 1b study Fanton et al supporting the potential role of IL-2 restoration in patients with SLE.

Concluding, Professor Furie noted studies of several molecules that are due to report Phase 2 data soon, including: BIIB059 SLE (LILAC A), iberdomite (CC-220), obinutuzumab LN (Week 104), anifrolumab LN and anti-CD40 (BI 655064). These combined with improved understanding of biomarkers, allowing individualised therapies will translate into better treatment outcomes. Trials of new molecules for lupus have taught us to be humble, logical and perseverant in the development of treatments for patients with lupus. We should be optimistic about the future management of lupus.

Four Hot Topics

Remission and low disease activity: the new targets for treatment: George Bertsias (Greece)

Professor Bertsias’ presentation highlighted the importance of identifying the adverse impact of organ damage accrual in patients with SLE, as well as a full understanding of the definitions of remission and LLDAS and the application of this in clinical practice.

Treat-to-target (T2T) is a concept used in several chronic diseases associated with adverse outcomes, including diabetes, hypertension, COPD and RA. T2T involves treating to achieve specific thresholds, reduction in disease activity, in individual afflicted by these diseases. By achieving these thresholds, long-term prognosis is improved. However, in patients with SLE, the T2T concept is more complex given the heterogeneity and multi-organ nature of the disease, moreover the optimal threshold for disease management has not yet been defined.

Professor Bertsias emphasized the goal of avoiding organ damage accrual as being central to the management of SLE. Irreversible damage is seen in 20–30% of patients within the first 2 years of diagnosis, rising to 50% within 5 to 10 years. As such these patients face increased disease burden, hospital visits and healthcare costs as well as reduced survival.

There are several potential targets when treating to target in SLE, one being disease severity, particularly in major organs, another being persistently active disease, with every unit increase in SLEDAI representing a 15% increased risk for damage. This has also been shown with BILAG, where every unit increase over 12 months results in a 15% increase in death and 8% increase for organ damage. Other important targets for prognosis and damage include SLE disease flare, which doubles the risk of organ damage, as well as steroid use and comorbidities.
In 2014 Ronald van Vollenhoven et al developed the treat to target approach, comprising 11 recommendations, for patients with SLE.\textsuperscript{125}

<table>
<thead>
<tr>
<th>Recommendation topic</th>
<th>Level of evidence (1–5)</th>
<th>Grade of recommendation (A–C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Aim for remission (or lowest possible disease activity)</td>
<td>3 (SLE)/ 1 (LN)</td>
<td>C (SLE)/ A (LN)</td>
</tr>
<tr>
<td>2 Prevent flares</td>
<td>2 (SLE)/ 1 (LN)</td>
<td>B (SLE)/ A (LN)</td>
</tr>
<tr>
<td>3 Don’t treat serology alone</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>4 Prevent damage</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>5 Improve HRQOL</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>6 Treat renal involvement early</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>7 Maintain IST for 3 years (LN)</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>8 Reduce/withdraw GC</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>9 Treat APS same as primary APS</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>10 Use antimalarials</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>11 Treat comorbidities</td>
<td>4, 5</td>
<td>C</td>
</tr>
</tbody>
</table>

Patients with lupus can face a spectrum of disease states, including high, moderate, and low disease activity, and remission—the most desirable state. However, the feasibility of achieving remission in all patients is not known.
LLDAS & DORIS
The Asia-Pacific Lupus Collaboration group developed LLDAS, a definition comprising 5 criteria that were subsequently validated in several studies. The preliminary report of LLDAS, shows that attainment of LLDAS for ≥2 years (or 50% of follow-up time) is linked to reduced organ damage accrual (by ∼50%) and flares (by ∼80%). More recently, the same group reported the prospective validation, highlighting that attainment of LLDAS for at least 50% follow up resulted in significantly reduced rates of flare and organ damage as well as a reduction in healthcare costs.

Another framework for defining remission in SLE is DORIS, which introduces an array of definitions and the concept of “off therapy” remission and “on therapy” remission. This group found that achievement of remission, notably clinical remission, is protective against organ damage; it found that remission for at least 2 years is needed for a significant reduction in organ damage. Moreover, this protection against organ damage was associated with improved patient reported outcomes.

Professor Bertsias summarised some differences between LLDAS and remission:

- Despite variability in reported rates, LLDAS is a more frequent outcome in ‘real-life’ SLE cohorts as compared to remission (e.g, lasting ≥1 year, 46.2–87.2% versus CROT 13.2–69.2%)
- There is a more stringent definition for remission = lower frequency (ie, 5-year complete remission off-treatment in <1%)
- LLDAS requires longer attainment than remission to induce favourable outcomes (e.g. ≥50% versus <25% with remission)
- About 40–80% of LLDAS cases overlap with remission, yet LLDAS/no-remission seems to be also protective against organ damage
- Predictive factors are similar for LLDAS and remission: disease duration, ethnicity (AA: less frequent/longer time to attain), baseline activity (especially renal) and serology and baseline organ damage
- In the context of clinical trials, LLDAS rates are higher than the DORIS definitions of remission; LLDAS has good discriminatory ability (active drugs versus placebo)
- There is still a need to fine tune the LLDAS definition of remission.

In conclusion, attainment of low disease activity or inactivity states is linked to favourable long-term outcomes, particularly lower flares and organ damage accrual. LLDAS and clinical remission on-treatment (DORIS) definitions represent two validated, feasible treatment endpoints in routine clinical care. Clinical SLEDAI-2K=0 is the criterion with the highest predictive value and yields increased rates of attainment. Still, further validation of these definitions across various clinical settings is needed. Importantly, implementing the aforementioned targets (LLDAS, remission) in the treatment/T2T strategy is yet to be demonstrated.
Belimumab helps lupus patients to achieve lupus targets: Andrea Doria (Italy)

Professor Doria reviewed the role of early treatment with belimumab in helping patients achieve remission or LDA, in line with current definitions of remission.

New therapeutic strategies in SLE pivot around the T2T principle, with the first target being achieving clinical remission or, in the absence of this, the lowest achievable level of disease activity. Professor Doria noted remission and low-disease activity are achievable in SLE today, however, maintaining remission and LDA remain difficult, with relapse being a common occurrence. There is, although, an inverse correlation between duration of remission and damage accrual.

Can belimumab be helpful in attaining remission or LDA in SLE? Presenting data from a post-hoc analysis of the BLISS-52 and 76 trials, Professor Doria highlighted the greater difference seen between belimumab 10 mg/kg and placebo in patients with higher disease activity at baseline (both studies), high anti-dsDNA antibody level ≥30 IU/mL (both studies), low C3 (<90 mg/dL) and/or C4 (<16 mg/dL) (both studies), SLEDAI-2K score ≥10 (BLISS-52 study only) and prednisolone dose ≥7.5 mg/day (BLISS-52 only). Moreover, patients with SLEDAI-2K score <10 and SDI=0 at baseline were more likely to attain LLDAS at Week 52. Similar results were seen in a study by Parodis et al, with authors stating that clinical SLEDAI-2K zero may be a pragmatic outcome measure in SLE studies. In an Italian multicenter study of 646 patients, cSLEDAI=0 had the best performance in predicting damage accrual compared with other definitions of remission over a 2-year period. Turning to clinical practice, Professor Doria demonstrated that the proportion of patients who can achieve a stable LLDAS and remission was higher than that obtained in randomised controlled trials, as shown in two recent studies. Sbeih et al demonstrated that it is easier to achieve a stable SRI4, LLDAS or remission at Month 12 in 81.7%, 58.1% and 37.1% of patients taking belimumab, respectively. Interestingly, the median times to achieve SRI4, LLDAS and remission were 91, 213 and 270 days, respectively. Similarly, Fanouriakis et al found that LDA, irrespective of serological status at baseline, is associated with reduction in corticosteroid dose and flares in patients taking belimumab. A recent Italian multicentre cohort study (BeRLiSS) of 466 patients receiving belimumab in 24 clinical practice settings, with a median follow-up of 18 months (range 1–60 months), showed that 71.7% of patients achieved LDA, 61.3% SRI-4, and 41.1% remission at 12 months, with these figures being maintained over time. The most important independent predictors of SRI-4 response included baseline SLEDAI2K, SLE duration ≤2 years and a baseline SLICC damage index=0. Independent predictors of remission and LDA included baseline SLEDAI-2K <10, baseline SLICC damage index=0 and prednisone intake ≤7.5 mg, and negative predictors of remission and LDA were number of flares in the 3 years before belimumab treatment initiation and baseline renal involvement. Professor Doria noted that patients spending at least 50% of follow-up in LDA (66%) or at least 25% of follow-up in remission (42.9%) accumulated less damage at the end of the follow-up. In conclusion, this study provided evidence that an earlier use of belimumab in patients with active SLE and low damage can maximise its efficacy in clinical practice.

Professor summarised his presentation highlighting that belimumab increases the probability of achieving remission and LDA in SLE patients. However, the proportion of
patients who can achieve remission and LDA largely depends on the definition used and in any case is higher in clinical practice setting than in RCTs. Finally, the BeRLiSS trial provides novel evidence that an earlier use of belimumab in patients with active SLE and low damage may maximise its efficacy in clinical practice.

**Can we withdraw low-dose prednisone in remitted patients? Zahir Amoura (France)**

Professor Amoura began his presentation with an overview of the minimum requirements for remission in SLE, measured by SLEDAI and achieved with prednisone (0–5mg), HCQ, immunosuppressive and biologics. Once remission is achieved, however, drug de-escalation strategies remain a matter for debate. Glucocorticoids play a central role in SLE management, yet there is general agreement as to the toxicity of high-dose GC and the need to avoid their long-term use. There is a need for GC withdrawal when patients are in remission, but while there is a lack of experimental evidence to justify their long-term use, there is also a lack of evidence to guide physicians in stopping GCs once remission is achieved.

**Existing Evidence**

An internet-based survey of 130 clinicians from 30 countries revealed that prednisone was the first medication to be reduced or withdrawn irrespective of persistent serological abnormalities, remission duration, minor or major organ involvement and whether prednisolone was used with HCQ alone or as part of a regimen also involving HCQ and an immunosuppressant. Furthermore, an Italian study by Tani et al revealed that 23% of the 77 patients who successfully stopped GC had flares in the following 2 years, 72% of which were considered mild. Time period since the last flare was the sole determinant predictor of disease flare identified. An Indian observational study of 148 patients found flares occurred in 21%, 41% of which occurred in the first year following prednisone withdrawal. Independent predictors of flare-free survival included duration of disease and duration of GC treatment before interruption and second immunosuppressive treatment.

**CORICOLUP Trial**

Due to the lack of experimental evidence for use of low-dose GC in patients in remission, the 12-month CORICOLUP RCT was designed to compare maintenance and withdraw of low-dose prednisolone for the prevention of flares. CORICOLUP showed that withdrawal of prednisolone in SLE patients, who had been in remission and with a stable treatment regimen for at least 1 year, was associated in a four-fold increase in the risk of mild/moderate and severe flare, according to the SELENA-SLEDAI (SFI) and BILAG indexes, at Week 52. Other therapy remained unmodified during the study, with 91% and 27% also receiving HCQ and immunosuppressants, respectively. Professor Amoura noted that the treatment was well tolerated with similar composite toxicity index (GTI) scores across.
maintenance and withdrawal groups. However, there are several limitations to this study, with no placebo group, it was a single centre study, patients were kept on prednisolone by their physician despite clinical remission, so there was no way of extrapolating patients in remission. Also, the withdrawal of prednisolone was abrupt and may have facilitated an effect on relapse.

Professor Amoura concluded his presentation stating the CORICOLUP study provides the strongest evidence to date that maintenance of 5 mg prednisone is superior to its withdrawal in order to prevent flares in SLE patients in remission and that maintenance of 5 mg prednisone prevents up to 75% of flares in SLE patients in remission. These results, however, need validation in another independent cohort.

Can we withdraw immunosuppressants in remitted patients? Margherita Zen (Italy)

Immunosuppressants: Long-Term Risks

Professor Zen began her presentation by highlighting that remission is an achievable outcome for patients with SLE, yet it is important to consider the risk of long-term IS use and the risk of IS withdrawal in long-term remission.

There are many side effects associated with the long-term use of CYC, the most common being organ failure and infection. A high number of adverse events is also associated with maintenance therapies, including AZA (42%), MMF (36%) and cyclosporine A (CsA) (32%), with severe infections being particularly common, affecting one in five patients. Furthermore, the oncogenic risk of IS drugs depends on the intensity and length of treatment:

- **CYC** When the cumulative dose exceeds 360 mg/kg
- **AZA** When treatment exceeds 10 years, and the cumulative doses 600 grams
- **MMF** Some studies reported an increased post-transplant risk of lymphoproliferative disease
- **CsA and tacrolimus**, have oncogenic effect related to interference with the immune surveillance. CsA can promote cancer progression by a direct cellular effect related to an increased production of TGFβ

**Immunosuppressant Withdrawal: Extra-renal SLE**

There is a paucity of data available on IS therapy discontinuation in non-renal SLE patients. One RCT of AZA in nine patients showed a high frequency of flare (78%) following withdrawal of AZA. Two retrospective studies of IS and GC found that 23.4% and 6.1% of patients were able to achieve IS and GC remission for at least one and two years, respectively.
A recent study reported that IS were successfully and safely withdrawn in 75% of patients with LN (47%), arthritis (15.7%), haematological abnormalities (5.3%), skin rash (6.3%), neuropsychiatric SLE (1.9%), vasculitis (1.3%), serositis (0.6%), and multi-organ involvement (21.9%). Patients who discontinued therapy due to remission were less likely to have subsequent flares than those patients who discontinued due to poor treatment compliance or tolerance.

The study also showed that HCQ maintenance therapy also reduced the risk of flare, with no significant differences between those treated with HCQ alone or HCQ + steroid, moreover there was no difference in flare between patients on steroids and those who withdrew all treatments. Multivariate logistic regression analysis showed that HCQ following IS withdrawal and duration of remission at IS withdrawal were the two strongest protective factors against flare recurrence. Notably, being on HCQ and in remission for at least two consecutive years reduced the risk of flare by 81% and being on HCQ and in remission for at least three consecutive years by 86%. No significant differences in damage were observed between patients who had discontinued IS compared with those who didn’t.

**Immunosuppressant Withdrawal: LN**

Studies of patients with LN in remission show a variable flare rate, following discontinuation of IS. A study by Moroni et al. found that patients who did not flare after therapy withdrawal had significantly longer treatment duration before withdrawal (98 versus 30 mo. p<0.01) significantly longer duration of remission before withdrawal (52.8 versus 12 mo. p=0.00), with many receiving HCQ (17 versus 2 patients, p=0.004).

Data from the Padua cohort who had glomerulonephritis had discontinued IS, HCQ use following IS discontinuation and duration of remission at IS discontinuation were the main predictors of flare. No significant differences in damage were seen following IS withdrawal. Professor Zen noted the value of repeat kidney biopsies, with many patients in clinical remission having active lesions having higher flare rates than those without lesions. This finding has also been found in another study by Parodis et al, which found repeat biopsy portends relapse.
In conclusion, Professor Zen reiterated that prolonged use of IS is associated with an increased risk of infections and other serious adverse events. Discontinuation of IS is possible in “selected patients” after remission achievement: Who had a prolonged stable remission and/or received HCQ as maintenance therapy after IS withdrawal. In her Padua Lupus Cohort, damage was similar in remitted patients who continued or withdrew immunosuppressants during the follow-up. Finally, in patients with LN, repeat kidney biopsy may help in predicting LN relapse.
Prime Time Session

Optimal assessment and monitoring of SLE patients in clinical practice: Alexandre Voskuyl (Netherlands)

Professor Voskuyl reviewed the approaches for optimal assessment of SLE in clinical practice, with the value of T2T being proven in other diseases and its place in SLE clinical practice being paramount.

Professor Voskuyl began by reminding us of some important facts about SLE, including persistently active disease and flares and their association with increased damage and mortality; damage accrual resulting from both disease and treatments (i.e. steroids); comorbid diseases like CVD, osteoporosis and infection; impact of disease on QoL, productivity and survival. Improving outcomes for patients with SLE, requires early diagnosis and ongoing assessment and monitoring of disease activity, damage and comorbidity.

Recently, several guidelines have published recommendations for the frequency of assessment, use of validated disease activity instruments, systematic assessment use of disease damage indices, and assessment of comorbidities including cardiovascular risk factors and corticosteroid associated adverse events (i.e. osteoporosis). In addition to these recommendations, there are other ways of improving SLE outcomes, including the implementation of timely and effective medical and non-medical treatment, quality control of management, continuing medical education, use of novel therapies and T2T.

Treat to Target

The concept of T2T is relatively simple, it involves Identification of a variable associated with bad disease outcomes, then treating this variable to a target level and adapt therapy if the target is not met after a prespecified period. Diabetes treatment has benefited from a T2T approach, as has both the short and long-term management of RA.

Six years ago, an international taskforce developed the following T2T principles for the management of SLE patients.

1. The management of SLE should be based on shared decisions between the informed patient and her/his physician(s)
2. Treatment of SLE should aim at ensuring long-term survival, preventing organ damage, and optimising health-related quality-of-life, by controlling disease activity and minimising comorbidities and drug toxicity
3. The management of SLE requires an understanding of its many aspects and manifestations, which may have to be targeted in a multidisciplinary manner
4. Patients with SLE need regular long-term monitoring and review and/or adjustment of therapy

Importantly, the taskforce developed 11 recommendations, of which Professor Voskuyl highlighted several:
1. The treatment target of SLE should be remission of systemic symptoms and organ manifestations or, where remission cannot be reached, the lowest possible disease activity, measured by a validated lupus activity index and/or by organ-specific markers.

2. Prevention of flares (especially severe flares) is a realistic target in SLE and should be a therapeutic goal.

3. Since damage predicts subsequent damage and death, prevention of damage accrual should be a major therapeutic goal in SLE.

4. Lupus maintenance treatment should aim for the lowest glucocorticoid dosage needed to control disease, and if possible glucocorticoids should be withdrawn completely.

5. There are many parameters which are important and should be part of T2T in SLE.

6. In lupus nephritis the definition of one target seems simple, however also in these patients’ multiple factors are to consider, like SLE.

There are many parameters (i.e., disease activity, flare, low-steroid dose, prevention of damage and QoL) that are important and should be part of T2T in SLE. In LN the definition of one target (i.e., renal disease) seems simple, however these patients’ have multiple factors that need considering, like in SLE.

Although it is clear that remission is defined by the absence of clinical symptoms, remission can be subclassified into different states of remission. As shown, patient can be in clinical remission independent of serological activity, and/or treatment with low dose steroids and/or treatment with HCQ and/or IS drugs. Complete remission, however is defined by the absence of clinical symptoms, without the use of steroids or antimalarials or immunosuppressants.160

There are similarities and differences in the published definitions of remission, such as being based on the absence of disease activity according to SLEDAI or BILAG or any other validated instrument, in combination with a low Physician Global Assessment (PGA). However, some do question the use of a PGA, with DORIA not stating a minimum requirement for PGA and DORIS setting this requirement at ≤0.5. Future research is needed to better understand this minimum requirement for remission.35,128

Low Lupus Disease Activity State (LLDAS)

Another way of defining a disease state is LLDAS. Disease outcomes in SLE are driven by disease activity over time. Though a continuum, certain domains are recognized. Active disease is measured in clinical research using a variety of instruments, all of which most experts acknowledge have multiple flaws. This is in part due to the intrinsic difficulty in assigning numerical scores to a heterogeneous disease state. In 2005 a definition of remission was proposed, but in the same study it was shown that <2% of patients achieved this state. This definition is too stringent for routine clinical practice or for clinical research.
Low disease activity is a state recognized intuitively by lupus doctors and is likely to occur more frequently than remission, yet it was never quantified with descriptors or validated as an outcome measure or treatment target. LLDAS can be defined as a patient having SLEDAI 2k ≤4 (no major organs), no new activity compared to previous assessment and a PGA ≤1 (scale 0–3). Treatment comprises prednisolone ≤7.5mg. If this is well tolerated standard maintenance doses of IS drugs or approved biological agents should be given.\textsuperscript{34}

Data from Golder et al, showing the percentage of patient visits according to disease state, revealed that complete remission occurs very infrequently, clinical remission on treatment is seen in about 15% of the visits, whereas LLDAS is seen in >50% of the visits.\textsuperscript{161}

Relevance of Remission and LLDAS
Professor Voskuyl highlighted the association of DORIS remission with reduced damage accrual for patients, with prolonged remission on treatment according to DORIS criteria being more attainable than strict remission (off treatment) and was seen in 25–37% of patients.\textsuperscript{34, 126, 133, 160, 162, 163} Several parameters have been found to be associated with attaining remission, including lower disease activity as diagnosis, lower damage index and absence of nephritis. Several studies have demonstrated a clear correlation between prolonged remission and reduced damage accrual.\textsuperscript{128, 129, 133, 164-166}

Similarly, LLDAS has been found in approximately 50% of patient consultations and is associated with a 30-40% reduction in damage accrual and also lower flare rates.\textsuperscript{161} In a separate cohort LLDAS was also associated with reduced mortality.\textsuperscript{163} Comparing remission with LLDAS it appears that remission is a higher proactive effect, although it more difficult to attain, while both states improve QoL. In clinical trials, remission has proven to be attainable as shown in a 24 month study of patients receiving IS plus steroids and/or malarials.\textsuperscript{167} Likewise recent studies have shown it is possible to achieve LLDAS with anifrolumab or belimumab.\textsuperscript{136, 137}

Professor Voskuyl concluded, noting that T2T in SLE as defined by LLDAS or remission, is frequently present in observational cohorts, and can be reached after initiation with IS drugs in large number of patients. Prolonged LLDAS is associated fewer flares and, like remission is associated with less damage. LLDAS and prolonged remission are also associated with better quality of life, are obtainable in clinical trials and can discriminate the effect of different treatment regimens.

Diagnosis and treatment of neuropsychiatric lupus: Marcello Govoni (Italy)
Professor Govoni's presentation provided insights into the challenges of diagnosing and treating neuropsychiatric lupus, including clinical insights, imaging, biomarkers and novel treatments

Professor Govoni began his presentation with a review of the 1999 ACR classification of NPSLE, including the 19 neuropsychiatric syndromes primarily accredited to SLE (12 to the
central and 7 to peripheral nervous systems), which can be further classified as focal (Table: Red) or diffuse (Table: Black).\(^{168}\)

<table>
<thead>
<tr>
<th>CNS</th>
<th>PNS</th>
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<tr>
<td>Aseptic meningitis</td>
<td>Guillain Barré syndrome</td>
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<tr>
<td>CVD</td>
<td>Autonomic neuropathy</td>
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<tr>
<td>Demyelinating sd.</td>
<td>Mononeuropathy</td>
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<tr>
<td>Headache</td>
<td>Myasthenia gravis</td>
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<tr>
<td>Movement disorder</td>
<td>Cranial neuropathy</td>
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<tr>
<td>Myelopathy</td>
<td>Plexopathy</td>
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<tr>
<td>Seizure disorders</td>
<td>Polyneuropathy (no ENG)</td>
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<td>Acute confusional state</td>
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<td>Anxiety disorder</td>
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<td>Cognitive dysfunction</td>
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<td>Psychosis</td>
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### Diagnosis of NPSLE

Professor Govoni noted that some neurological observations such as small fiber neuropathy (SFN), posterior reversible encephalopathy syndrome (PRES), chronic inflammatory demyelinating poly neuropathy (CIDP) and neuromyelitis optica spectrum disorder (NMOSD) have not been included in this classification, although a number of reports of their association with SLE have been published. The burden of disease in patients with NPSLE was outlined in a metanalysis showing 56.3% of SLE patients experiencing NPSLE, 93.1% of whom had CNS involvement and the remaining having PNS involvement.\(^{168}\) Moreover, up to half of SLE patients will develop neuropsychiatric involvement early in their disease course,\(^{170}\) with up to 40% of patients having neuropsychiatric events as a presenting symptom of SLE.\(^{171}\) Epidemiological data for PNS disease are however scant, with the reported prevalence being highly variable ranging from 6 to 18% in some retrospective, cross-sectional studies and single or multiple mononeuropathy, cranial neuropathies and polyneuropathies most frequently reported. Notably, PNS involvement has not been included the recent ACR/EULAR classification criteria for SLE.\(^{172}\) Two recent multicentre studies analysed PNS involvement in SLE yielding similar results, with around 7%, being polyneuropathy cranial neuropathies and mononeuritis, most frequently observed clinical settings.\(^{173, 174}\)

Diagnosis of NPSLE is complex as none of the NPSLE syndromes have specific features for SLE, with many features (ie. headache, mood disorder, cognitive impairment) common in healthy people. Moreover, no specific neuroimaging or serologic markers are specifically available. Given this, expert opinion remains the ‘gold standard’ for diagnosis, including careful attribution of the neuropsychiatric event to the underlying disease. Current attribution models are outlined in the following table.

### SLICC Cohort Based\(^{175}\)
1. Time interval between the NP event onset and the diagnosis of SLE
2. Presence of concurrent (or confounding) non-SLE factor(s)
3. The low specificity of some NP events

### Italian Algorithm\(^{175}\)
1. Favouring factors are considered, too
2. Each item has been weighted (score 0 to 3)
3. The higher is the resulting global score (0-10) the greater is the

### Leiden Model\(^{176}\)
- Multidisciplinary evaluation and tight FUP re-assessment
  - NPSLE directly related to SLE
  - Undefined NPSLE
  - Non-NPSLE
    - Primary NP disease
    - Medication
    - Complication of SLE
When considering the overall performance of these models only up to one third of neuropsychiatric events can be attributed to SLE, thus multidisciplinary assessment and close follow up are the best strategies for diagnosing NPSLE, with initial diagnostic work up being similar for both SLE and non-SLE patients.

Neuroimaging is essential for excluding aetiologies other than SLE, with conventional MRI being the imaging of choice to depict anatomy and macro-architecture of CNS. However, it is important to note around 40% of NP events in SLE occur without corresponding neuroimaging abnormalities and, conversely, many abnormalities detected by conventional MRI in patients with SLE are not associated with any clinical syndrome or neurological signs. An MRI protocol has been recommended by EULAR. Other applications of MRI including PWI, 1H-MRS, MTI, DWI, DTI can reveal brain perfusion abnormalities, impaired neuronal metabolism and biochemistry, yielding information about micro-architecture and neuronal connectivity of nervous tissue also in patients with normal cMRI. In addition, functional MRI can inform about abnormal patterns of metabolic activation of brain regions in performing simple tasks. PET scans may be useful in revealing metabolic abnormalities in patients with normal MRI. It is however important to note that no single technique can cover all aspects of NPSLE diagnosis, and a multimodal approach is recommended.

**Treatment of NPSLE**

There are a number of unmet needs challenging the treatment of NPSLE. Randomised controlled trials are scarce, with only three being published in the past 26 years. This absence of evidence requires a pragmatic treatment strategy based on expert opinion and observational data. Currently, there is a lack of reliable biomarkers for disease activity, no defined outcomes measure for NPSLE and no clear therapeutic target. Given these limitations, a road map for a reasonable therapeutic approach to NPSLE has been provided by EULAR recommendations, with GC and IS, along with anti-aggregation or anticoagulation and symptomatic therapies being the cornerstones for treatment of NPSLE. These options have been endorsed by recent 2019 update of EULAR recommendations for the management of SLE.

In respect of a general treatment approach to NPSLE, the efficacy and safety of symptomatic treatments have been tested in non-randomized observational studies, notably for antidepressants, anxiolytic and anti-seizure drugs, as well as psychotherapy and behavioural rehabilitation of cognitive dysfunction. Therapies for some conditions such as delirium, transverse myelopathy and cognitive dysfunction are, however, not available. Effective management of modifiable factors, including metabolic, endocrine and infectious comorbidities, fibromyalgia and cardiovascular disease is important as well as minimisation of GC exposure in stable or chronic disease. Specific treatment options must be supported by a correct diagnosis, accurate work up to assess comorbidities and modifiable risk factors. Severity of NP and pathophysiology are also important.
There are two, probably complementary and sometimes overlapping, pathogenetic pathways for NPSLE. The first is driven by ischemic damage enlarged and small blood vessels, caused by aPL, immune complexes, complement and intravascular thrombosis, and correspond with neuropsychiatric events like stroke, seizures, movement disorders and some myelopathies. The second is mainly driven by an autoimmune mediated neuro-inflammatory pathway with complement activation, increased permeability of the blood brain barrier, intrathecal migration of neuronal autoantibodies leading to neuronal apoptosis, local production of immune complexes and pro-inflammatory cytokines and other inflammatory mediators. Like the first pathogenetic pathway, the clinical phenotypes associated with this pathway are mostly, but not exclusively, diffuse neuropsychiatric manifestations such as psychosis, mood disorders, cognitive dysfunction and acute confusional states. Experimental evidence suggests several factors are involved in the complex pathogenesis of NPSLE, including, pro-inflammatory cytokines and other inflammatory mediators, cell mediated inflammation as demonstrated in murine models and different autoantibodies. Notably, immunohistochemical and histopathologic studies have focused on complement activation especially associated with brain microthrombi in the context of a brain microangiopathy. Another emerging area of interest is the role of the microglia activation. At the core of all these mechanisms there is a blood brain barrier dysfunction, resulting from different pathologic damage.

In practice, when an ischemic-vascular-thrombotic pathway is highly suspected, treatment should be based on anti-aggregation and/or anti-coagulation, like management of APS. For primary and secondary prophylaxis careful personalized risk stratification is needed, as SLE patients with aPL are (by default) at higher risk than aPL carriers without SLE When a prevalent inflammatory pathway is suspected to be the most relevant or even in the context of a high underlying SLE disease activity, acute treatment (similar to LN) comprises high-dose CG and CYC. For maintenance treatment or to prevent relapses HCQ, AZA or MMF can be used whilst aiming to taper GC dose. New treatment targets for NPSLE have been reviewed by Nicoloupulos et al 2019.177

Professor Govoni concluded his presentation, noting the improvement in diagnosis and attribution of NPSLE, as well as evolving neuroimaging techniques, understanding of biomarkers and novel treatments for NPSLE.

**Covid-19 and SLE – What do we know today?**

Professor Conti reviewed the current evidence for risk of Covid-19 infection among patients with autoimmune rheumatic diseases, focusing on SLE, and highlighted the importance of ensuring robust evidence are available to understand outcomes in SLE patients with Covid-19.

Professor Conti began his presentation noting that six months following the beginning of Covid-19 pandemic in China, data on the risk of SARS-CoV-2 infection among patients with autoimmune rheumatic diseases are now available, before briefly explaining its basic biology. 178-181 The Covid-19 pandemic is of particular interest to the rheumatology community as it increases the risk of infection, HCQ has been shown to inhibit SARS-CoV-2
in vitro, tocilizumab is used in the treatment of cytokine release syndrome. Professor Conti’s presentation set out to answer five pertinent questions about SLE and Covid-19.

1. **Are SLE Patients at Increased Risk from Covid-19?**
A survey of 165 SLE patients from northern Italy, with 77% on HCQ, found a higher incidence (2.5%) than in patients in the general population (0.47–0.76%), with generally mild disease course, which was mostly self-resolving. Another study from Germany, showed similar rates of Covid-19 infection, or suspected infection, in patients treated with or without HCQ, whereas patients taking IS did not have a higher rate of infection or symptoms. Conversely, GC dose was positively associated with infection and hospitalisation. An interesting study from Spain found that prevalence of Covid-19 in patients with SLE were the same as in the general population and lower than in patients with some other rheumatic inflammatory diseases.

2. **Do SLE Patients Have a Worse Prognosis When They Contract Covid-19?**
A French study of 17 patients with SLE and Covid-19, receiving long-term HCQ treatment, found 76% developed complications due to respiratory failure (65%), ARDS (29%) and two patients died. This indicates that HCQ does not seem to prevent COVID-19, at least its severe form, in patients with SLE. A US study found that IS treatment before admission to hospital did not seem to influence the severity of infection in patients with SLE. Finally, the Covid-19 Global Rheumatology Alliance reported that in 80 patients with SLE, the frequency of hospitalisation did not differ between in those taking and those not taking HCQ.

3. **Does HCQ Have an Effect on Covid-19?**
In early February and March 2020, in vitro studies showed that CQ and HCQ were found to decrease the viral replication in a concentration-dependent manner. Since the publication of these data, some observational studies have found patients treated with HCQ along or in combination with azithromycin experienced a faster viral clearance than those who did not. However, a multicentre study of 667 patients with Covid-19 found HCQ alone or in combination with azithromycin did not improve clinical outcome at Day 15 compared with standard care. Another study of the prophylactic use of HCQ found it did not prevent Covid-19 when used as postexposure prophylaxis within 4 days after exposure. HCQ has also been associated with QTc prolongation, with longer time to clinical recovery, lower overall clinical recovery, higher all-cause mortality and total adverse events.

4. **Does Lockdown Have an Effect on Disease Activity?**
HCQ shortage and missed in-person visits may have affected SLE disease activity, with patients terrified that they might lose access to medication (ie. HCQ) that prevent their disease from damaging other vital organs. Moreover, 8.8% of patients in a German
survey reduced their daily dose of HCQ to overcome potential supply issues\textsuperscript{194}. Generally, QoL was not significantly affected by lockdown.

5. \textbf{Are aPL a Cause of Thrombosis in Covid-19 Patients?}
High rates of thrombotic complications have been found in critically ill patients with Covid-19, despite prophylaxis with LMWH,\textsuperscript{195} with other studies showing presence of focal vasculitis and microthrombi in the alveolar capillaries of autopsy patients.\textsuperscript{181, 196} Another study has found that the aPL antibodies in Covid-19 are different to those detectable in APS. From a total of 122 severe or critical COVID-19 patients, there were 16 thrombotic events (13.1%), despite anticoagulation, 5.7/6.6\% positive for IgG/IgM aCL; anti-\(\beta2\)GPI IgG/IgA/IgM were found in 15.6/6.6/9.0\% patients, respectively. There was no association between aPL positivity and thrombotic events.\textsuperscript{197}
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