8th Annual Meeting of the Lupus Academy Meeting Report

Warsaw, Poland

6–8th September 2019

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

The 8th Annual Meeting of the Lupus Academy was held in Warsaw in September 2019, 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:

- Understand the influence of cytokines in systemic lupus erythematosus (SLE) pathogenesis and translational perspectives.
- Discuss current classification criteria for the effective management of SLE.
- Describe different lupus manifestations, their comorbidities and management of these in clinical practice (e.g. cardiovascular, kidney, CNS etc).
- Apply principles of the management of challenges like infection, nephritis, refractory lupus and pregnant patients with lupus.
- Discuss outcomes measurement in SLE including treat-to-target and low-disease activity states in principle and practice.
- Demonstrate understanding of targeting novel treatment pathways and their effect on clinical outcomes, including type 1 interferons, B cells, plasma cells and interleukin 12 and 23.
- Describe novel biomarkers used for monitoring lupus disease activity.
- Understand the best course of action in predicting and managing lupus flares and membranous lupus nephritis.

Keynote Lecture

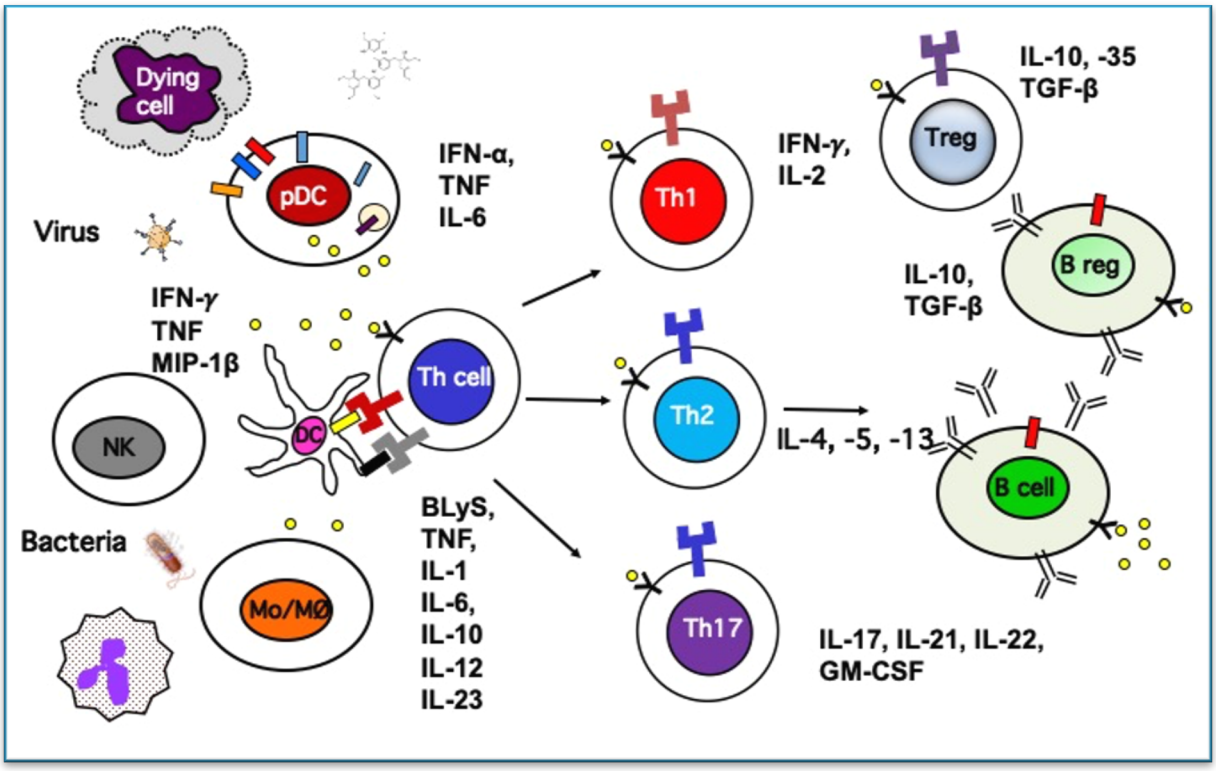
Cytokines in SLE: Translational perspectives 2019: Lars Rönnblom (Sweden)

Professor Rönnblom reviewed the pleiotropic effects of cytokines and their potential role in autoimmunity. Highlighting specific cytokines involved in the lupus disease process, Professor Rönnblom presented different possibilities for modulating the effects of these in patients with lupus, noting the importance of developing our understanding of these cytokine pathways.

Professor Rönnblom began his presentation by highlighting some basic facts about cytokines, noting that the constitute a very large group of proteins including interleukins (IL), chemokines, interferons (IFN) etc, that they can be produced by several cell types and act on many cell types, with cell-cell communication effecting immune response. Most cytokines have pleiotropic effects, making it difficult to classify them as anti-inflammatory or pro-inflammatory. Indeed, these cytokines can be difficult to measure given there are a number of molecules that can interfere with anti-cytokine antibodies and basal cytokine numbers are low. Today, gene expression of cytokines or their gene signature is often utilised.

Cytokines involved in immune activation are shown in **Figure 1**, with the immune system producing a number of well-known cytokines well known for triggering innate and adaptive immune responses, as well as activation of regulatory cells.

Figure 1. Cytokines and immune activation



Important Cytokines in Patients with Lupus

There are several methods used to study the role of cytokines in lupus including measuring cytokines in patients, experimental models and animal models. However, given systemic lupus erythematosus (SLE) is a heterogenous disease, determining which model and which patients best represent SLE is a challenge as an animal model only represents a single patient.

Hooks et al (1979) found that 71% of SLE patients and 21% with inactive disease had elevated IFN, leading to the conclusion that IFN may contribute to immune aberration in these patients.(1) Moreover, anti-inflammatory cytokines increase just before a flare compared to non-flaring patients,(2, 3)highlighting the importance of immune dysregulation of in flaring SLE patients.

Gene Expression Profiles in SLE

In 2003 there were four papers showing that patients with SLE had increased IFN-1-regulated gene expression, with patients with major organ manifestations (ie. renal, CNS or haematologic) exhibiting more prominent gene signatures than those without.(4, 5) More recently, a study in which gene expression profiles were divided into two scores (a and b), where scores allow attribution of score to manifestation (eg. skin) or disease type (eg. lupus or arthritis). Other genes, including granulocytes and B cells are also upregulated in lupus, with strong IFN and neutrophil signatures.(5) IMore recently, single cell transcripts have been performed in biopsies of patients with lupus nephritis, allowing pinpointing of each cell type and targeted therapy in individual patients.(6)

Interferon

IFN was the first cytokine described in any detail. Characterized as a protein interfering with virus replication, IFN regulates around 10% of our genes.(7) Today, IFN is recognised as being a large family of proteins with an overlap in signalling pathways. IFN-a induces B-lymphocyte stimulator (BLyS) production triggered by monocytes.(8) B cells promote IFN-α production by podocyte dendritic cells (pDC), with dose dependent response;(9) indeed, B cells move to pDCs stimulating ongoing interferon production and autoimmune reactions as seen in SLE patients. Activated T-cells also stimulate pDCs to increase IFN-α production as do GM-CSF and IL-3. (10)

Type I IFN and the cytokine tumour necrosis factor (TNF) cooperatively reprogram the macrophage epigenome to promote inflammatory activation.(11) Which explains IFN blocking negative feedback signals from TNF thus increasing inflammatory response to infection in lupus patients. TNF-a has also been shown to be increased in lupus patient. Notably, in patients with lupus nephritis, the more severe the disease the higher the level of TNF there is in the glomeruli.(12) Indeed, anti-TNF treatment has been shows to improve SLEDAI and proteinuria in lupus patients.(13) This is activity is the result of anti-TNF promoting anti-dsDNA, moreover TNF prolongs survival of lupus mice and down regulates the IFN-α response.(14)

BLyS

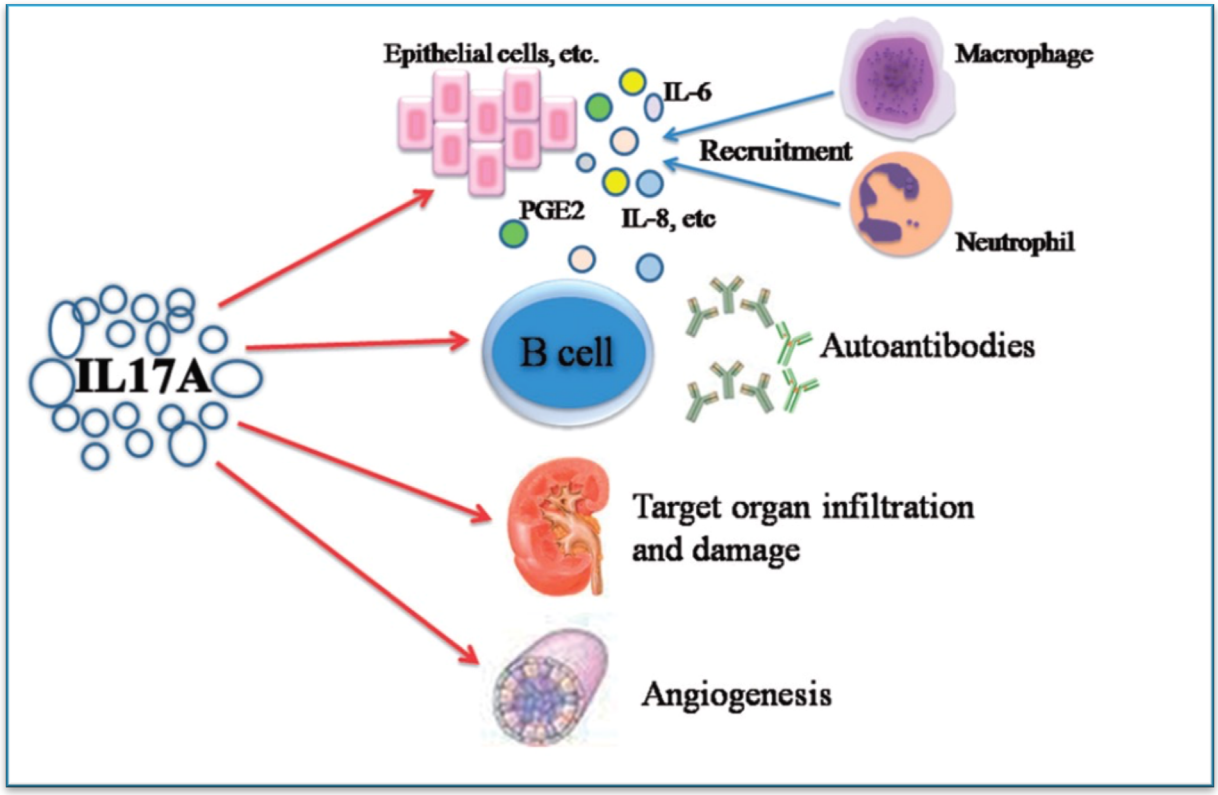
BLyS was initially developed to treat immunodeficiency but was not successful. However, BLyS overexpression in mice was seen to result in a lupus-like disease and has since become a cutting-edge treatment for some patient with lupus.(15) Some longitudinal observations of BlyS have shown that 505 of SLE patients have normal BlyS levels, whereas 25% have persistently elevated levels and 25% have intermittent levels, highlighting that all lupus patients are different in terms of treatment need and response.(16)

IL-12, IL-23 and IL-17

IL-12 and IL-23 are also increased in SLE. IL-12 promotes cell-mediated immunity and IL-23 drives IL-17 production; there is a proven correlation between elevated IL-17 and lupus disease activity in

some patients.(17, 18) IL-17 has a number of effects in the inflammatory system including angiogenesis, organ infiltration and B cell activation (**Figure 2**). IL-17 is also involved in the mucosal defence system by recruiting innate immune cells to the mucosa(19) and the IL-17 inhibitor secukinumab has proven effective in lupus nephritis.(20)

Figure 2. IL-17 in SLE



IL-2

A proportion of patients with lupus have increased serum levels of IL-2, but the number and function of T-reg cells is reduced in these patients.(21) There is evidence that low-dose IL-2 treatment increase T-reg and reduce disease activity in patients with lupus.(22) More recently, a trial has shown that low-dose IL-2 treatment in a trial across 11 autoimmune diseases resulted in increased T-reg activity and decreased disease activity in patients with low disease activity.(23)

Table 1. Cytokines Involved in SLE

Cytokine	Characteristics	Function
Interferon Type I-III	All increased	Antiviral, immune adjuvant
BLyS/APRIL	Increased	Promote B-cell survival

TNF	Increased	Proinflammatory, immune regulation
IL-10	Increased	Pro- and anti-inflammatory
IL-2	Decreased production	T cell factor, T-regs dependent
IL-6	Increased	B cell maturation
IL-12	Increased	Activate T cells and natural killer cells
IL-17	Increased	Induce several cytokines
IL-21/23	Increased	B-cell stimulation

Challenges of Treatment Selection

Despite advances in our understanding of cytokines in SLE, there remain challenges in integrating genetics, clinical manifestations and cytokines in therapy. Targeting interferon production triggers is an important consideration in the future management of SLE. Therefore, including gene expression profiles in the treatment selection process, for example a strong STAT4 signal is associated with more severe SLE disease including renal failure.(24) Indeed, STAT4 signals via both IL-12 and type 1 IFN, and increases the response from activated SLE T cells.(25-27) Conversely, the STAT4 risk gene variant in healthy individuals resulted in decreased IFN production, suggesting they had a capacity to suppress STAT4 function.

Conclusions

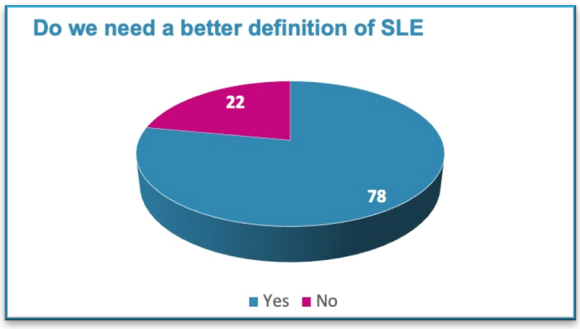
Professor Ronnblom concluded his presentation highlighting that a large number of cytokines are increased in SLE, but the cytokine profile varies within the same patient and between patients. Moreover, cytokines are complex, and one cytokine can have many effects, both proinflammatory and anti-inflammatory. When choosing effective treatments, the cytokine profile in a patient needs to be integrated with genetics, cellular and humoral immune activation and clinical manifestations. Finally, although precise cytokine modulation in SLE is a challenge, our increased knowledge of involved pathways holds promise for better treatments in future.

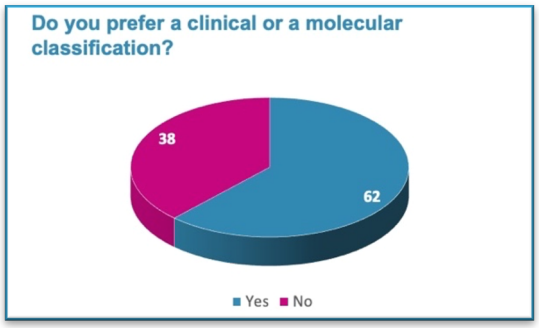
Debate: New developments in Basic Science and Clinical Research: Defining SLE

Experiences from clinical research and clinical practice are important in improving our understanding of disease and its management. The classification of autoimmune diseases, notably early SLE, enables earlier treatment and less disease damage accrual. To date, clinical classification criteria have focused on ACR and SLICC, with the most modern criteria being developed jointly by EULAR and ACR. In addition, clinical research is focusing on molecular classification systems, which look at a molecular basis for classification as opposed to clinical disease-based classification. The following debate provided interesting perspectives from both classification proposals, with broad agreement from the

audience on the need for better definition of SLE as well as improvements to existing tools and classification criteria.

Ricard Cervera introduced the topic, which this year focused on the latest developments in defining lupus. Providing a short introduction to lupus, the origins of this disease and the importance of our own experiences of the numerous manifestations that make defining lupus difficult. Noting the first classification of lupus in 1971 by ACR was not the best example and was quickly replaced in 1982 by ACR. These criteria have been used for many years, which has received several updates, including those in 1997, before the SLICC group introduced updated and improved classification criteria in 2012, with greater sensitivity and specificity for assessing lupus. Most recently, ACR and EULAR have sought to combine classification criteria to further improve lupus assessment. Yet, our understanding of the pathophysiology, management and future treatment of lupus continues to evolve. Therefore, Professor Cervera asked the audience the following questions, before introducing speakers to debate the clinical and molecular classification of lupus—a complicated topic!





We need better classification criteria for lupus: Marta Mosca (Italy)

Professor Mosca highlighted several clinical challenges presented by SLE including its variably clinical picture with many difficulties for early diagnosis, the mimicking conditions that also make diagnosis difficult and the need for new guidelines including the development of EULAR/ACR criteria and their performance in early SLE.

SLE Has a Complex Clinical Picture and Classification Criteria

Lupus is a complex disease with variable phenotypes, not one with a single manifestation; lupus is difficult to diagnose and manage. Lupus patients present in different ways and, therefore, hold the clues as to what we know and understand about lupus as a disease. These differences result from both genetic and environmental factors, with studies showing marked differences in early SLE between Hispanics from Texas and Puerto Rico, including higher disease activity, greater organic involvement and higher frequency of anti-dsDNA antibodies and more damage accrual in Hispanic

lupus patients from Texas.(28) Likewise, in Europe SLE is mild and rare in Caucasian Europeans and more severe in Africans, outside Africa, Brazilians and Mexicans, whereas there is an increased risk of photosensitivity, discoid risk and decreased antibody production in Northern Europeans, highlighting the relevance of genetic factors in SLE.(29) SLE Classification criteria must therefore consider the large variety of manifestations and phenotypes and diseases subsets identified by clinical and autoantibody profile, gender, age of disease onset, ethnicity etc. Moreover, SLE may be considered as one disease or many, depending on numerous factors. Lupus as one disease is characterized by the fact that also there are different disease expressions between patients, during the disease course patients accrue clinical manifestations. Therefore, in the absence of diagnostic biomarkers, signs and symptoms that tend to occur together have been identified and classification criteria have been established. Before continuing the argument for a clinical basis for classification of SLE, Professor Mosca clarified the key differences between diagnosis and classification (**Table 1**). A feasible set of research criteria are needed to classify lupus patients.

Table 1. SLE versus Classification

Diagnosis	Classification
Clinical implications	Research implications
Aim: individual prognosis & therapy	Aim: homogenous group (science)
Lots of different pieces of information	Feasible set of objective criteria
Sensitivity issues critical (therapy!)	Sensitivity issues annoying
Diagnosis will be questioned again	Specificity at one time important

Criteria for classification are important, but clinicians can overrule these, therefore they do not dictate diagnosis. Indeed, no feasible set of criteria can include all the information that may be of help for diagnosis. ACR/SLICC criteria have 83–96%/94–96% sensitivity and 93–96%/82–92% specificity, respectively,(30, 31) but even the best criteria will miss the diagnosis in some patients and could be dangerous.

Professor Mosca outlined the 1997 (revised) ACR criteria before highlighting their limitations,(32) including dermatological manifestations (including some manifestations but excluded others), exclusion of patients who present with one organ involvement (eg. Kidney) and that not all patients present with classical classification criteria at disease onset; that is there were difficulties in early classification and disease diagnosis. Given that patients are seen in clinics, the clinical criteria were seen as useful and worked on by the SLICC groups, eventually being developed into and new classification system for lupus, the SLICC (2012) guidelines.(31) The SLICC classification rule would diagnosis lupus if the patient satisfies four of the clinical and immunologic criteria, , including at least one clinical criterion and one immunologic criterions, or if they have biopsy-proven nephritis compatible SLE in the presence of ANAs of anti-dsDNA antibodies. The SLICC 2012 criteria were

considered to have good sensitivity and specificity with respect to the ACR criteria.(33) However, there are limitations, including difficulties in early diagnosis.

Early Diagnosis and Classification of Lupus

Early diagnosis, and classification, is important for minimising active disease and resulting damage, preventing severe organ involvement, changing disease course, and encouraging new studies and secondary prevention.

The time from first symptom to diagnosis has been estimated to be between 0.5 and approximately 4 years, which is too long. Initial presentation with non-specific signs and symptoms also found in other conditions, and constitutional, mucocutaneous and articular manifestations are most common at disease onset.(34-36)

Regarding classification, about 55% of the patients have only 1 ACR criteria as the initial manifestation of SLE. The mean time to the development of 4 criteria or to diagnosis is 29.4±52 months. Arthritis and photosensitivity are the most frequent initial clinical manifestation prior to criteria diagnosis.(28) In summary, early performance of ACR and SLICC criteria diagnosis is poor in the first 5 years of disease.(37)

There are many problems with early diagnosis of lupus, including ANA-negative SLE, uncommon manifestations and organ-dominant SLE. Additionally, other diseases like UCTD, MCTD, rhupus, infection and haematologic diseases can mimic SLE.(37) Early lupus presents as malar rash, arthritis and haematological manifestations, with arthralgias, fever, alopecia, raynauds, non-hemolytic anemia, lymphadenopathy and arterial hypertension being common.

Development of the New EULAR/ACR Criteria

Do we need new classification criteria? Yes. According to Professor Mosca, there is a need for an intuitive rule that helps understanding and teaching SLE and we need to be able to classify early patients. The EULAR/ACR criteria, is more sensitive than but equally specific as the ACR criteria, it is easy to memorize and benefits from worldwide consensus. Professor Mosca provided an introduction to and overview of the EULAR/ACR 2019 criteria,(38) highlighting when and how to use the criteria as outlined in **Table 2**, noting that not all items are equal in these criteria unlike previous classification systems.(30, 31)

Table 2. EULAR/ACR 2019 SLE Criteria

EULAR/ACR 2019 SLE Criteria
Entry ANA ≥1:80 or equivalent (ever)
At last one clinical criterion
Variables derived from a large effort and analysis of early SLE cohorts

Weighted scheme with a cut off ≥10
Attribute when no more likely other cause
Count highest in each domain only

The development of the ACR/EULAR Classification Criteria involved a multicentre study of 616 patients presenting with these features of early SLE (n=389) as well those with mimicking conditions (n=227).(39) This study found that standard items of existing classification criteria are more prevalent in SLE than in mimicking conditions. Non-infectious fever is more prevalent in early SLE than in mimicking conditions (34.5% vs. 13.7%). The following were more common among mimickers: Raynaud's phenomenon (22.1% in SLE vs. 48.5% in mimicking conditions, p<0.001), sicca symptoms (4.4% vs. 34.4%, p 0.001), dysphagia (0.3% vs. 6.2%, p<0.001), and fatigue (28.3% vs. 37.0%, p=0.024) and rashes outside the typical SLE spectrum such as skin vasculitis, (5.9% in SLE vs. 11.9%, p=0.009). This study showed immunological abnormalities were also most prevalent in patients with lupus. Patients with early SLE are much more likely to have ANA and antibodies to dsDNA and Sm. Anticardiolipin IgM, anti-beta 2 glycoprotein-I antibodies, positive Coombs tests, autoimmune hemolytic anemia, hypocomplementemia and leukopenia were more common among SLE patients. Antibodies to Ro (SS-A) and La (SS-B) did not differentiate early SLE and mimicking conditions.

Analysis of the ACR/EULAR criteria in a subset of patients were submitted to the ACR for validation and were shown to have good sensitivity and specificity in the classification of patients with short disease duration, however, addition data are required to understand the performance of these criteria in early SLE.

Conclusions

Professor Mosca concluded by highlighting that lupus starts with clinical manifestations and a wide range of symptoms and that the association of symptoms has been used to identify SLE. In the absence of a disease- specific biomarker, SLE classification has been based on clinical and serological manifestations. Subsequently, classification criteria have been developed, updated and modified, with the new EULAR/ACR criteria offering an opportunity to classify early disease and perform prevention studies.

We need a different approach: A molecular classification for connective tissue diseases. Marta Alarcón-Riquelme (Spain)

Professor Alarcón-Riquelme began her presentation highlighting several objectives including, the possibility of stratifying patients with lupus using molecular transcriptome data, how stratification of lupus can be of clinical use and help identify and prioritize new drugs, the presentation of recent results on disease stratification and also how unsupervised clustering integrating transcriptome and methylome data can be used to stratify SLE and other systemic autoimmune diseases.

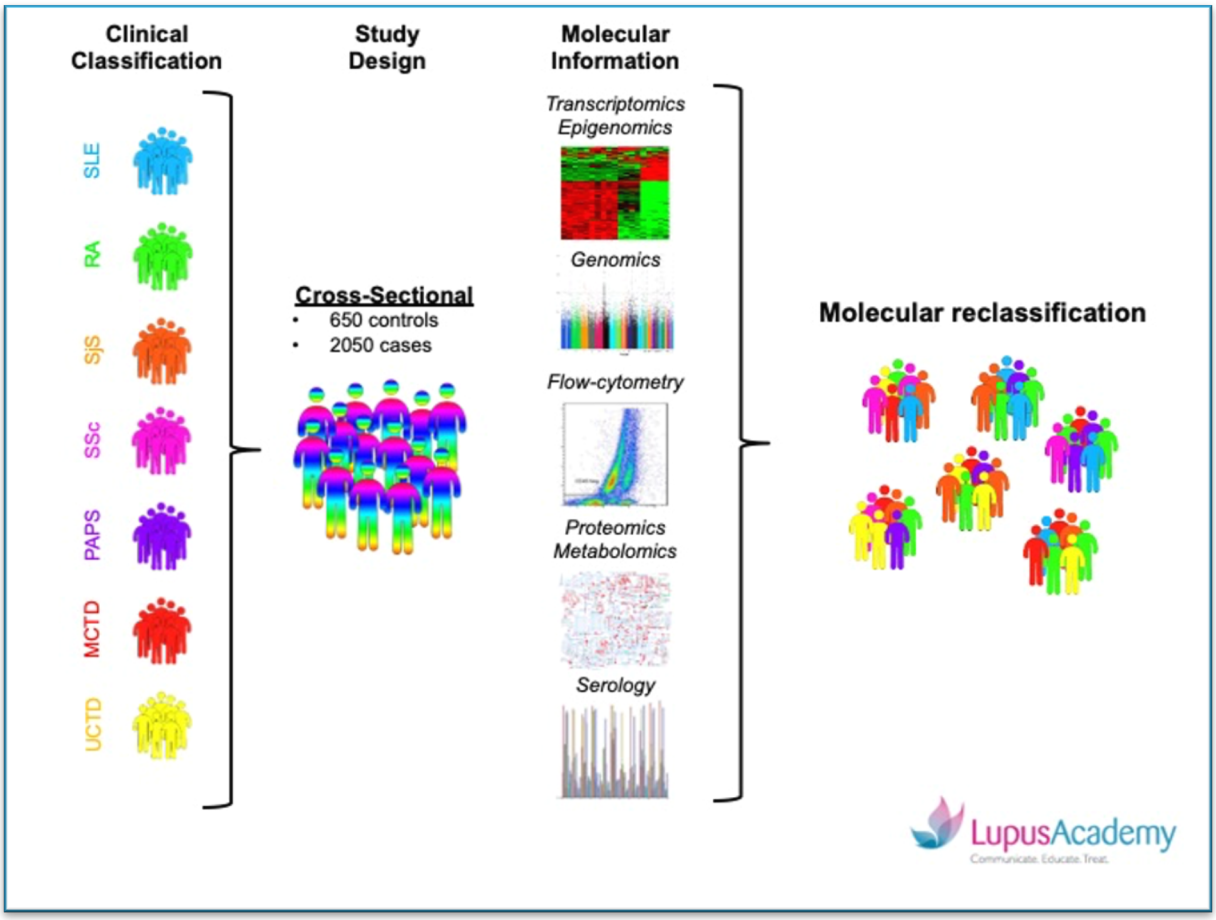
Professor Alarcón-Riquelme emphasized that detail is not unimportant and represents molecular and cellular perspectives, whereas the big picture is representative of the clinical perspective. She continued to highlight that lupus is a heterogenous disease and, given this, we need to understand the molecular basis for this heterogeneity and understand if individual lupus patients share molecular pathways with patients with other diseases and if dissecting the molecular heterogeneity would help us improve the way we define therapies.

Stratification of SLE using longitudinal data is important. Professor Alarcón-Riquelme presented a longitudinal study, which looked at gene expression over time in SLE and the correlation of this with SLEDAI.(40) Genes that correlated with SLEDAI, were used to divide patients into three groups, with differences were exhibited by relationship with neutrophils in two of the groups (Clusters 1 and 2), where the percentage of neutrophils increased with disease activity, but in the third group (cluster 3) neutrophils decreased with disease activity, whereas lymphocytes increased. Patients from the second cluster were found to have a very strong interferon (IFN) signature, where IFN genes followed the disease activity. Looking at the incidence of lupus nephritis development across these clusters, similar numbers of paediatric patients across the three groups developed proliferative nephritis, whereas in adults less than one third as many patients developed proliferative nephritis in cluster 3 as compared with the other two clusters. There is a distinct correlation between disease activity and cellular activity in this and other lupus disease manifestations. In addition, drugs with similar gene expression patterns as these SLE clusters are based on the types of cells that express their targets: neutrophils or lymphocytes. The neutrophil-lymphocyte ratio also seems to be important in these clusters; ie. lymphocytes and lymphocyte genes correlate positively with disease activity. Lymphocytes are NOT reduced. Also, neutrophils and neutrophil genes correlate positively with disease activity. Lymphocytes are reduced. The ratio between neutrophils and lymphocytes may determine response to treatments, and collection of these data should be encouraged to provide a broader picture of how patients with different gene profiles respond to different treatments.

PRECISESADS: Reclassification of Systemic Autoimmune Diseases.

Professor Alarcón-Riquelme introduced the PRECISESADS reclassification of systemic autoimmune diseases, a project with elaborated protocols for performing multicenter flow cytometry and patient recruitment, with centeralised sampling and processing (DNA, RNA). The project included patients with lupus, rheumatoid arthritis, scleroderma, mixed connective tissue disease and primary anti-phospholipid syndrome (**Figure 1**).

Figure 1. Diseases Studied for Molecular Reclassification using Transcriptomics and Methylomics.



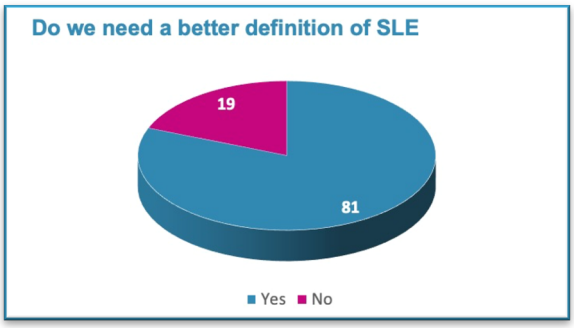
The first analysis took gene expression and methylation data for the whole genome and selected features for each disease and mapped them across four clusters (1) Inflammatory mediators, (2) Blood, (3) T-cells and (4) Interferon. Serological characterization of patient types by cluster reveals, notably, TNF-α enrichment in the interferon cluster as well as BAFF. Clusters 2 and 3 are represented by anti-CCP, antibodies, highlighting the presence of rheumatoid arthritis and scleroderma patients. Characterization by flow cytometry revealed Cluster (1) had neutrophils, (2) enrichments, (3) T-cells and NK like T-cells (4) interferon expression in all cell types, but with no enrichment. The next stage was to map clinical manifestations were correlated to principal components and then these were attributed to clusters. Clusters 1 and 2 shared fibrosis phenotypes in both skin and muscle skeletal systems Cluster 1 included kidney inflammatory process, while cluster 2 presented lipids metabolism defect. Cluster 3 presented less aggressive phenotypes but enriched in sicca syndrome. Cluster 4 enriched on the most extreme phenotypes (kidney, nervous system involvement, etc…). Cluster 2, termed the heterogenous cluster, included mainly healthy controls with a healthy-like molecular pattern and low disease activity, whereas clusters 1,3 and 4 were associated with more disease activity. Over time, molecular patterns in these clusters remained stable over time, with the majority of stable patients being found in cluster 2. Moreover, the majority of patients whose molecular patterns switch clusters, did so to cluster 2 and returned to their original cluster. This reflects patients with lupus, in which the neutrophil-lymphocyte ratios appear important and may have relevance in the clinic, facilitating new treatment approaches for SLE. Professor Alarcón-Riquelme highlighted the gradient of autoimmunity where disease diagnosis is irrelevant and where the molecular detail instead allows stratification of individual patients into a specific molecular cluster,

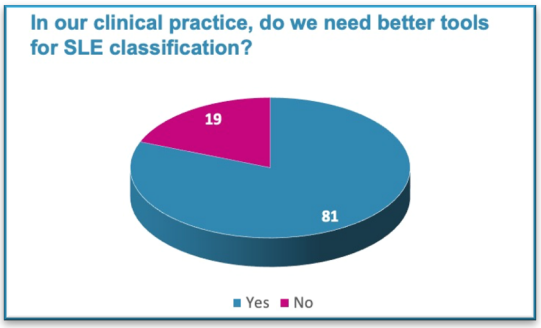
identification of the tissue or organ effected by SLE, and ultimately precision treatment of the patient.

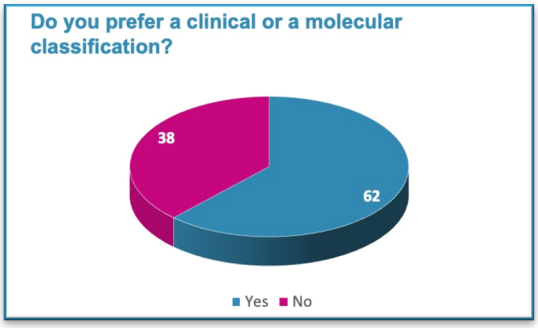
Professor Alarcón-Riquelme concluded her talk, by highlighting remaining questions around the two or three disease trajectories that SLE may take, including the roles of genes and the microbiome in each cluster, the possibility that autoimmune and inflammatory diseases may have underlying different underlying causes and also the need to prove that patients are stable for longer periods.

The short discussion following both clinical and molecular arguments highlighted a mutual respect for both positions, with acknowledgment that molecular classification has a place in autoimmune and inflammatory diseases in future, but there needs to be more research into the clusters in this area to validate the position.

The audience voted again on the same questions asked at the outset of the debate, the results were similar to before the debate, with a very small (3%) increase in belief that there is a need for a better definition of SLE, a marked (15%) increase in the belief that we need better tools for SLE classification, but interestingly, no change in the majority vote of 62% vs 38% in preference for clinical classification over molecular classification.







Plenary I: Lupus Manifestations and Comorbidities: How Have Our Strategies Improved?

Cardiovascular outcomes and SLE in 2019: Murray Urowitz (Canada)

Professor Urowitz's presentation reviewed cardiovascular outcomes in patients with SLE, beginning with clinical, subclinical and preclinical atherosclerotic vascular events (AVE) in SLE, the magnitude of improvement of AVE incidence in SLE in modern times and finally the importance of effective

management of cardiovascular risk factors in SLE patients, resulting in the minimization of AVE occurrence.

Professor Urowitz began his presentation by giving an overview of the past (clinical disease), present (subclinical and preclinical disease) and future (controlling the disease) of coronary artery disease (CAD) in SLE.

SLE and CAD: The Past

The past perspective of CAD in SLE, including angina, myocardial infarction and sudden death, show mortality in SLE follows a bimodal pattern, the prevalence of atherosclerotic vascular disease is between 6% and 17%, women with SLE have a 5 to 50 fold increase in their risk of CAD and the mortality attributable to CAD is between 3.5% and 36.4% in SLE patients.(41-44) This highlights the significant relationship between SLE and CAD, with a trend showing significant decreases between the 1970s and 2013. However, regardless of which decade data were taken from the prevalence increases consistently with time, this was also true for broader atherosclerotic vascular events (AVE). Moreover, 21.5% of deaths in SLE patients result from AVE; the other causes including active SLE (19%), infection (34.6%), malignancy (11.7%) and other causes (25.9%). The death rates from infection are consistent over time, they drop with active SLE, but increase with AVE the longer the SLE disease duration (**Table 1**). AVE is therefore a major comorbidity with significant consequences.

Table1. Causes of Death by Disease Duration

	< 5 years	5 to 10 years	10 to 20 years	≥ 20 years
No.	46	43	54	62
Infection	22 (48%)	16 (37%)	17 (31%)	16 (26%)
Active SLE	17 (37%)	7 (16%)	6 (11%)	9 (15%)
AS	6 (13%)	8 (19%)	14 (26%)	16 (26%)
Malignancy	4 (9%)	4 (9%)	5 (9%)	11 (18%)
Other	3 (7%)	13 (30%)	18 (33%)	19 (31%)

SLE and CAD: The Present (Subclinical and Preclinical Disease)

The Toronto Lupus Cohort aimed to identify AVE-risk in patients earlier in the SLE disease process. This involved looking at subclinical abnormalities such as intermedia thickening (IMT) versus plaque area in coronary arteries, perfusion studies and brachial artery flow-mediated dilation. Carotid ultrasound studies measuring IMT or plaque in thee thickening, plaque measurement is much more indicative of future CVD, with evidence showing an OR of 10 for plaque and 2.7 for IMT.(45) Moreover, plaque was also associated with highlight LDL and low HDL levels, whereas carotid IMT did not correlated with any traditional CV risk factor. Perfusion studies, specifically a dual isotope myocardial perfusion assay, in patients of mean 45 years, long disease duration (15 years) and low disease activity (SLEDAI 3.6), showed 40% to have perfusion defects also only 10% had a recorded

history of CAD. Moreover, many of these (asymptomatic) patients had significantly reduced ejection fraction, highlighting the 'silent' incidence of CAD in SLE patients. Finally, brachial artery flow-mediated dilation, works on the same basis as the coronary artery with a cuff being used to measure dilatation of the brachial artery, these results showed the fitness of the brachial artery and as a surrogate marker for the coronary artery. In 92 patients with SLE, 22% of patients with no symptoms of CAD had abnormal dilatation of the brachial artery. This, along with 35% of asymptomatic patients (from the perfusion studies) showing perfusion defects represents a significant group of patients harboring otherwise 'silent' CAD.

Professor Urowitz highlighted that subclinical disease is just the tip of the iceberg, with around 10-16% having had a cardiovascular event, but 30% of SLE patients have an abnormality that has not yet manifest as an event, representing a large percentage under the iceberg waiting to surface. Professor Urowitz studied preclinical disease by looking at the frequency of myocardial infarction (MI) prior to the diagnosis of SLE in 1837 patients from the SLICC cohort.(46) This study found that 23 MIs occurred before or after the first 2 years of disease, 16 MIs occurred at a mean of 6.1 ± 7.0 years prior to diagnosis and 7 occurred within the first 2 years of follow-up. Two possible explanations for MI prior to or early in diagnosis of SLE included (1) Earlier or low-grade disease activity not diagnosed, or (2) A concomitant alternative to a predisposition to atherosclerosis and SLE. Professor Urowitz highlighted the role of benign autoimmunity in SLE where patients have abnormal laboratory tests but no signs or symptoms of SLE, followed by full blown lupus. He continued to question why the same isn't true for AVE, which also develops overtime and its development may be facilitated by benign autoimmunity or may be SLE and AVE are occurring concomitantly and independently. Studies are needed to explore this hypothesis.

SLE and CAD: The Future (Controlling the Disease)

Professor Urowitz returned to the SLICC registry for atherosclerosis in SLE, including 43 centres from 16 countries, in North America, Europe, South America and Asia.(46) This group was formed to conduct a longitudinal study to (1) determine the incidence, prevalence and nature of atherosclerotic coronary artery disease (CAD) in SLE, (2) Identify associated risk factors for the development of CAD and its outcomes and to discern the contribution of disease and therapy to the occurrences of these risk factors and (3) Develop interventional approaches to modify identified risk factors. Professor Urowitz outlined the patient characteristics from this early disease/inception cohort of 1835 patients followed for 8 years. The cumulative prevalence of AVE was 3.5% at 8 years, at 10 years this had risen to 4.4%, further analysis revealed the incidence of AVE in this cohort was 0.46 per 100 person-years, much lower than the expected 8–13%. The University of Toronto (UTLC) looked at their own data from 1975–1987 (early cohort) and 1999–2011 (late cohort) of patients with any AVE diagnosed within the first 17 years of disease. The early cohort revealed an 11% incidence of AVE compared to 3.8% of the late cohort, with an incidence of 1.8 vs 0.44 incidence per 100 patient years. In fact, a reverse propensity score showed a significant (60%, p=0.0013) reduction in AVE in the early compared to the late cohort. The late cohort was similar to that reported by the SLICC registry, whereas a dramatic difference was seen in the early cohort. Professor Urowitz looked at the potential factors contributing to this difference, noting that hypertension, cholesterol and diabetes treatments were greater in the late cohort compared with the early cohort (**Table 2**). New medicine and new treatments were responsible for the improvements in hypertension and

cholesterol outcomes in the late cohort; likewise, improvements in outcomes for smokers have improved. Conversely, differences in both treatment and outcomes were not different between cohorts for diabetes. Control of risk factors with management and treatment interventions markedly improved across all parameters measured in the late cohort compared to the early cohort (**Table 3**). Likewise, the mean SLEDAI decreased.

Table 2. Patients Receiving Treatment for Hypertension, Cholesterol and Diabetes During the First 17 Years of Follow-up.

Treatment	Patients n (%)	Cohort	P Value
Anti-hypertensive	29/234 (12.4%)	1 (1975–1987)	0.0001
	124/262 (47.3%)	2 (1999–2011)	
Cholesterol	4/234 (1.7%)	1 (1975–1987)	0.0001
	63/262 (24%)	2 (1999–2011)	
Diabetes	11/234 (4.7%)	1 (1975–1987)	0.30
	18/262 (6.87%)	2 (1999–2011)	
Smokers	80 (34.2%)	1 (1975–1987)	0.0007
	54 (20.6%)	2 (1999–2011)	

Table 3. Control of Risk Factors.

Risk Factors	1975–94	1999–2017	P Value
% of years in normal BP	72.0	86.7	0.0001
% of years in normal cholesterol	39.7	72.3	0.0001
% of years in normal glucose levels	84.8	93.2	0.0001
% of years smoked	24.7	11.3	0.0001
Disease activity over first 5 years AMS	5.7±5.2	4.5±3.4	0.003

In conclusion, Professor Urowitz reiterated that good medicine and careful observation has improved AVE events in the modern era, significantly decreasing AVE disease and providing hope for continued improvements for the management and prevention of AVE events in patients with SLE.

Macrophage activation syndrome in SLE: Zahir Amoura (France)

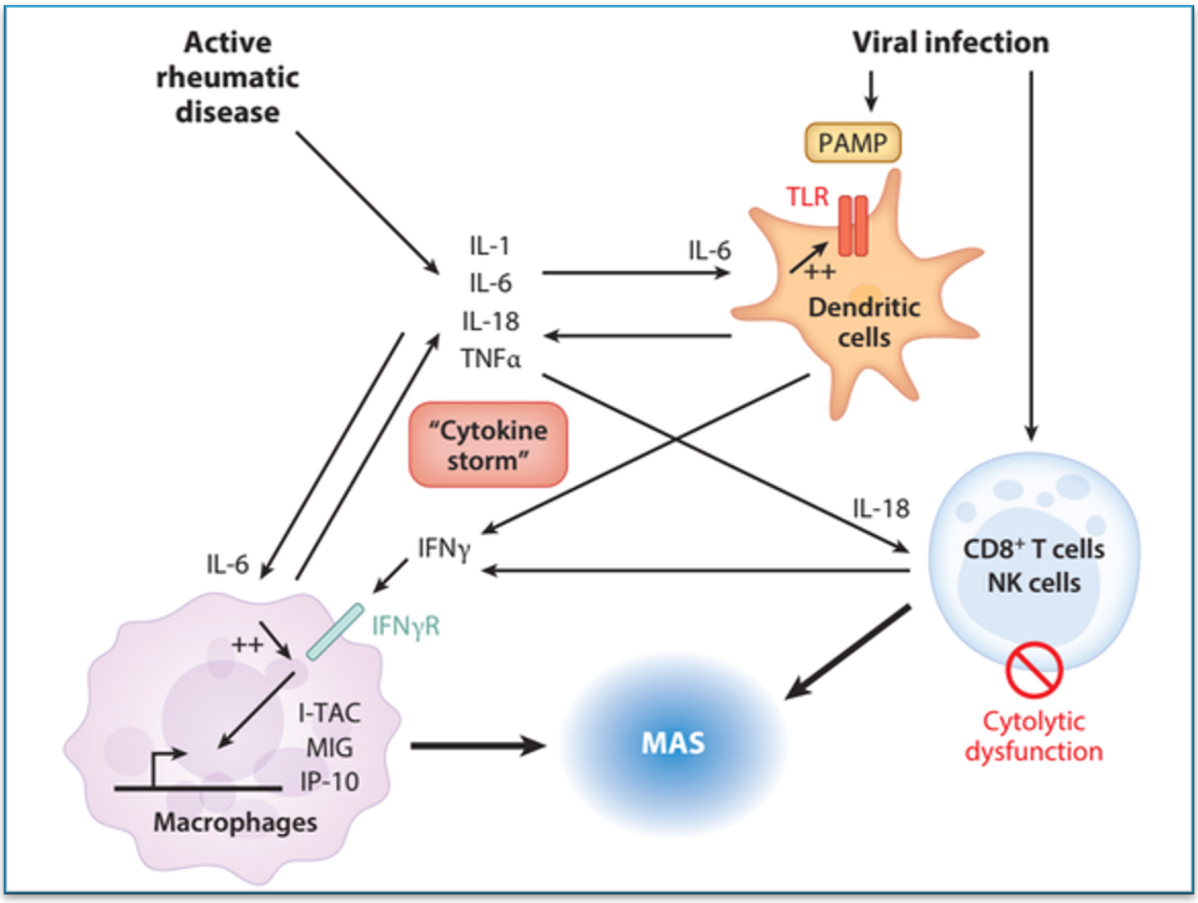
Professor Amoura's presentation highlighted the MAS can mimic a flare of the underlying disease because both entities share some common features, such as fever, lymphadenopathy, and splenomegaly and blood cytopenias. This overlap can hinder effective diagnosis and management of the underlying MAS. This presentation highlights the key features and management of MAS in patients with SLE.

Professor Amoura began his presentation by noting the importance of diagnosing macrophage activation syndrome (MAS) in systemic lupus erythematosus (SLE), highlighting the need for differentiatial diagnosis and the importance of effective treatment for SLE-associated MAS.

Hemophagocytic Lympho Histiocytosis: Definition

The term MAS refers to a subset of patients with hemophagocytic lympho histiocytosis (HLH) arising on a background of systemic autoinflammation or autoimmunity. HLH is an aggressive and life-threatening syndrome of excessive immune activation that mostly affects children but is also observed in adults. It is a genetic or sporadic disorder that can be triggered by a variety of events (eg. Infections) that disrupt immune homeostasis. HLH is divided into two definitions, primary HLH and secondary HLH. Primary HLH describes mendelian inherited conditions leading to HLH; mostly paediatric. It results from defects in the cytolytic function of cytotoxic T-cells and/or NK cells (perforin-mediated cytolytic pathway) and defects in inflammasome regulation. Secondary HLH occurs in adults as the result of infection (mainly virus as EBV, HIV and CMV) but also bacteria (tuberculosis), parasites (leishmania) and fungi, malignancies (lymphoma) and macrophage activation syndrome autoinflammatory (JIA, Still) or autoimmune disorders (SLE). Other causes (organ or stem cell transplantation, metabolic, traumatic, iatrogenic causes immunosuppression, vaccination, surgery, haemodialysis and, rarely, pregnancy). Since up to one-third of adults with HLH have more than one trigger, it is important to identify secondary figures during diagnosis. Hematophagocytosis refers to the pathological finding of activated macrophages, lymphocytes, leucocytes or platelets, characterized by cytopenia (>2 linages) and fever of unknow origin. Although the pathogenesis of HLH is unknown, it is thought to result from the inability of the immune system to restrict the stimulatory effect (cytokines storm) of viral triggers (**Figure 1**).

Figure 1. Pathophysiology of HLH: Cytokine Storm.



Hemophagocytic Lympho Histiocytosis: Diagnosis

Diagnostic criteria for HLH can be found in Table 1 and were developed for children, but are not validated in adults.(47)

Table 1. The Diagnosis of HLH Can Be Established If Criterion 1 or 2 Is Fulfilled.

1. A molecular diagnosis consistent with HLH

2. Diagnostic criteria for HLH fulfilled (5 of the 8 criteria below)
• Fever
• Splenomegaly
• Cytopenias (affecting >2 of 3 lineages in the peripheral blood)
  ○ Hemoglobin <90 g/L (hemoglobin <100 g/L in infants <4 wk)
  ○ Platelets < 100 x 109 /L
  ○ Neutrophils <1.0 x 109/L
• Hypertriglyceridemia and/or hypofibrinogenemia
  ○ Fasting triglycerides >3.0 mmol/L (ie, >265 mg/dl)
  ○ Fibrinogen <1.5 g/L
• Hemophagocytosis in bone marrow or spleen or lymph nodes. No evidence of malignancy.

- Low or no NK cell activity (according to local laboratory reference) Ferritin >500 µ,g/L
- sCD25 (ie, soluble IL-2 receptor) >2400 U/ml

It is important to note that hematophagocytosis is not mandatory for the diagnosis of MAS and hematophagocytosis alone is not sufficient for the diagnosis of MAS.

SLE Associated MAS

Macrophage activation syndrome is a life-threatening complication of SLE with an estimated prevalence of 0.9%. (48)It is, however, difficult to diagnose and existing data, particularly in adults, is limited.(49, 50) Professor Amoura presented data from a French nationwide study of 103 episodes in 89 adult SLE patients, most of whom were female with a median age of 33 years.(51) MAS episodes were new in 46% of patients, the rest having MAS within years of SLE diagnosis. All patients had fever and one third had splenomegaly, hepatomegaly or adenomegaly. In addition, 30–40% had skin rashes and arthritis; although these two symptoms were due to SLE flare rather than MAS. Most patients had severe clinical manifestations including acute lung injury (15%), seizures (10%), confusional state (18%), myocarditis (21%) and pericarditis (23%). Although proteinuria was present in >10% of patients, kidney disease was rare, therefore the presence of proteinuria during SLE associated MAD does not mean there is lupus nephritis. Laboratory features included increased ferrintnemia, presence of neutropenia, anemia and thrombopenia but hypofibrinogenemia but hypofibrinogenemia, which is a marker of MAS, was rare. Hemophagocytic activity was present in two thirds of patients. In contract to SLE flare, CRP was often increased as was procalcitonin, in MAS without infection. Severe clinical features of MAS can include multiple organ disfunction and in this study 32% of patients were referred to the intensive care unit, (ICU), where 5% of the patients died. Multivariate analysis revealed that thrombopenia and high CRP levels were the only variables associated with increased risk of admission to the ICU. Clinical and serological manifestations of SLE flares included arthritis (37%), lupus skin rash (43%), low complement C3 (56%) and increased dsDNA (63%). Key differences between MAS and SLE flare are summarized in **table 2**.

Table 2. Differential Diagnosis: MAS and SLE.

	MAS	SLE Flare
Arthritis	-	+
Photosensitive skin rash	±	+
Splenomegaly	+	±
Low C3	-	+
Increased anti-dsDNA	-	+

Increased CRP	+	-
Increased PCT	+	-
Hyperferritinemia	+	-
Low fibrinogen	+	-
Increased fasting triglycerides	+	-
Hemophagocytosis	+	-

Concomitant infection was found in one third of episodes (39/103) and resulted from pyogenic bacteria such as e coli staphylococcus aureus. Epson Barr virus was also found in 22 (30%) cases and cytomegalovirus in 12 cases.

Management of MAS

Management of MAS involves treating the cause, ie. the lupus flare and or infection. Non-specific treatments includes high-dose IV steroids, with the addition of immunosuppressive treatment in cases of severe organ involvement. Cyclophosphamide and etoposide are most commonly used for lupus flare as well as cyclosporine and intravenous immunoglobulin. In Professor Amoura's current study, patients were given steroids alone as first line treatment and 60% of patients were treated successfully. Thirty-two episodes were managed with second line treatment with IV cyclophosphamide or etoposide and five episodes were treated with rituximab. Professor Amoura highlighted that although his study showed that the majority of patients were successfully treated with glucocorticosteroid and immunosuppressive drug, biologic therapies targeting specific cytokines may be appropriate, including high dose IL-1 inhibition, IL-6 blockade, and anti-IFN-γ therapy.

Conclusion

Professor Amoura concluded by emphasizing MAS is a severe complication of SLE that results in one third of patients being hospitalized in the ICU. MAS could be the first manifestation of SLE and is mostly a "one-off" event. Investigations should include identification and treatment of concomitant infection. Successful management of MAS can be achieved in two thirds of all cases with steroids and immunosuppressive drugs like cyclophosphamide and etoposide.

Evidence-based treatment of SLE comorbidities: George Bertsias (Greece)

Professor Bertsias presentation described the primary prevention strategies for systemic lupus erythematosus (SLE) comorbidities including cardiovascular diseases, osteoporosis and infection as well as the screening and treatment options for key comorbid diseases in patients with SLE.

Professor Bertsias began his presentation highlighting the higher prevalence of comorbidities in patients with SLE versus the general population. These comorbidities have a diverse frequency and can occur early or late in the disease course, affect both males and females and often present as multimorbidities.(52) These comorbidities have a negative impact on patients with SLE, including

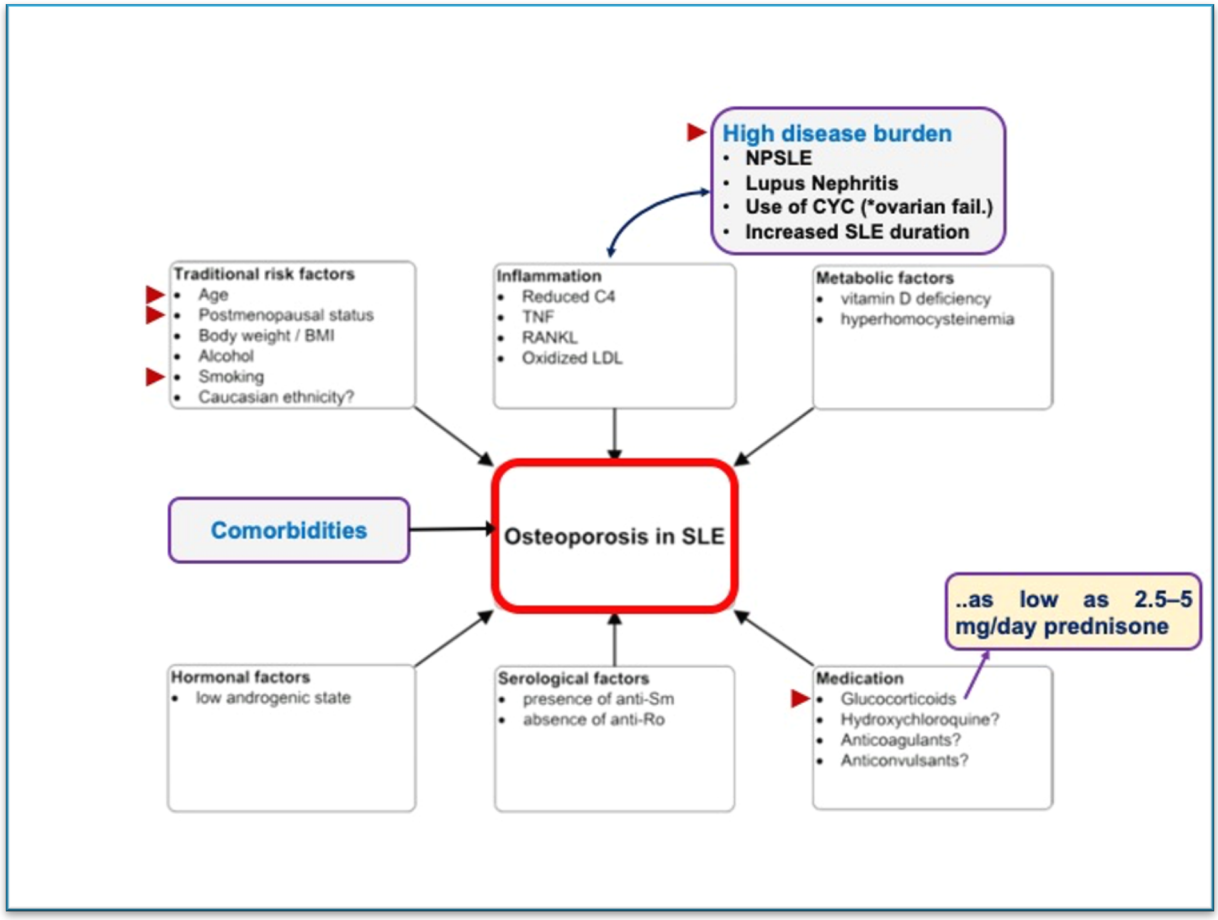
reduced quality of life, increased organ damage, increased hospitalisation and increased mortality.(53-57)

Professor Bertsias focused his presentation on the treatment of three SLE comorbidities, including osteoporosis, cardiovascular disease and infection, highlighting the importance of identifying modifiable risk factors, early diagnosis and which general and SLE-specific treatments are of benefit.

Osteoporosis: Fragility Fractures in SLE

There are multiple risk factors responsible for low bone mineral density (BMD) and increased bone fragility in SLE (**Figure 1**), importantly cumulative exposure to glucocorticoids has as a significant effect on bone health.(58-63)

Figure 1. Risk Factors for Low BMD and Increased Bone Fragility in SLE.



Prevention and treatment of low BMD and osteoporosis in SLE it important to assess and counsel patients for risk factors and evaluate fall risk, measure for decreases in height, lifestyle changes including smoking cessation, abstinence from alcohol and regular weight bearing exercise and normal weight/BMI maintenance. It is also important to ensure minimisation of glucocorticosteroids (GCs)and also consider use of immunosuppressive or biologics. DEXA scans are also important in some patients (ie. GCs, history of fragility fractures, post-menopausal women, premature

menopausal or hypo-gonadal and patients >50 years old with risk factors. Vitamin D and calcium supplementation are also important.(64)

Measures for preventing and treating BMD or osteoporosis in SLE in patients who are postmenopausal included calcium, vitamin D and bisphosphonates. Measurement of GC-adjusted FRAX score is key in determining which of these treatments is most important for the individual.(64-66) The situation is however less clear in premenopausal and younger women. The situation is less clear in patients who are premenopausal or <50 years old. Patients with fragility fractures and Z scores <-2 or T scores <-2.5 should be treated with calcium, vitamin D and bisphosphonates. Those on GCs for ≥3 months or have taken GCs for ≥3 months within the last 12 months, need to be risk assessed for osteoporotic fractures using FRAX-based (GC-adjusted) of ≥40 years, rapid bone loss (≥10%/year) or those undergoing continue GC (≥7.5 mg/day) for ≥6 months. Treatment of these patients should include calcium, vitamin D and bisphosphonates if they are considered moderator to high risk. Medications used to increase bone mass density and reduced osteoporosis are generally equal in terms of efficacy in the general population; however, there are some considerations in choosing the most appropriate treatment (**Table 1**).

Table 1. Pharmacological Interventions for Bone Density and Osteoporosis

Drug class	Consideration in SLE
Calcium Supplementation.	• In LN-CKD, limit to total intake (dairy + suppl.) to maximum 1000 mg/day
Vitamin D Supplementation	• In LN-CKD, various analogues can be used to treat concomitant hyperparathyroidism / metabolic bone disease
Biphosphonates	• Efficacious, similar to other population groups • Cautious use in CrCl <35 ml/min • Avoid in women with pregnancy contemplation
Denosumab	• Safe in SLE • Efficacious in GC-induced osteoporosis • Pregnancy class C
Teriparatide	• Safe in SLE • Pregnancy class C

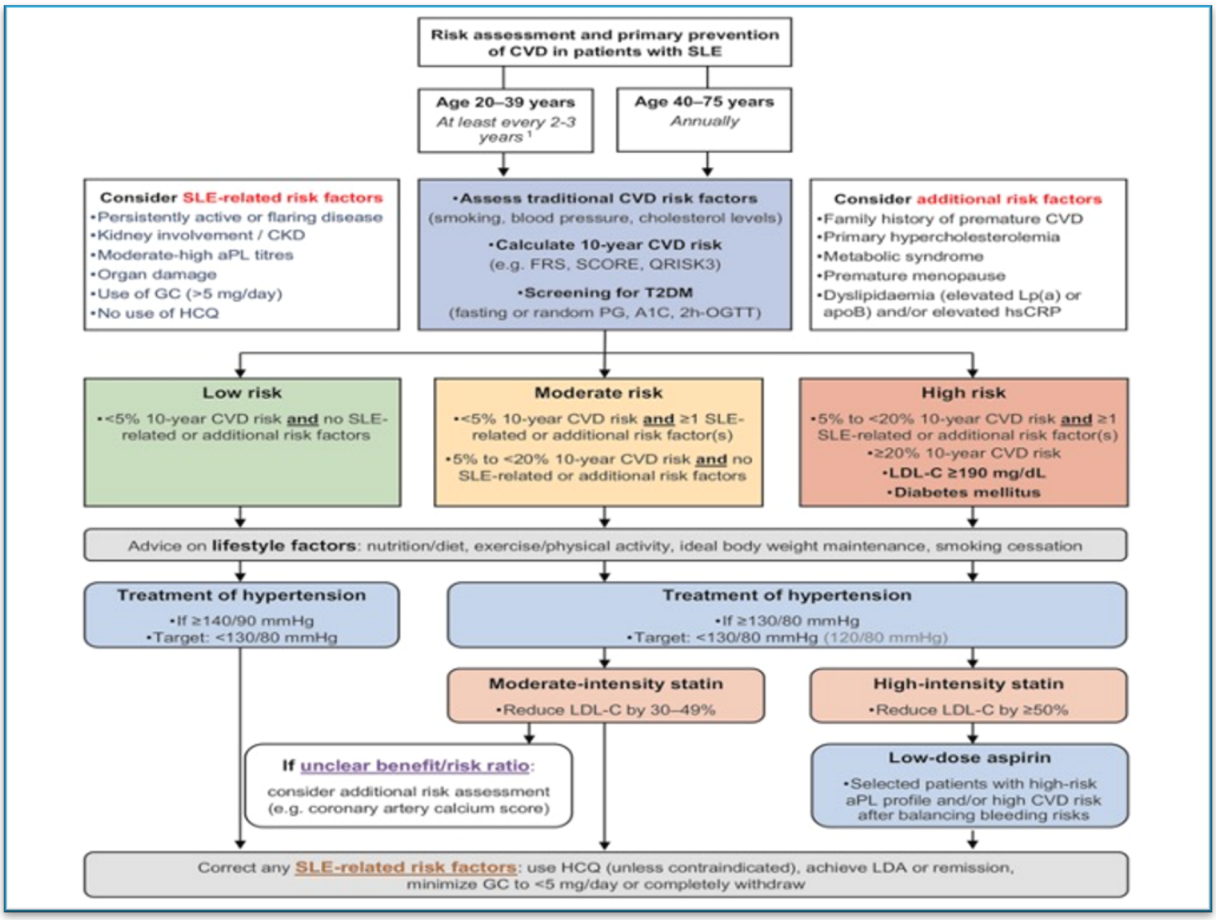
Atherosclerosis in SLE

Patients with SLE are at increased risk for clinical and subclinical atherosclerosis. Traditional risk factors account only for a proportion of this risk, with measures like the Framingham risk score underestimate the risk posed to SLE patients.(67-74) SLE-specific cardiovascular risk factors include disease duration, high disease burden, disease activity, organ damage, presence of antiphospholipid antibodies, glucocorticosteroids, and lack of hydroxychloroquine use, which has a cardioprotective effect.

Risk prevention in SLE is important. There are a number of trials supporting drugs, namely aspirin and statins in the primary prevention of SLE; however, both aspirin(75-78) and statins (79-82)require further investigation and better data to fully support their use. There is a need to rethink the use of aspirin for the primary prevention of CVD, given that it has a very marginal effect in the general population.(83-87) Indeed, the 2019 AHA/ACC guidelines recommend against aspirin in individuals older than 70 years and provide a weak recommendation (Class IIb) that aspirin might be considered among adults aged 40–70 years.

Professor Bertsias highlighted that SLE patients who spend longer in a low disease activity state have reduced cardiovascular risk;(88-90) looking at this along with revised AHA/ACC guidelines, Professor Bertsias explored if these could be extrapolated for patients with SLE,(91) highlighting the management of risk factors is important in improving outcomes (**Figure 2**).

Figure 2. Risk Assessment and Primary Prevention of CVD in SLE.



Infection in SLE

Infections represent a major cause of morbidity and mortality in SLE, with advanced age, disease activity, nephritis, high GC usage (≥7.5), immunosuppressive therapies, low complement, recent hospitalisation and neutropenia/lymphopenia all increasing risk.(92-98)

The prevention of infection focuses on GC reduction, use of hydroxychloroquine, monitoring of drug toxicity and use of vaccinations. Early recognition and management of severe infections in patients with SLE is important with red flags including high grade fever >39.4 C, duration of fever >5-7 days (or >3 days if under potent immunosuppressive treatments), deteriorating status severe leukopenia (esp. ANC <500-1000/mm^3) and if the fever is combined with any of the following clinical signs/symptoms: Clouding of the conscious level; intense headache or nuchal pain; difficulty swallowing; rash; chest pain; shortness of breath; intense abdominal pain; bloody stools; swelling of a limb; and signs of skin infection (redness, swelling). The treatment paradigm for sepsis has also changed with earlier diagnosis, early treatment (antibiotics), and early adjuvant treatment. Use of the quick SOFA is important in enabling this.(99-102)

Conclusions

Professor Bertsias concluded by summarizing key points from his presentation, namely, SLE patients are at increased risk for comorbidities as a result of both traditional and disease-specific risk factors (high inflammatory burden, exposure to toxic treatments, particularly glucocorticoids). Despite the lack of high-quality evidence, preventative strategies pertaining to the general population seem to be effective also in SLE; in this context, the Treat-to-Target principle may offer additional benefit by reducing the risk for comorbid diseases. Aspirin and statins can lower the risk for CVD in patients with SLE but we need better evidence for their personalized used based on risk stratification. In sepsis, early recognition and supportive/empiric treatment is of paramount importance.

Hot Topic Lecture

APS in SLE patients: Best treatment practice: Munther Khamashta (UK)

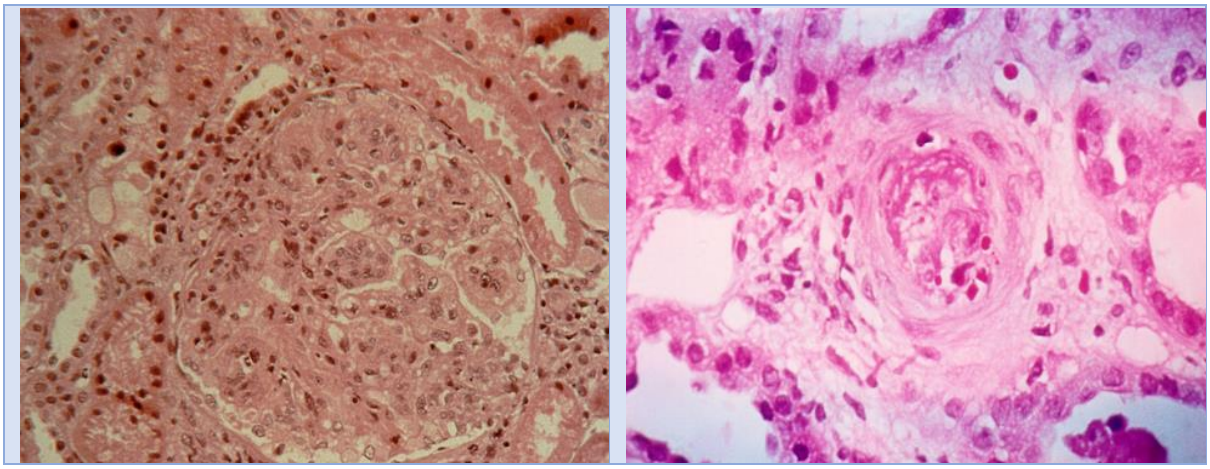
Professor Khamashta reviewed the diagnosis, classification, primary prevention and treatment of APS in both pregnant and non-pregnant individuals. Highlighting the value of recent revisions to classification criteria, development and validation of GAPS scoring, imperfections of exciting treatments like aspirin and heparin patients with obstetric APS, with long-term anticoagulation remaining the treatment of choice for thrombotic APS.

Professor Khamashta began his presentation by giving a short overview of the major clinical features of APS, including recurrent arterial / venous thrombosis; recurrent pregnancy loss; thrombocytopenia; livedo reticularis – a prominent marker; primary or secondary to connective tissue disease (e.g. lupus).(103) Many other clinical features are linked to antiphospholipid syndrome (APS) including leg ulcers, transverse myelitis, headache, chorea, epilepsy, cognitive disorders, heart valve lesions, haemolytic anaemia, pulmonary hypertension. It is unknown whether these are thrombotic in nature or not. Often, these manifestations are missed by doctors from disciplines other than rheumatology.

Classification criteria for APS have changed little since 1999(104, 105) and Professor Khamashta highlighted that now is the time for change. Recently, recommendations for the management of APS in adults were published by the European League Against Rheumatism based on evidence from a systematic literature review and expert opinion.(106) Professor outlined the important features of vascular disease in both SLE and APS (**Table 1**).

Table 1. Vascular Disease in SLE and APS.

SLE	APS
Small vessels	Large and small vessels
Vasculitic nature	Thrombotic nature
Immune complex mediated	Coagulation disorder
Immunosuppression	Anticoagulation



Patients with SLE can be easily misdiagnosed and miss treated with immunosuppression, when patients with APS need treating with anticoagulation. Indeed, 30-40% of patients with SLE are aPL+ and 50% of patients originally diagnosis with SLE have been shown to develop APS after 10 years,(107) whereas 5% of patients originally diagnose with APS develop SLE after 10 years.(108) Therefore, there is a need for primary prevention therapies in patients with SLE, as highlighted by Tincani et al (2017).(109)

The risk of thrombosis in patients with aPL is high (3-4%) per year across healthy men, unselected aPL+ patients, obstetric patients and SLE patients. Assessment of aPL related manifestations includes a full thrombophilia screen, assessment of autoimmune disease activity, cardiovascular risk factors, presence of aPL and, importantly, lupus anticoagulant (LA);(110) the presence of LA combined with anti-cardiolipin (aCL), and anti-β2-glycoprotein I (β2GPI) antibodies indicates the patients are at higher risk of APS.(111) Therefore primary prophylaxis is important in these patients.

Primary Prevention of APS

The development and validation of the Global Anti-Phospholipid Syndrome Score takes into account, not only APS, but also cardiovascular risk factors(112) has been validated in France and Japan.(113, 114) Professor Khamashta highlighted that this score would be useful to monitor the risk for a single patient during the follow-up and determine when to start primary thromboprophylaxis and also to stratify patients according to their risk when enrolling them into controlled trials.

There are no trials providing definitive evidence for aspirin, hydroxychloroquine or warfarin in APS. One randomised controlled trial looking at aspirin found no difference. The ALIWAPAS trial comparing aspirin and low-dose warfarin (INR 1.5) provided no answers because of low recruitment numbers (82 vs 84) and only four events per group.(115)

Professor Khamashta reviewed best treatment for venous thrombosis and atherothrombosis, highlighting results from a 1995 study, which became standard of care.(116) This study showed that treatment of patients with high intensity INR (>3) the chance of recurrent thrombosis over 6–7 years was low. However, haematologists did not accept this SOC for venous thrombosis because of the high risk of bleeding; however management of atherothrombosis should be continued even when aPL become negative.(117) Long-term use of oral anticoagulants for atherothrombosis in APS is

recommended as the risk of new thrombotic events in those APS patients who stop anticoagulation is high, even in those patients where aPL antibodies have been absent for a long time. (118)

Direct Oral-anticoagulants and APS

The future of treatment for APS includes direct thrombin inhibitors (dabigatran) and Factor Xa inhibitors (rivaroxaban). There is much experience with DOACs in healthy patients and DOACs) could be considered in APS patients with venous thrombosis who are not able to achieve a target INR despite good adherence to VKA or those in whom VKA is contraindicated (e.g. allergy or intolerance to VKA).(119) Rivaroxaban should not be used in patients with APS with triple aPL positivity. (120) Based on the current evidence, the use of DOACs in patients with APS and arterial events is not recommended due to the high risk of recurrent thrombosis. For patients with recurrent arterial or venous thrombosis despite adequate treatment, addition of LDA, increase of INR target to 3.0–4.0 or switch to low molecular weight heparin may be considered. However, EULAR recommendations reviewed and concluded that, whilst considering data from the study by Pengo et al, that although rivaroxaban should be avoided in triple positive patients, they could be used in patients with no major events and those who are intolerant to warfarin or have atherothrombosis.(120) However, EMA (April 2019) suggested DOACs should not be used in APS and patients should be given the choice to switch back to warfarin. Further discussion is needed to ensure APS patients can access the most effective treatments for thrombosis.

Recurrent Thrombosis

There are several options for management of recurrent thrombosis in patients with APS, including the addition of antiplatelet therapy (including low dose aspirin or clopidogrel), immunosuppressive drugs, statins (121)and hydroxychloroquine.(122) Low molecular weight heparin,(123) rituximab (124) and hematopoietic stem cell transplantation (HSCT)(125) are also options for recurrent thrombosis in APS. A study of autologous HSCT in SLE and APS patients showed that 9.3% of aPL negative patients were reported after HSCT and 73% were able to discontinue anticoagulation following HSCT.(126)

Patients presenting with catastrophic APS are rare, with <1% of APS patients affected. (127) Thrombotic microangiopathy is common affecting patients in many ways including skin, kidney, brain and heart. The common characteristics of CAPS include acute onset, multiple vascular occlusion in <1 week, organ involvement (as described) , high titres of aPL, and common precipitating factors like infection. Prognosis is poor with 35% mortality. Treatment for CAPS includes plasma exchange, IVIG, rituximab and eculizumab.(128)

aPL-associated thrombocytopenia affects 30% of patients with APS and is associated with infrequent bleeding. Severe aPL-associated thrombocytopenia is rare but is occasionally the first manifestation of APS. However, aPL-associated thrombocytopenia does not protect against thrombosis(129). Recommendations for the management of mild to moderate aPL-associated thrombocytopenia (platelets >$50x10^9$/L) includes no treatment, just careful monitoring. Severe aPL-associated thrombocytopenia (<$50x10^9$/L) needs treatment with corticosteroids, or in corticosteroid-resistant cases, low dose aspirin, IVIG, immunosuppressives, warfarin, splenectomy, antimalarials, danazol, dapsone, rituximab and eltrombopag.

aPL and Pregnancy Loss

In patients with three consecutive miscarriages, the chance of having APS is 10%, there is a 20% chance of APS with loss of foetus in the 2nd or 3rd trimester and 30% chance in patients with intrauterine growth restriction and late lost (still birth). However, with treatment there is an 85% success rate.

Recommendations for the management of pregnancy in aPL+ women include aspirin, heparin or a combination of the two.(130) If aspirin or heparin fails, the addition of low-dose steroids (in Europe)(131) or IVIG (USA),(132) hydroxychloroquine(133) or statins(134) are effective. In severe cases plasma exchange is effective. EULAR has also published recommendations.(135)

Professor Khamashta highlighted results from the Euro-phospholipid study of 1000 APS patients(127) across 20 centres, 53% of whom had primary APS and 42% who had SLE. Over a 10 year period DVT, stroke/TIAs, pulmonary embolism and myocardial infarction were all significantly reduced in the general population with warfarin.(136) In those with pregnancy, outcomes were significantly improved with aspirin and heparin (**Table 2**). Therefore, it is important to counsel the mother on the risk of premature birth.

Table 2. APS and Obsetric Manifestations over 10 years (n=1,000).

	Baseline	10 years
Pre-eclampsia	5%	6%
Early pregnancy loss <10 weeks	35%	17%
Late pregnancy loss ≥10 weeks	17%	5%
Live birth with prematurity	11%	48%
Live birth with IUGR	2%	26%

Conclusions

Professor Khamashta concluded, with the following key points:

1. Clinical and laboratory Classification Criteria are being revised
2. Global APS Score has now been developed and validated
3. Although treatment with Heparin and Aspirin in patients with obstetric APS has improved pregnancy outcome, it remains imperfect
4. Long-term anticoagulation remains the treatment of choice in thrombotic APS

State-of-the-art Lecture: Measuring Outcomes

T2T, LLDAS and remission: Operational definitions meet reality?: Andrea Doria (Italy)

Professor Doria examined the existing definitions of treat-to-target (T2T) and low disease activity (LDA) in SLE, questioning which are achievable targets and do these improve disease outcomes. He also questioned elements that maybe missing from the definitions and their utility as endpoints in randomised controlled trials and as treatment targets in clinical practice, bringing to the fore the question of what the simplest definition of remission and its performance in predicting damage.

Professor Doria began his talk by highlighting the complexity of the T2T and LDA topic, drawing reference to T2T approaches in other therapeutic areas like cardiology, diabetes and rheumatoid arthritis and approaches used in these diseases,(137-140), which involves (1) identifying the target (2) therapeutic intervention, (3) reassessment and (4) modification of treatment if the target is not met.

The treat-to-target principle for systemic lupus erythematosus (SLE) was published in 2014 and focuses on achieving remission or, in the absence of this, LDA.(141) These principles are similar to RA, yet remission and disease activity are less clear in SLE in clinical practice. Disease activity in lupus can be defined as aabnormalities due to ongoing immune inflammatory pathways involved in SLE, which are mostly reversible.(142) Disease activity in SLE in clinical practice presents as inflammatory and non-inflammatory clinical manifestations and serological manifestations (**Table 1**).(142)

Table 1. Clinical and Serological Markers of SLE Disease Activity.

Clinical disease activity	Serological disease activity
Inflammatory related manifestations	**Autoantibodies**
Skin rash	Anti-dsDNA
Polyartritis	Anti-C1q
Serositis	**↓ C3 and/or C4**
Glomerulonephritis	
Cerebritis	
Non-inflammatory manifestations	
Hematologic cytopenia	
Neurological manifestations (cognitive dysfunction, psychosis, etc)	
Ischemic/microischemic lesions (antiphospholipid antibody-mediated)	

In clinical practice, (serologically active clinically quiescent) remission is defined as the absence of signs, symptoms, urinary and haematological abnormalities due to the disease immune pathways and persistence of serological abnormalities. Complete remission (clinical and serologic) is defined as

the absence of signs, symptoms, urinary and haematological abnormalities due to the disease immune pathways and negative anti-DNA, normal C3 and C4.(142) However, studies of remission in SLE (1985–2014) have used different definitions of clinical remission.(143) More recently a framework for defining remission in SLE (DORIS) has been developed.(144)

Framework for Remission in SLE and LDAS in SLE

The DORIS framework for remission in SLE comprised four domains, clinical disease activity, serological activity, treatment and duration. Principles were also developed to further guide this definition of remission including:(144)

- Definitions of remission in SLE will be worded as follows: remission in SLE is a durable state characterized by … (reference to symptoms, signs, routine labs).
- For defining remission in SLE, a validated index must be used, e.g., clinical-SLEDAI = 0, BILAG 2004 D/E only, clinical ECLAM =0; with routine laboratory assessments included and supplemented with Physician Global Assessment.
- A distinction will be made between remission off therapy and remission on therapy, where remission-off-therapy requires the patient to be on no other treatment for SLE than maintenance antimalarials; and remission-on-therapy allows patients to be treated with maintenance antimalarials, stable low-dose glucocorticoids (prednisone ≤5 mg/d), stable maintenance immunosuppressives and/or stable maintenance biologics.

The task force also agreed that the most appropriate outcomes (dependent variables) for testing the prognostic value (construct validity) of potential remission definitions are: Death, Damage, Flares, and measures of Health-related quality of life. In addition, a definition of lupus low disease activity state (LLDAS) has been created and is defined as SLEDAI-2K ≤4, PGA ≤1, prednisolone ≤7.5 mg/d and use of HCQ, immunosuppressives and biologics if required.(145) An overview of definitions of remission and LLDAS can be found in **Table 2**.

Table 2a. Minimum Requirement for Fulfilling Definitions of Remission. (144, 146-150)

Definition	Disease activity	PGA	Pred	HCQ	IS	Biologics
Zen, 2015	cSLEDAI-2K=0	-	≤5 mg/d	Yes	Yes	Yes
Doris, 2017	cSLEDAI-2K=0	≤0.5	≤5 mg/d	Yes	Yes	Yes
GLADEL, 2017	SLEDAI≤0	-	≤5 mg/d	Yes	Yes	Yes
Polackek, 2017	cSLEDAI-2K=0	-	No	Yes	No	No
Tselios, 2019	cSLEDAI-2K=0	-	Yes	Yes	Yes	Yes
Alarcón, 2019	SLAM=0	-	≤5 mg/d	Yes	No	No

Table 2a. Minimum Requirement for Fulfilling Definitions of Low Disease Activity. (145, 147-150)

Definition	Disease activity	PGA	Pred	HCQ	IS	Biologics
APLC, 2016	SLEDAI-2K≤4	≤1.0	≤7.5 mg/d	Yes	Yes	Yes
GLADEL, 2017	SLEDAI≤4	-	≤7.5 mg/d	Yes	Yes	Yes
Polackek, 2017	cSLEDAI≤2	-	No	Yes	No	No
Tselios, 2019	cSLEDAI≤2	-	Yes	Yes	Yes	Yes
Alarcón, 2019	SLAM≤3	-	≤5 mg/d	Yes	No	No

Similarities and differences exist between the key Zen and DORIS definitions of remission as outlined in **Table 3**.

Table 3. Similarities and Differences between ZEN and DORIS Definition of Remission.

	ZEN[1] definition			DORIS[2] definition			
	Clinical		Complete	Clinical		Complete	
	on Cs	off CS		on TX	off Tx	on TX	off Tx
cSLEDAI=0	✓	✓	✓	✓	✓	✓	✓
PGA<0.5	-	-	-	✓	✓	✓	✓
Anti-dsDNA/low C3/C4	✓	✓	-	✓	✓	-	-
HCQ/CQ	✓	✓	✓	✓	✓	✓	✓
Prednisone ≤5 mg/d	✓	-	-	✓	-	✓	-
Immunosuppressants	✓	✓	-	✓	-	✓	-
Biologics	✓	✓	-	✓	-	✓	-

Remission and LLDAS Targets

Five-year remission and damage accrual in different SLE cohorts show that consistent numbers (35–42%) of patients across the cohorts achieved remission according to DORIS (151, 152) and Zen definitions (88, 146, 153).Moreover, a study of 1,356 patients over 30 years by Petri et al showed that there is an overlap between remission and LLDAS definitions (145). Data from the Toronto Lupus Clinic showed that 10 year remission was achieved by 10% and LDA by 18% of patients, moreover, patients with LDA spent 76% of their time in remission compared with 47% of those not achieving remission or LDA .(149)

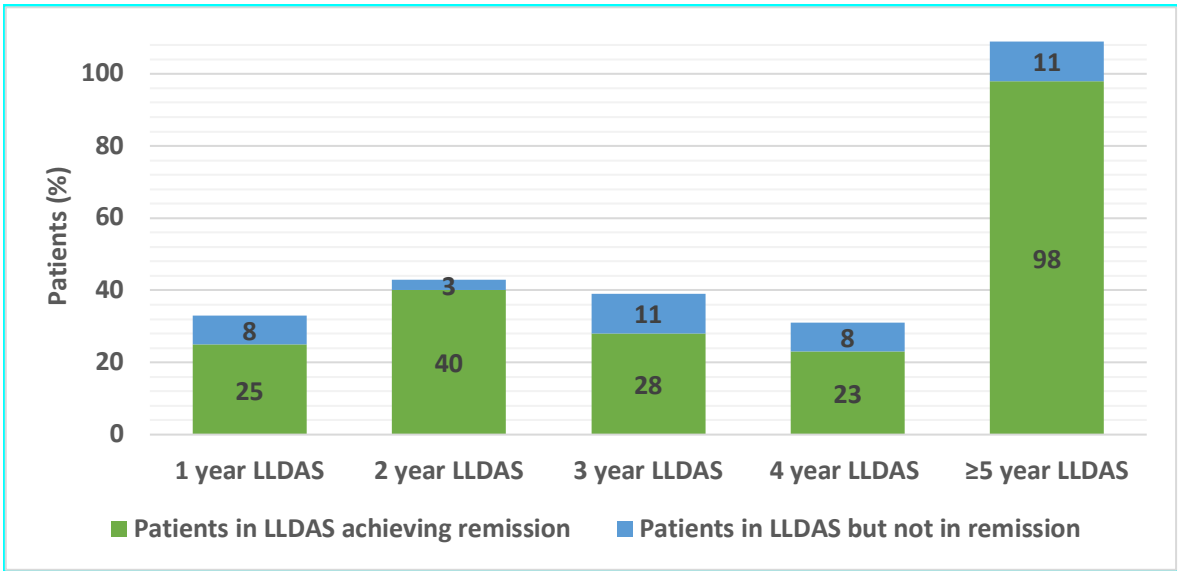
Remission and LDA and Disease Outcomes

Five-year remission and damage accrual data from different cohorts indicate that patients who achieve prolonged remission have less damage than those who don't according to both Zen and Doris definitions.(88, 146, 151-153) Moreover, different durations and levels of remission result in different levels of outcomes in patients; interestingly, there was an inverse relationship between remission and damage accrual.(154) These data compliment data from Petri et al (2018), which looked at rates of new damage in subgroups defined by previous levels of disease activity.(90) Another study looking at patients achieving remission on corticosteroids, found that these patients experienced higher levels of damage on corticosteroid treatment and that duration of remission, without corticosteroids, is more important than level of remission in the short term.(154) These data are supported by that of Franklyn 2016, which showed that patients in a LLDAS were at lower risk of damage accrual.(145) Similar data have been found in studies by Petri et al and the GLADEL cohort. (90, 147) Moreover, remission and LDA are associated with improved QoL, decreased mortality and reduced healthcare costs. (150, 151, 155-157)

LDA and Remission: What is Missing?

LLDAS is associated with decreased damage progression in Caucasian patients with SLE but does overlap with remission, with a high percentage of patients with LLDAS who fulfilled the definition of remission **(Figure 1)** and 90.9% having a clinical SLEDAI-2K of 0.(158)

Figure 1. Patients with LLDAS Achieving Remission Criteria: Overlap.



Professor Doria noted that the overlap in patients with remission and LDDAS is to be expected. This is largely because the Zen, Doris and LDDAS definitions were based on studies with the same treatments (hydroxychloroquine, immunosuppressants and biologics), SLEDAI and physician attitudes to PGA and prednisolone, which can be used differentiate remission levels in these patients.(144-146) Moreover, the LLDAS is based on SLEDAI-2K, which is a categorical instrument used to identify the presence or absence of disease in each organ system and is, therefore, not able to differentiate between the level of disease activity in each organ domain. Therefore, LLDAS should

be seen as a more liberal definition of remission rather than a description of disease activity, the SLE-DAS, much like the DAS-28 used in rheumatoid arthritis.(159) SLE-DAS enables accurate definitions of SLE remission and LDA as achievable targets in disease management.

Remission and LDA: Suitable Endpoints in Randomised Controlled Trials?

A number of studies have shown that remission and LLDAS can be used successful as endpoints in RCTs, including those with azathioprine, mycophenolate mofetil (MMF)(160) for remission and those with belimumab(161) in a post hoc analysis of BLISS 52 and 76 and anifrolumab for LLDAS as shown in the MUSE and ADDRESS Studies.(162, 163)

Remission and LDA as Treatment Targets in Clinical Practice

An Italian multicentre study of 466 patients from 24 lupus cohorts demonstrated that both LDA and remission can be used as treatment targets in patients with different refractory manifestations treated with prednisone (<5 mg /day), hydroxychloroquine, MMF, methotrexate, azathioprine and cyclosporine. In total, 64% of patients spent >50% of time in LDA and 42.9% in remission.(164)

Simplest Definition of Remission with that Can Best Predict Damage

Different definitions of remission have been tested in a 5-year multicentre cohort of 646 SLE patients. (165) The study analysed six definitions of remission, including both serological and clinical disease activity status, and found that a consistent proportion of patients achieved remission outcomes, with the cSLEDAI=0 definition being most liberal and DORIS definition (cSLEDAI=0 + prednisone $\leq$5 mg/day, plus PGA <0.5). The performance of these different definitions in predicting damage accrual found that duration of remission was inversely correlated with damage accrual, moreover all definitions of remission showed that remission was a negative predictor of damage, with SLEDAI-2K being the most pragmatic outcomes measure for SLE studies in the short to medium term.

Conclusions

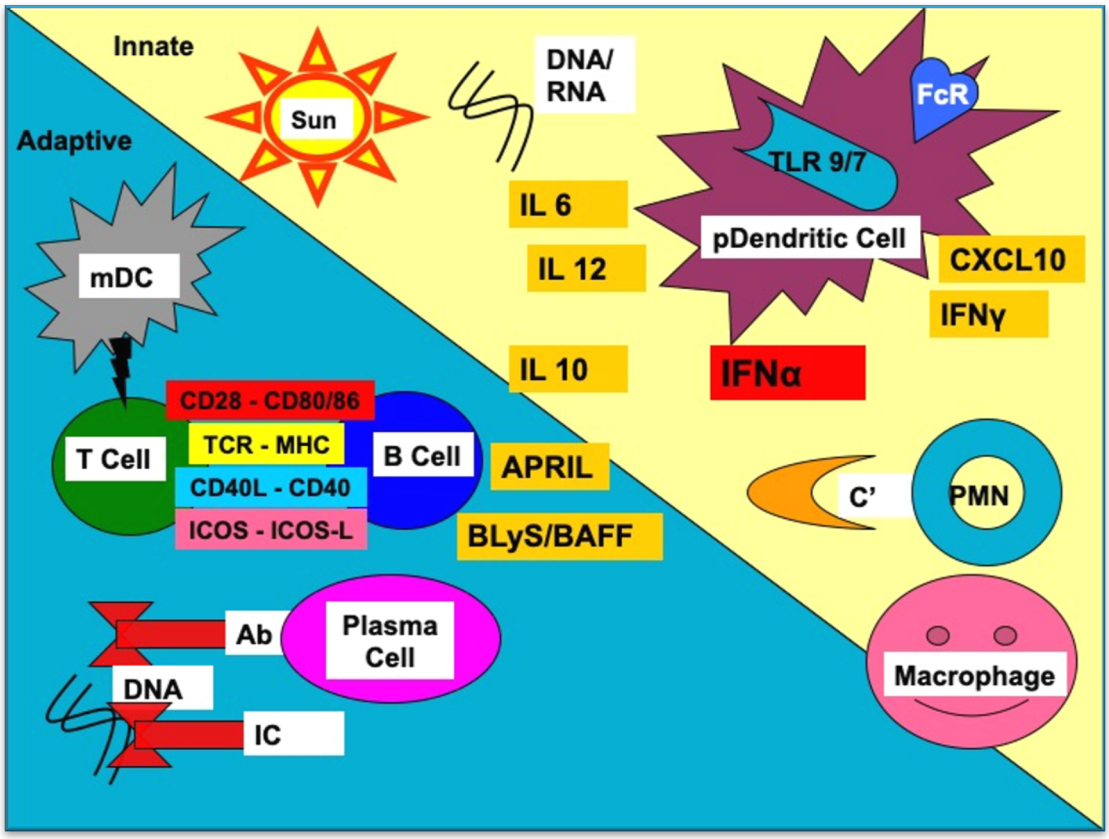
Professor Doria concluded by highlighting that remission is an achievable target in SLE patients and that, up to now, LDA has not been properly defined. He also noted that cSLEDAI=0 seems to be a good outcome measure in RCTs, wherease cSLEDAI=0 plus PDN ≤5mg/day seems to be more appropriate in the long-term studies (>5 years) or in clinical practice setting.

Plenary II: Novel Therapeutic Approaches to Improve Clinical Outcomes

Targeting Type I interferons: Richard Furie (USA)

Professor Furie's insightful journey throughout the type I interferon (IFN) pathway, in the pathogenesis and treatment of lupus, provided insights into the potential value of IFN as a treatment target. Several strategies involving this key cytokine have been explored, with rescent research leading to potentially disparate results of two trials of the same targeted therapy.

Professor Furie faced the challenge of presenting the interferon pathway in 20 minutes. The pathogenesis of lupus is complex at the best of times, however, Professor Furie provided an eloquent overview of the innate and adaptive immune systems and how their interplay results in the pathogenesis of lupus (**Figure 1**). There are some of the key players in the immunopathogenesis of lupus. In the genetically susceptible host there is an environmental trigger, for example the sun, which induces apoptosis of the skin cells, releasing RNA and DNA, the DNA enters the plasmacytoid dendritic cell, signaling toll-like receptor (TLR) 9, resulting in the elaboration of many cytokines including interferon alpha. Crossing over to the adaptive immune system, myeloid dendritic cells are activated by many of the cytokines, which in turn triggers an interaction between T cell and B cell via the T cell receptor and major histocompatibility complex, as well as other important costimulatory molecules. All of these things have been or are potential drug targets in lupus. B cells are dependent upon some key cytokines, they can differentiate into plasma cells, which release antibodies (ie. DNA antibodies) that form immune complexes, activate complement, attract neutrophils and activate macrophages. This process is repeated.



Interferon Signature and SLE

Professor Furie's talk focused on the 'early events', highlighting the roles of interferons type I (IFN-α, -β, -ω, -ε, -κ, which [importantly] bind to IFNAR), type II (IFN-γ, which binds to IFNGR) and type II (IFN-λ). The relationship between interferon and lupus dates back to 1979. Patients with SLE have elevated IFN-α levels, SLE sera induce IFN gene signatures, 60%-75% have IFN gene signatures in peripheral blood mononuclear cells (PBMC) and clinical and serologic activity correlate with IFN gene expression. The 'burning' issue is whether or not IFN inhibitors can reduce SLE activity.
The IFN-α gene signature of patients with SLE has confirmed the role of IFN in the pathogenesis of SLE.(5)

Targeting IFN Indirectly

There are several treatment pathways that can be used to target IFN in SLE. Hydroxychloroquine has been shown to improve rash and arthritis, improve survival, reduce lipid levels, have antithrombotic effects, reduce risk of early cumulative damage and prevent flare. (166-170) Hydroxychloroquine works by increasing the pH of lysosome 4 to 6, resulting in inhibition of TLR signalling and pDC response to TLR9, but only weakly affecting responses to TLR7/8 stimulation(171), the result being reduction in pDC production of IFN and tumour necrosis factor (TNF).(172) Given this there are several downstream targets to consider in SLE. A small Phase I study of eliminating RNA stimulus (RNAse) for pDC and TLR(173) has led to a Phase II study of patients with active skin disease. Studies targeting TLRs include DV1179, which targets TLR7/9 and IMO-8400 and oligonucleotide inhibitor of TLR 7,8 and 9, have shown varying levels of success; however, these left the burning question of which TLR should be targeted (ie. 7,8 or 9 or a combination of these).

Targeting IFN Directly

Professor Furie noted it makes MOST sense to target interferon directly. There are currently several strategies for this including: the IFN-α-kinoid (κ) vaccine; or more typically, monoclonal antibodies to IFN-α (sifalimumab; rontalizumab; AGS-009), more recently and successfully IFNAR (anifrolumab) and IFN-α,ο sparing β (CNTO6358).

The IFN-α-κ vaccine in SLE has been tested in a Phase IIb RCT of 185 patients.(174) The study found that IFN-κ induced neutralizing antibodies in 91% of patients, however the mean inhibition was about 30%, which is mild compared with anifrolumab, which has a 90% inhibition of gene signature. Indeed, anifrolumab's Phase II data have shown much promise in SLE with robust clinical efficacy and tolerability data.(175) Anifrolumab's CLASI activity was particularly good, with a rapid and ≥50% improvement in patients with CLASI activity score ≥10 at baseline (n=77). Phase III studies of anifrolumab (TULIP I and II) however showed conflicting results, with TULIP I failing to meet its primary endpoint and TULIP II meeting its primary endpoint. More recent results show promise.

Professor Furie postulated the possibility of 'going after' the factory for IFN and the different ways to do this.

15:50 Slide 31

Targeting B cells and plasma cells: David Isenberg (UK)

Professor Isenberg highlighted the role of B cell development and anti-CD20 antibodies in the treatment of systemic lupus erythematosus (SLE) in the contest of the broader treatment target pathway. Data from several studies and the UK-BIOGEAS registry have highlighted the value of CD-20 targeted therapies including rituximab and ofatumumab for patients with SLE. In addition, Professor Isenberg presented the utilisation of proteasome inhibitors, such as bortezomib, for the treatment of SLE.

It is almost 20 years since B-cell depletion using rituximab [anti CD20] was introduced for the treatment of systemic lupus erythematosus (SLE).(176) Despite the failure of two major clinical trials(177) both the ACR and EULAR guidelines recommend rituximab for the treatment of lupus nephritis and NHS England permits its use more widely.

Well over 50,000 SLE patients worldwide have been treated with rituximab and it seems to be very effective for many haematological, musculoskeletal, dermatological and renal aspects of lupus.(178) Increased risk of infection and hypogammaglobinaemia remain concerns.(179) Newer fully humanized anti- CD20 monoclonal antibodies (e.g. ofatumumab) offer a way forward for those who become allergic to rituximab, which is 20% murine. Research indicates that there are at least two types of anti-CD20 antibodies. In contrast, anti-plasma cell therapies have been much less widely utilized. Some studies using bortezomib (anti-proteasome) have been reported(180) and studies with experimental anti CD19 monoclonals are under way. Although significant reductions in autoantibodies (and immunoglobulins) and a rise in serum complement have been noted, precursor B-cells and T-cells largely remain unaffected resulting in a rapid re-population of short-lived plasma cells. This result suggests that this approach will need to be combined with other B-cell therapies.

Targeting interleukin 12/23: Ronald van Vollenhoven (Netherlands)

Professor van Vollenhoven explained the significance of the IL12/23 pathway in the pathogenesis of systemic lupus erythematosus (SLE), before presenting current evidence of ustekinumab treatment in patients with both organ-specific and SLE and the potential for IL12/23 blockade in the future treatment of SLE as investigated in Phase III studies.

Multiple novel approaches to treating systemic lupus erythematosus (SLE) in recent years have resulted in the approval of a single B-cell directed therapy, but also in the failure of several promising drug candidates. As many immunological pathways are disrupted in SLE,(181) it was recognized that immunomodulatory drugs approved for other conditions might also be effective in SLE. Grammer et al. employed a systematic analysis of existing drugs and found that the interleukin (IL)12/23 antagonist ustekinumab had a relatively high a priori likelihood of being effective in SLE.(182) Thus, IL12 plays an essential role in the activation and function of various T cell subsets seen in the inflammatory infiltrates in the tissues of patients with SLE, including follicular T-helper cells, T-helper- 1 cells, and cytotoxic T cells; while IL-23 drives the expansion and survival of pathogenic T-helper-17 cells and decreases IL-2 production thereby diminishing regulatory T cell activity.(183) Moreover, in animal models of SLE, the selective deletion of the p40 subunit, which is shared by IL12 and IL23, resulted in decreased disease activity;(184) and several SLE-risk genes are related to the IL12 pathway. The IL12/23 antagonist monoclonal antibody ustekinumab binds the p40 subunit and thereby interferes with the activity of both IL12 and IL23. It has been approved in many countries for the treatment of psoriatic arthritis, psoriasis and Crohn's disease, and there is

extensive clinical experience with the drug in patients with these diseases where the safety profile is considered favorable. Based on these considerations, a Phase II clinical trial of ustekinumab was conducted in patients with active SLE despite conventional background therapy. The patient population in this trial was reflective of that seen in practice and in most clinical trials, with a large predominance of women and the most commonly affected organ systems being the skin and the joints. In the 24 week randomized, controlled portion of the trial, a statistically significant difference was seen in the response rate of patients on ustekinumab versus placebo. Thus, in the ustekinumab group 62% of patients achieved the SRI-4 versus 33% in the placebo group (p=0.0057).(185) Differences favoring ustekinumab were also demonstrated for some other outcomes such as the individual measures for skin and joint involvement and the number of flares. After Week 24, all patients continued on active ustekinumab treatment. At Week 48, the original ustekinumab group had maintained the responses, while the original placebo group showed improved outcomes. The safety and tolerability of ustekinumab in this relatively small trial were consistent with the much larger experience in other diseases and generally good. A Phase III clinical trial to confirm and extend these results is currently underway (NCT03517722).

Targeting novel intracellular pathways: Thomas Dörner (Germany)

Professor Dorner further discussed the potential for novel therapeutic targets in systemic lupus erythematosus (SLE), highlighting the significance and promise of the janus kinase (Jak) and Bruton's kinase (BTK) pathways and current developments in SLE. The role of Jak and Stat inhibitions in the blockade od interferon I, II and III, as well as interleukins 6,12, 23 and others was explored, with type I IFN and B linage cells being promising targets of key SLE signatures.

Systemic lupus erythematosus SLE is characterised by abnormalities in cellular and humoral immunity, while disturbances in cytokine production became very clear in recent years. Identification of increased IL-6, IL-17, IL-12 and IL-23, BAFF, and especially type I IFN production by different cell types, provided the rationale for targeting these cytokines and their corresponding cytokine receptors using biologics. Since these cytokine activate various intracellular pathways, such as Jak/Stat signalling, activation of the NfκB or using spleen tyrosine kinase (Syk), Bruton's tyrosine kinase (BTK), small molecules inhibiting these pathways are being investigated in various clinical studies. It should be emphasised that most of the above-mentioned intracellular pathways may vary between different immune cells and tissues and can have interactions which have not been fully delineated. However, certain strategies target multiple key pathways along with inhibiting various cytokines (multiple targeting therapy)(186) which holds the promise to cover broadly heterogeneous SLE, a therapeutic principle that has already been introduced in antihypertensive and ant infectious treatment algorithms.

As a first example in patients with SLE, treatment with the Jak1/Jak2 blocking agent (jakinib) baricitinib showed improvements of skin and joint manifestations among patients with a daily dose of 4 mg/d but less pronounced under 2 mg/d in a Phase II trial over 24 weeks.(187) Another Phase Ib/IIa trial using tofacitinib as Jak1/Jak3 selective inhibitor in SLE has been reported without substantial safety concerns and early signs of efficacy.(188) In addition to jakinib in studies with SLE, there are also trials of inhibitors of other pathways (BTK, Syk etc.) that hold promise for a new era of more efficacious and well tolerated therapies that may address the current and substantial need for the effective treatment of SLE.

Keynote Lecture

Novel biomarkers for monitoring lupus activity: Edward Vital (UK)

Professor Vital described the need for better biomarkers in SLE, before explaining how we can better understand the role of interferon (IFN) and systemic lupus erythematosus (SLE) disease expression in the midst of potential challenges of measuring biologic parameters in clinical practice. Ultimately, teht use of biomarkers will allow us to make better treatment decisions and achieve goals set out by EULAR recommendations.

It is widely acknowledged that we need better biomarkers for management of patients with systemic lupus erythematosus (SLE). While many have been proposed, few new markers have yet made it into clinical practice due to lack of robust validation studies. Historically, antibody titres, complement proteins, immunoglobulin titres and acute phase markers are widely used in clinical practice, although the evidence base and utility of these is also limited. The need for better biomarkers was highlighted in the recent EULAR guidelines for the management of SLE and for treating to target and it is worth considering these guidelines for questions that biomarkers should answer, and appropriate endpoints for clinical validation.(189)

In the EULAR guidelines for management of SLE a research agenda emphasised the need to predict susceptibility to develop SLE, involvement of particular organ systems over others, and response to specific therapeutic agents over others.(189) Several of the 2014 EULAR treat to target guidelines suggest the need for biomarkers too.(141) For example: prevention of flares is an objective that would be easier to meet if these could be predicted. Glucocorticoid tapering or withdrawal is recommended, but this may be difficult if we cannot predict which patients would flare. Finally, these guidelines state that treatment should not be escalated based on solely on persistent serological activity, highlighting the weakness of routinely used biomarkers.

In clinical validation studies, like outcome measures, biomarkers must be shown to demonstrate truth (e.g. they measure what they say they measure), discrimination (e.g. classifying patients correctly and predicting prognosis), and feasibility (e.g. use of standard samples types, transportation and reliable assays in clinically accredited laboratories). Additionally for biomarkers, there may be issues of pre-analytic validation. Some of the most promising biomarkers in the field of SLE measure type I interferon (IFN) activity. type I IFN (i.e. IFN alpha, beta, kappa, epsilon and omega) are known to be important in lupus based on genetic susceptibility data. They are difficult to measure directly in serum due to binding to the abundant IFNAR receptor, and non-circulating sources. Instead, most assays measure cellular responses. The best validated of these measure expression of a set of genes known to respond to Type I IFN – an 'interferon signature'. Interferons are a complex system with many different ligands and responder cells. Recent data have shown that IFN stimulated genes cluster into subgroups with different clinical significance, rather than a single 'interferon signature'. This may improve their clinical utility. Gene expression assays for interferon have helped to stratify therapies that target interferon, and other therapeutic targets. These assays also predict clinical flares, glucocorticoid use. More recently, it has been shown that interferon scores can predict onset of SLE. (190) In this latter work, the separation of interferon-stimulated genes into subgroups was crucial.

The measurement of IFN-I status using whole blood IFN stimulated gene (ISG) expression has two key weaknesses in interpreting pathogenic processes. First, changes in expression may reflect expansion or contraction of certain circulating leukocyte populations that differ in their level of ISG expression.[4] This characteristically occurs in inflammatory diseases. In the case of SLE, lymphopenia is almost universally seen.(191) So any difference in whole blood gene expression may not necessarily indicate a change in production or exposure to IFN-I. Second, analysing whole blood ISG expression does not allow detection of key pathogenic processes among the noise of other, less relevant, effects of IFN-I on biology. For example, B cells are a key mediator in SLE. In these respects, flow cytometric biomarkers, such as memory B cell tetherin, may be advantageous, as they indicate the response to interferon in a particular cell type. Another important area of biomarkers that also uses flow cytometry is monitoring of B cell numbers after rituximab therapy. It was initially thought that rituximab induced complete B cell depletion, which left the explanation for poor clinical responses unclear, and left no biomarker to guide retreatment decisions. These assumptions were reversed by assays optimised to reliably measure plasmablasts in a routine clinical context as well as other B cell subsets in lower numbers. Plasmablasts have low expression of CD20 and are not directly killed by rituximab. They have a short half-life in the circulation, so their continued presence in the absence of other B cell subsets after rituximab may indicate ongoing B cell activity in other tissues. Such 'highly sensitive flow cytometry' studies demonstrated first that B lineage cell depletion was often incomplete in non-responders, which has ultimately led to trials of more intensive B cell depletion therapies. Further, plasmablast repopulation has been shown to be a predictor of impending relapse after rituximab in several studies. Other biomarkers with evidence of clinical validation include cell-bound complement, which may offer advantages of soluble complement product assays, other gene expression signatures, such as plasmablast and neutrophil signatures, and serum proteins, some of which may reflect interferon status. The challenge in future years will be to harmonise measurement of these biologic parameters and implement into clinical practice.

Hot Topic Lecture

Mind antibodies and CNS involvement in SLE: Differential diagnoses: Harald Prüss. (Germany)

Professor Prüss highlighted the importance of neuropsychiatric differential diagnosis of lupus, including autoimmune encephalitis and psychosis, before reviewing the role of antineuronal autoantibodies in autoimmune brain diseases and discussing why immediate immunotherapy is important for neuropsychiatric symptoms in patients with lupus.

Central nervous system involvement in systemic lupus erythematosus (SLE) is a highly important aspect of the disease that is not well understood. It involves several components of the immune system possibly related to certain conditions within the specialised brain compartment. Important differential diagnoses include the growing spectrum of autoimmune encephalitides. Here, autoimmune mechanisms causing dysfunction of the brain are increasingly recognised and brought about a paradigm shift in neurology and psychiatry. Identification of numerous pathogenic autoantibodies against neuronal tissue resulted in unprecedented diagnostic and therapeutic opportunities. Current clinical and experimental data show that diverse neuropsychiatric abnormalities may be the sole symptoms of brain autoimmunity. Affected patients are at risk that such treatable etiologies are overlooked as rheumatic or psychiatric disorders. In some patients the diagnosis can be made by detection of specific auto-antibodies directed against neuronal or glial

surface proteins. These epitopes include voltage-gated potassium channels or glutamate receptors, but also novel antigens not yet tested for autoimmunity, such as cell adhesion molecules or enzymes. The identification and recombinant production of disease defining human monoclonal autoantibodies from these patients now allow detailed analyses of the pathogenic effects, of signalling cascades leading to neuropsychiatric symptoms and potential triggers of autoimmunity. It has become clear that the perpetual discovery of novel antibodies will continue and ultimately result in a better understanding of pathological mechanisms and therapies in patients with impairment of memory, cognition, affect and mood.

Roundtable: Treatment Challenges

When and how to escalate therapy in an impending flare: Bevra Hahn (USA)

Professor Hahn's presentation explored the challenges of differentiating between infection, thrombosis and flare in patients with systemic lupus erythematosus (SLE), highlighting the key biomarkers associated with SLE flares and the most appropriate course of treatment for these patients.

Twenty to thirty percent of patients with systemic lupus erythematosus (SLE) patients experience a disease flare each year. Official definitions are available: The most used are based on physician decisions to change treatment; if treatment is added or escalated, that defines flare. Much research has focused on detecting flares before symptoms occur. The most effective and available is a decline in serum complement levels (C3 or C4), which often precedes symptoms; a recent study showed falling complement has a positive predictive value of 0.74 (very good) and a negative predictive value of 0.90 (excellent).(192) Other biomarkers include rising titers of anti-dsDNA, falling platelet counts and for nephritis increase in proteinuria and appearance of red blood cells in the urine. Other blood markers, less available but probably better, include increased proportions of activated monocytes and naïve B cells, increases in levels of serum cytokine/chemokines ICAM-1 and IP-10, and increased numbers of RBC, platelets or B cells binding the complement split product, C4d. Several urinary biomarkers are likely to predict flares of nephritis, including MCP, NGAL and TWEAK, but these are not consistent across studies. As soon as symptoms of flare begin, the patient saying s/he is flaring is the best sign and is usually accompanied by changes in the laboratory values associated with that individual, such as falling platelet, WBC or RBC counts, increase in proteinuria, rising erythrocyte sedimentation rate, etc. Prevention of flare is a major goal of therapy and the effective treatments that induce improvement also reduce flare rates, including hydroxychloroquine, glucocorticoids, cyclophosphamide, mycophenolate, azathioprine, belimumab, rituximab, and calcineurin inhibitors. The physician must also rule out other causes of the 'flare' that are NOT SLE. In my experience, fever in an SLE patient is more often a sign of infection than of lupus flare (presence of shaking chills and of very high levels of C-reactive protein are more likely in infection); the urinary tract is the most common source of infection, followed by upper respiratory tract infection and pneumonia, septicemia is also common.(189, 193) Appropriate cultures should be obtained before escalating immunosuppression. Risk of infection will be lower if the patient has received all appropriate immunisations and is taking preventive medications while immunosuppressed. Similarly, ischemia of heart, brain, gastrointestinal tract can result from clotting with or without vasculitis, and you may consider anticoagulation while evaluating for active SLE. Serositis can result from uremia. When the physician decides SLE is flaring there are several approaches that suppress flare; probably the quickest is to give an intramuscular dose of long-acting

glucocorticoid, such as 40–80 mg of triamcinolone acetonide or 20–40 mg of methylprednisolone acetate, which usually suppresses flare and lasts 2–4 weeks. If flare recurs, increase the daily glucocorticoid dose (patients often do this themselves – before consulting the physician). If there is still disease activity and you cannot taper prednisolone/prednisone to less than 10 mg daily, increase immunosuppression, either by increasing dose of immunosuppressive being given (e.g. azathioprine) or adding a new immunosuppressive.(194) During this time, consider whether the patient is compliant with the regimen you established prior to flare: Compliance (defined as taking the medication as directed 80% of the time) occurs in only 50–70% of SLE patients: Poor compliance is associated with young patients, those with poor social and economic support systems, less educated, and those with strong beliefs in adverse effects of Western medications and/or utility of other healing approaches.(195) Most SLE patients use complementary supplements: Those that should be discouraged include St John's wort, which interferes with metabolism of many drugs. Vitamin D levels should be normalised. N-acetylcysteine, polyphenols, omega-3 fatty acids, fish oil and thundervine herb may all have benefits but have not reached general acceptance in the medical community. Since the number of SLE flares is strongly correlated with damage to many body systems, with poor quality of life, and with most of the causes of death of SLE patients, physicians and other caregivers are obligated to identify SLE flares early and suppress them.

Management of refractory discoid lupus: Annegret Kuhn (Germany)

Professor Kuhn reviewed best practice for managing refractory discoid lupus (DLE), highlighting existing unmet needs for effective management, including the importance of adequate photoprotection, calcineurin inhibitors for certain cutaneous lupus subtypes, hydroxychloroquine for disfiguring and widespread lesions in patients with DLE and the need for more evidence investigating the use of belimumab in patients with specific cutaneous lupus manifestations.

Discoid lupus erythematosus (DLE) is the most common form of chronic cutaneous lupus erythematosus (CCLE) and occurs as localised form (ca. 80%) or disseminated/generalized form (ca. 20%). The localised form presents with lesions on the face and scalp, especially the cheeks, forehead, ears, nose, and upper lip, whereas the generalized form presents with lesions involving the upper part of the trunk and the extensor aspects of the extremities.(196) The lesions of DLE consist of sharply demarcated, coin-shaped ('discoid') indurated erythematous plaques with adherent follicular hyperkeratosis.(197) During the course of the disease the lesions may expand at the periphery with an active erythematous border and hyperpigmentation, resulting in atrophy, scarring, telangiectasia and hypopigmentation in the center of the lesions. At the scalp, eyebrows and bearded regions of the face, DLE can progress to total, irreversible scarring alopecia. In the perioral region, the lesions can lead to characteristic pitted acneiform ('vermicular') scarring.(198) Mucosal DLE presents with chronic buccal plaques, showing typical roundish lesions with peripheral white hyperkeratotic striae and central atrophy, erosion or ulceration. Exposure to the sun or irritating stimuli ('Koebner phenomenon'), such as trauma, can provoke or exacerbate the disease.(199) DLE lesions occur in approximately 15–25% of patients in the course of SLE, but more than 95% of patients with DLE lesions suffer from cutaneous disease only. First-line treatment options in DLE include topical corticosteroids or calcineurin inhibitors; in patients with disfiguring and widespread disease, systemic agents need to be applied.(200) The first line systemic treatment is antimalarials, but some patients are therapy-resistant and immunosuppressive agents, such as methotrexate or mycophenolate mofetil, are used as alternative therapeutic option. The monoclonal

antibody belimumab, which is approved for SLE as an adjunct therapy for patients with autoantibody-positive disease who despite standard therapy show high disease activity, may be effective, but needs to be evaluated using validated skin scores.

Membranous nephropathy: How aggressive should I be?: Dimitrios Boumpas (Greece)

Professor Boumpas' presentation highlighted differences between membranous and proliferative lupus nephritis, with focus on effective management and targeted treatment of membranous nephropathy, refractory disease and the use and effects of of adjuvant therapy. Professor Boumpas noted that while mycophenolate mofetil (MMF) is the first choice, rituximab and calcineurin inhibitors are effect, in the short term at least, with a combination of CNIS and rituximab being effective for refractory disease.

Compared to proliferative lupus nephritis (PLN), membranous lesions are less inflammatory, have a more benign course, require less aggressive therapy, and have better prognosis.(201) The 2012 EULAR/EDTA recommendations for lupus nephritis(202) were recently updated.(189) Goals of therapy Optimisation (preservation or improvement) of renal function with at least 25% reduction in proteinuria at 3 months, 50% at 6 months and a urine protein/creatinine ratio (UPCR) target below 0.5–0.7 mg/g by 12 months (complete renal response). Initial therapy Glucocorticoids and immunosuppression if UPCR exceeds 1 mg/g despite the optimal use of renin angiotensin-aldosterone system blockers, or from the beginning when nephrotic-range proteinuria is present. In pure Class V nephritis, mycophenolate mofetil (MMF) (dose 2–3 g/day; or mycophenolic acid [MPA] at equivalent dose) in combination with pulses IV methylprednisolone (total dose 500–2500 mg) followed by oral prednisone (20 mg/day, tapered to $\leq$5 mg/ day by 3 months) can be used as initial treatment based on better efficacy/toxicity ratio. Alternative options include high dose IV cyclophosphamide (0.5–0.75 g/m^2 monthly for 6 months), calcineurin inhibitors (ciclosporin, tacrolimus) or their combination with MMF/MPA, particularly in patients with severe nephrotic syndrome. Subsequent therapy MMF/MPA (dose: 1–2 g/day) – especially if it was used as initial treatment – or azathioprine (AZA); 2 mg/kg/day – preferred if pregnancy is contemplated – for at least 3 years, in combination with low-dose prednisone (2.5– 5 mg/day) when needed. If sustained complete response, gradual drug withdrawal, glucocorticoids first, can then be attempted, with immunosuppressives following after 3–5 years in complete response. Continuation, switching or addition of calcineurin inhibitors can be considered in pure Class V nephritis at the lowest effective dose taking into consideration the possibility for nephrotoxicity. Refractory disease Treatment may be switched to one of the alternative initial therapies mentioned above or rituximab (1000 mg on days 0 and 14). In a recent randomised controlled trial of rituximab in idiopathic membranous nephropathy, rituximab was equal to cyclosporine in achieving remission at 12 months (60% vs 52%) but superior to cyclosporine in maintaining remission at 24 months (60% vs 20%).(203) Adjunct therapy ACE-inhibitors or angiotensin receptor blockers for patients with UPCR >0.5 mg/g or hypertension. Antilipidemics and hydroxychloroquine at a dose not to exceed 5 mg/kg/day. Anticoagulant treatment in cases of nephrotic syndrome with serum albumin <20 g/L, presence of antiphospholipid antibodies or other pro-thrombotic conditions.

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