10th Annual Meeting of the Lupus Academy Meeting Report

April 2021

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

The 10th Annual Meeting of the Lupus Academy was held online in April 2021, 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 18 *AMA PRA category 1 Credit*™.

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:

- Explain best diagnostic approach and novel therapeutic options for the optimal management of patients with lupus
- Describe how drug de-escalation strategies work and how these translate into improved clinical outcomes for patients with SLE
- Discuss the role of complement in SLE and specific manifestations of lupus and allied diseases
- Describe recent developments in novel treatment options and optimising treatment strategies for the management of SLE
- Demonstrate practical implementation of case-based learning strategies in diagnosis and treatment of cutaneous lupus, lupus nephritis, paediatric SLE, pregnancy and SLE, and NPSLE
- Demonstrate understanding of the scientific and clinical implications (including COVID-19) of new research that is transforming treatment for patients with SLE

- Explain the role of interferon and use of interferon inhibition in the future management of SLE
- Describe diagnostic challenges in different manifestations including antiphospholipid syndrome and lupus nephritis
- Discuss clinical practice challenges associated with CAPS, refractory cutaneous lupus, osteonecrosis and alveolar haemorrhage.

Opening Session

Kidney biopsies in SLE: Too few or too many?

Professor Hans-Joachim Anders reviewed the role of kidney biopsy in patients with lupus nephritis as a predictor of disease pathophysiology, disease course, flare, and treatment outcomes. He highlighted that kidney biopsies are needed to detect inflammation when it is least obvious, not when it is obvious.

Goals of Kidney Biopsy
There are several priorities when treating lupus including,

(1) Improving mortality in SLE, which is a primary aim; the main issue surrounding this is infection control, cardiovascular risk and blood pressure control.

(2) Organ survival (kidney, heart, lung and bone) and quality of life.

(3) Pregnancy complications/outcomes for both mother and child.

(4) Symptoms unrelated to organ failure and mortality (i.e. skin, joints and fatigue).

Kidney biopsy is important in managing all of these aforementioned situations. Urinalysis is important for all patients with LN and, with the presence of blood and protein, subsequent kidney biopsy should be carried out. Physicians are often taught to conduct biopsy based on nephritis Class, however Professor Anders suggested future biopsies should focus on the degree of inflammation and whether this is focal or global, rather than the Class of disease.

The First Kidney Biopsy
The first kidney biopsy is essential for diagnosis and is currently used to define disease stage (Class), but in future may be used to map disease/inflammation distribution. In research, the first kidney biopsy was performed to determine biomarkers and omics. However, in the past 30 years, this biomarker biopsy has done little to inform change in clinical practice, the same is true for omics—inflammation is inflammation, and the long-term treatment strategy is not something that can be determined by the first kidney biopsy. However, one study in patients with membranous LN contradicts this. In certain patient subgroups (i.e. exostosin 1 and exostosin 2 negative), patients were more likely than others to progress to end stage

renal disease (i.e. Exostosin 1 and Exostosin 2 positive), despite lesions looking similar under the microscope.[1] Despite this, the first kidney biopsy cannot outweigh treatment (i.e. immunosuppressive) response in terms of prognosis prediction, neither can it validate prognostic biomarkers. In addition, the first biopsy cannot define which drug to use or clarify upstream causes of SLE pathogenesis.

Do We Perform Too Few Biopsies?
The normal kidney has a life span of about 120 years, with gradual podocyte and nephron loss over time. Following the first LN episode, this reduces by 20–30 years, with subsequent LN episodes drastically reducing kidney life span further.[2]

Given clinical and urinary parameters are unreliable for predicting immunological response to treatment, it may be of use to perform a second kidney biopsy (protocol biopsy) after one year of treatment. Clinical parameters, including proteinuria of 800mg after 12 months is a good predictor of treatment success, but even though some patients do not reach this level, they do not necessarily face poor outcomes. Therefore, a protocol biopsy should be used to fully understand the immunological response in terms of how much SLE activity exists and how much damage has occurred, remnant nephron hyperfiltration, and drug toxicity, which in term would inform how much immunosuppression is needed, risk stratification/ prognosis and specific interventions that may be needed.[3]

Despite the argument for performing more biopsies there is still a lack of evidence. To this end the Re Bio Lup trial is currently gathering new evidence to support use of a protocol biopsy to improve patient outcomes.[4] Moreover, these biopsies have been used for many years in kidney transplantation and are well documented in literature. Some have performed protocol biopsies to determine when to stop treatment. A recent publication by Brad Rovin's group supports that biopsies performed during maintenance therapy may help inform the decision to withdraw or continue immunosuppression, resulting in good disease control [5]. Repeat biopsy is needed to rule out differential diagnosis, particularly if LN is not responding to immune suppressive treatment. Situations where repeat biopsy may be of use are shown in the **Figure** below.[6]

Figure: Repeat Biopsy Indications.
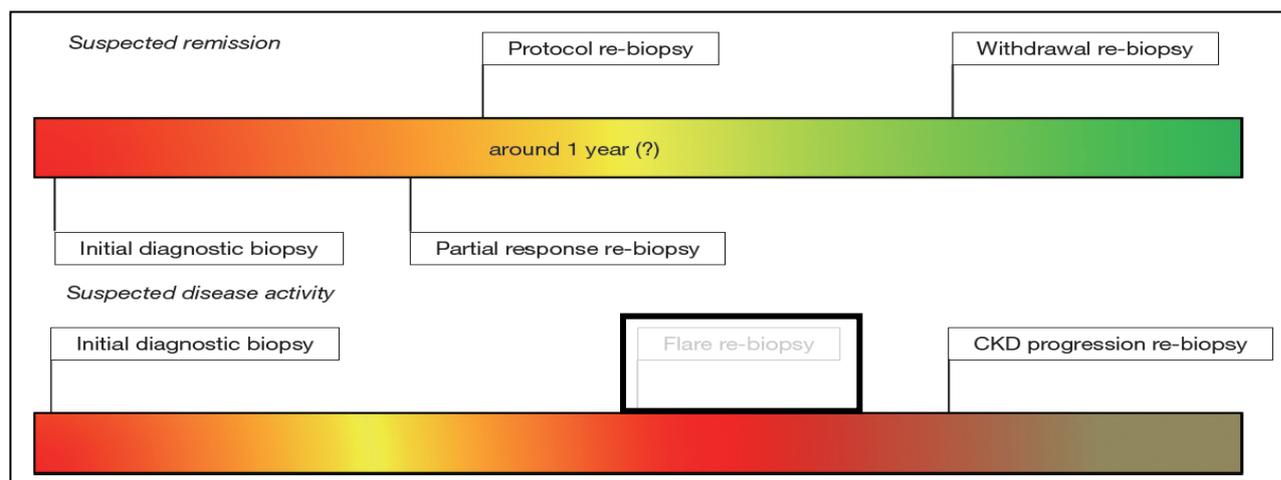
Patients who wish to become pregnant should have a kidney biopsy to ensure the kidney is able to cope with the 9 months of hyperfiltration whilst pregnant, if not they are at risk of glomerular necrosis, renal flare and disease progression, resulting in potential dialysis following pregnancy.

Do We Perform Too Many Biopsies?

Kidney biopsy presents risks, including bleeding complications in patients with low platelet counts, therefore patients in this group should be treated with caution when considering repeat biopsy.[7] The least useful repeat biopsy is the flare re-biopsy. Only 20% of patients with nephritic flare biopsies have informative results.[8] Similarly, proteinuria flares are subject to a broad differential diagnosis. Proteinuria can be associated with scaring, hyperfiltration, and isn't necessarily the result of disease activity. Some patients who have gained weight due to steroids have more fluid for the kidneys to process, thus treatment side effects may be contributing to the stress on the kidneys.[9] Therefore, given proteinuria does not always indicate disease activity, repeat biopsy can be helpful.

Conclusion: How to Manage Lupus Nephritis

Lupus Nephritis is a chronic autoimmune disease with immune memory similar to alloimmunity and is managed following treatment concepts similar to those used in transplantation. Treatment comprises combination therapy with low-dose steroids and a steroid bolus in cases of acute rejection. The first biopsy is important for diagnosis and treatment selection, with combination therapy becoming standard for active LN. A personalised treatment approach is important. In future monotherapy may be a first line option, but only after the individual's disease pathogenesis is identified. Protocol biopsy at 12 months helps risk stratification, but further evidence from the "Re Bio Lup" trial is needed to support this.[4] If patients do not respond to treatment, repeat biopsy is needed, particularly given refractory LN may not exist and the treatment non-responsiveness may be the result of misdiagnosis or

nonadherence to treatment. Finally, biopsy is important before stopping or changing treatment and in women who wish to become pregnant.
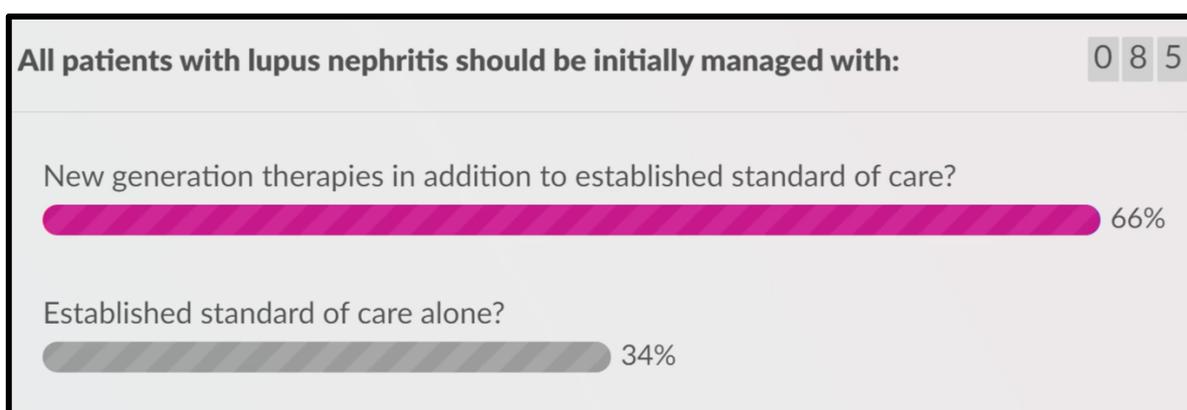
Debate

In With the New, Out With Old? Should All Patients with Lupus Nephritis Receive New Generation Therapies in Addition to Established Standard of Care?

The Matter of the Debate: *Ronald van Vollenhoven (Netherlands)*

Professor Ronald van Vollenhoven opened this virtual debate on treatment of LN with new and established therapies. Lupus nephritis is a key manifestation of SLE, with GC treatment being standard in the 1970s, followed by the introduction of cyclophosphamide (CYC) in the 1980s. In 1992 Boumpas et al found that GC plus CYC was more effective that GC alone, becoming standard of care for many years.[10] In 2000 Chan et al found mycophenolate mofetil (MMF) was as effective as cyclophosphamide, placing MMF in the centre of the LN treatment armamentarium[11]. Interestingly, in 2002 the EURO-Lupus group found a simplified regimen worked just as well with CYC 500 mg/2weeks for 3 months.[12] Together, these treatments have become standard of care for LN. However, while the results of the Euro-Lupus trial were positive for standard of care treatments,[13] other research has shown that while long-term treatment of LN has shown improvement, there is still a high incidence of renal failure in patients with LN.[14] [15]

New treatments for LN include the calcineurin inhibitor (CNI), voclosporin, which has good efficacy and tolerability compared with other CNIs.[16] Likewise, belimumabs recent approval for LN is supported by evidence showing improved renal response verse standard therapy.[17] In the future there will be other new treatments for LN, including the anti-CD20 mAb, Obinutuzumab, which has demonstrated complete renal response in a Phase 2 trial.

When asked which treatment should be used for the initial management of LN, the majority of the audience voted in favour of the new generation drugs plus standard of care.

All patients with lupus nephritis should be initially managed with: 0 8 5

New generation therapies in addition to established standard of care? 66%

Established standard of care alone? 34%

YES: Onno Teng *(Netherlands)*

Professor Onno Teng began his argument FOR the motion by dissecting his statement, noting that his position relates to all LN patients, the initial treatment of LN and the use of both established therapies. His talk then reviewed the data, challenges and the future management of LN.

The Evidence

Two key studies support the use of new generation therapies for the management of LN in addition to standard of care. The BLISS-LN study was a 104-week study looking at renal response and relapse, which showed significant improvements in renal response and a 50% reduction in renal relapse with the addition of belimumab to standard of care.[17] Moreover, all patients in the study with LN Class III–V responded better with belimumab plus standard of care than with standard of care alone, regardless of induction therapy (i.e.. MMF or CYC). A second study, AURORA, investigated the CNI voclosporin as an add-on therapy.[18] Some older CNIs have proven efficacy in LN, but toxicity and loss of kidney function were an issue. AURORA however, found more positive results with voclosporin plus MMF and steroids, with significant numbers of patients achieving renal response with voclosporin, when added to standard of care.[18] The addition of voclosporin also helped patients achieve >50% reductions in proteinuria, an important indicator of long-term renal outcomes. Voclosporin's adverse event profile was also favourable in this study, with no reduction in kidney function and no increase in hypertension or hyperglycemia. Overall, the clinical efficacy and safety profile of this third generation CNI looks promising.

The Challenges

The challenges of treating LN include the burden of steroids and the burden of relapse. Damage accrual is a well-known side effect of GCs, but also results from disease activity and disease severity. An analysis of the 32 randomised controlled trials in patients with LN over the past 30 years, found that GCs were the most common induction treatment resulting in severe infection.[19] Thus emphasising GCs pose a high burden to patients with LN, and new generation drugs can allow lower GC dose, thus reducing patient burden. Relapse is also a burden, with about 50% of patients experiencing renal flare at 10 years with CYC/azathioprine (AZA)/MMF and tacrolimus versus MMF regimens.[20, 21] Conversely, the BLISS-LN study showed a 50% reduction in renal relapse with belimumab versus placebo. This is the first positive RCT to demonstrate a 50% cut in relapse[17] with estimates that voclosporin will also reduce renal relapse incidence.

The Future
In the future it will be possible to combine strategies to fight inflammation and autoimmunity. There are several Phase 3 studies that are currently looking at new treatment options for LN, including SymBioSe-2 looking at belimumab and rituximab, OOBIILUP and Regency looking at obinutuzumab, and SELUNE looking at secukinumab. The design of these studies is striking because these studies stop non-targeted immunosuppression after initial treatment. Moreover, non-renal SLE studies (i.e. BLISS-BELIEVE) have adopted a similar design.[22] In conclusion, new generation drugs create possibilities for designing new combination strategies, they aim to stop (non-targeted) immunosuppression and aim to treat inflammation as well as resetting autoimmunity.

NO: Dimitrios Boumpas *(Greece)*
Professor Dimitrios Boumpas began is argument AGAINST the motion by revisiting the basis for the debate, the update of the joint EULAR/EDTA recommendations for the management of LN,[23] which highlight the use of biologic agents in refractory patients and belimumab as an addon therapy following initial therapy with standard of care.

Standard of Care
Professor Boumpas noted that while some may consider current treatment strategies as too cautious or conservative, is now the time to change this strategy and is there an urgent need to do so? He highlighted that LN is highly heterogenous, but most patients respond to standard immunosuppression within 6-12 months, with proteinuria being the best single predictor for ESRD at 10 years, highlighting the aim to reduce proteinuria to 0.7 gm-1/d by 12 months of immunosuppressive treatment. Even patients without a complete response at 12–24 months (defined as proteinuria below 1 gm/day and stable creatinine) have an overall good 10-year prognosis if proteinuria is sub-nephrotic and creatine is stable (fixed proteinuria). With immunosuppressive therapy (prednisone) patients with LN have a 40% probability of renal failure after 10 years. [24] Another study has shown that almost half of patients receiving methylprednisolone are overtreated at 5 years and do not need additional therapy.[10] Likewise, it is also important to remember that the higher the level of baseline proteinuria the longer it takes to clear; studies have shown that proteinuria resolves in 28% of patients within one year, 52% of patients within 2 years and a further 22% within 5 years.[25, 26]

This brought Professor Boumpas to the important question of risk stratification and identifying patients who are most likely to experience problems with LN. Flare increases the risk of subsequent active disease, damage and death in LN, however not all patients are at high risk of flare. Risk factors include African American ethnicity, younger age of disease onset, prior disease activity, need for steroids or

immunosuppressives in the past year, withdrawal of hydroxychloroquine and immunologic activity.[27-31]

New Generation Therapies

Overtreatment of lupus is an important consideration when choosing treatment. Professor Boumpas reviewed the use of multitargeted therapies and new CNIs (voclosporin), noting that one cannot rush to conclusions based on proteinuria as the reduction of proteinuria comes from an additional "mechanical" effect (stabilisation of the cytoskeleton of the podocytes) that may overestimate the effect on the control of renal activity.[32] Revisiting the EULAR/EDTA recommendation that the combination of MMF and a CNI is an alternative initial treatment for LN, particularly in those with nephrotic-range proteinuria, Professor Boumpas stated that given all patients are different, not all patients would benefit from such an approach. Looking more closely at biologic therapies, he postulated that there is little trial evidence to support the use of rituximab as an initial add-on therapy. Obinutuzumab too needs more evidence to support its use in LN as an initial add-on therapy. Looking at the data for belimumab in LN, [17] Professor Boumpas highlighted that while the effect of belimumab was significant, given the new EULAR/EDTA recommendations the results are non-comparable to previous studies. Moreover, the effect seen was with belimumab combined with high dose steroids, which is not the case in all patients receiving standard of care. Likewise, there was no clear difference in the cyclophosphamide group. More data are also needed to assess the effect of belimumab on relapse. Combining early phase trials such as those combining rituximab and belimumab also require more data before concluding their value as initial therapy for LN.[33]

Professor Boumpas concluded this argument against rushing into use novel therapies from the point of diagnosis, reiterating the risks of overtreatment for most patients with LN, particularly in patients that receive cyclophosphamide as initial induction therapy whereby the benefit of adding biologics such as belimumab is not clear. Moreover, most patients will not flare and identifying risk of flare is best done following initial standard therapy. Assessment of treatment response and risk stratification for flare rate should be carried out before initiating new generation therapies.

Rebuttal: Onno Teng *(Netherlands)*

Professor Onno Teng began his rebuttal of the arguments presented by Professor Boumpas, noting three counter arguments: firstly, a perseverance with the burden of steroids and burden of relapse; secondly, that over treatment is an overstatement, since when is achieving remission wrong?; thirdly, that both Professor Boumpas' arguments regarding flares and targeting immunological activity are arguments in favour of the new generation therapies. In addition, Professor Teng highlighted that 'fear is a bad advisor', in that data from studies of new generation therapies have

shown they are well-tolerated, with good mortality outcomes. Moreover, belimumab works with cyclophosphamide, with good renal flare outcomes, thus reducing flares and targeting immunological outcomes are arguments in favour of the new generation therapies. Rebutting Professor Boumpas' questions 'What is the urgency of using new generation therapies?' Professor Teng highlighted the damage accrual seeing in patients (Leiden Cohort) taking low and high steroids. By doing nothing, damage accrual over years will be harmful and the need for new drugs will become greater.

Rebuttal: Dimitrios Boumpas *(Greece)*

Professor Dimitrios Boumpas' rebuttal too broke down Professor Teng's argument by (1) addressing the data from belimumab and voclosporin studies; (2) highlighting the challenges of steroid sparing and decreasing relapse rates; and (3) Speculation on future studies combining new treatments. In respect of voclosporin and CNIs, it would be unwise to rush to conclusions based on proteinuria as the reduction of proteinuria comes from an additional "mechanical" effect (stabilisation of the cytoskeleton of the podocytes) that may overestimate the effect on the control of renal activity. Per protocol biopsies and long-term data that may help us with this problem are still missing. Regarding rituximab, this has been used as initial add-on therapy in very few trials so evidence is currently limited. Despite the LUNAR trial, rituximab has proven to be efficacious, but data come mainly from patients with either relapsing or refractory disease and not new-onset.[34] The RITUXILUP trial used RTX as a substitute for steroids with good results but single prospective study; it failed to recruit patients in a multicentre, randomised protocol. [35] The effect is significant (11% difference between the two arms) under a new definition that makes the results non-comparable to previous studies. BLISS LN showed a superior effect of belimumab against standard of care but with high steroid dose (0.5–1mg/kg as induction and 10 mg at 6 months); in addition there is a need for additional data on relapse rates. Overall, neither rituximab nor belimumab has robust evidence to support their use as initial treatment to reduce steroids or avoid relapses. Professor Boumpas concluded by adding that until there are more robust data, he would only consider adding novel therapies, in patients with improving proteinuria, after 6–12 months if there is residual proteinuria at the 1–2 g/d range and especially in the presence of risk-factors including active serology.

Overall Conclusions

When asked which treatment should be used for the initial management of LN, the majority of the audience voted in favour of the new generation drugs plus standard of care.

The results of this second vote were similar to the initial vote in favour of using new generation drugs for the management of LN.

All patients with lupus nephritis should be initially managed with:　0 9 5

New generation therapies in addition to established standard of care?

58%

Established standard of care alone?

42%

## Plenary I: Novel Strategies for Optimizing Outcomes in SLE

Preventing damage and reducing mortality in lupus. How are we doing? Murray Urowitz (*Canada*)

Professor Murray Urowitz's presentation reviewed the evidence for damage accrual in SLE and the nature of damage accrual resulting from both disease and medication, notably corticosteroids, and the association with morality. He then looked at medications that protect against damage accrual, including hydroxychloroquine and belimumab.

Professor Urowitz highlighted the causes and proactive factors against damage accrual before providing an overview of lupus patient types including relapse remitting (common), persistently active (trial), monophasic (lucky) patients. Presenting evidence from the Toronto cohort highlighted that 78% of all patients were relapsing remitting, with monophasic and persistently active patients each accounting for 11% of the cohort, with mean remission time of just 57%, 9% and 0.5% in each of these groups. Damage accrual is measured using the SLICC/ACR damage index, which measures factors relating to lupus, its treatment or concomitant issues. [36] In the Toronto cohort mean damage (ACR/SDI) in patients with lupus measured between 1970 and 2005 was less than 1 In the first decade of recruitment, however in subsequent decades damage accrued with the original entrants in 1970 according 3.49 on the damage accrual index between 1997 and 2005. Therefore, the longer patients are followed, the more obvious the damage accrual becomes. Focusing on the inception patients, Professor Urowitz highlighted the inexorable damage in this cohort over 15 years. [37] (**Figure**)

Figure: Damage Accrual Over time.

Reproduced from Gladman et al, J Rheumatol. 2003;30(9):1955-9.[37]
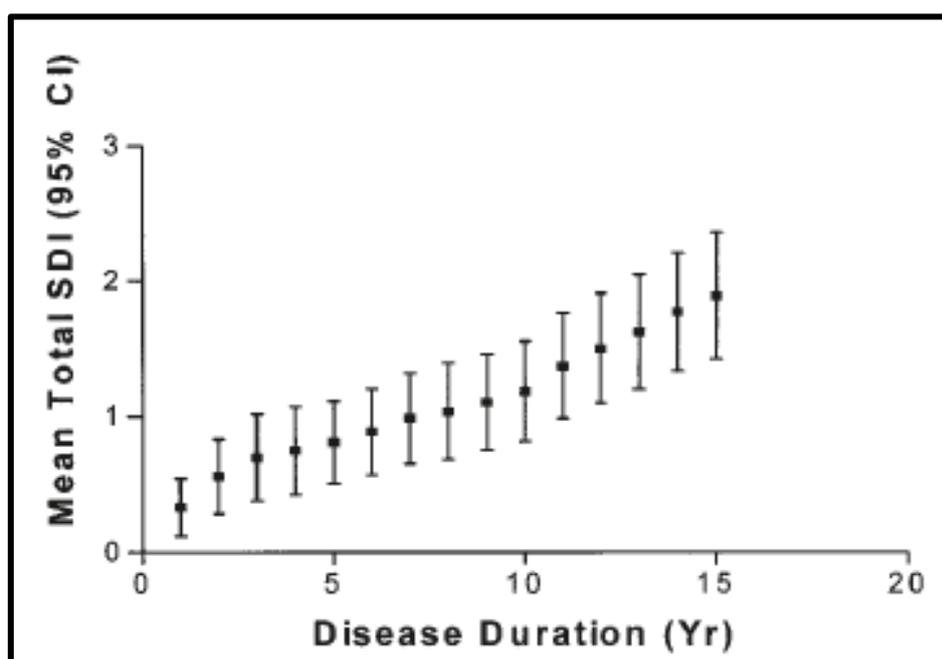
Looking at organ-specific damage in his cohort, Professor Urowitz highlighted the most common as musculoskeletal manifest as avascular necrosis osteoporosis and vertebral collapse or fragility fractures, and ocular (usually cataracts), both of these being corticosteroids side effects. Cardiovascular system and neuropsychiatric system damage, resulting from lupus inflammation following sclerosis, is also likely to be associated corticosteroid use. In addition, there's the damage related to the disease. Over the 15-year observation period, damage associated with corticosteroids rose significantly to 80% across the cohort. Moreover, the dose of corticosteroid affects the levels of damage, with Petri et al showing incremental corticosteroid dose escalations from 1-9, 10, 19 and >20 mg/d are each associated with a significant (p≤0.0001) in damage accrual.[38] Early damage is also a predictor of mortality, with Rahman et al finding that patients with no early damage have a significant improvement in survival compared with those with early damage. [39] 25% of the patients with early damage died within 10 years as compared to only 7.3% with no early damage, therefore early damage is a very significant predictor of mortality.

During the past 20 years, studies have shown that antimalarials prevent flares, protect against organ damage, reduce the risk of thrombosis and improve survival. Antimalarials are a cornerstone treatment for lupus and are protective against damage, particularly if used from diagnosis. Professor Urowitz, presented more evidence from the Toronto lupus cohort, showing that flare is reduced and damage is minimised over a 5 year period, with 75 of 77 patients taking antimalarials being damage free, which was significantly better than those not taking antimalarials.[40]

Belimumab, Bliss 52 and Bliss 56 1 year trials showed belimumab was effective in protecting against disease activity, however these studies were unable to provide long-term date on efficacy, AEs and, importantly, damage accural.[41, 42] The long-term trials of belimumab, as reported by Bruce et al, found patients with SLE treated with long-term belimumab plus SoC had a low incidence of organ damage accrual, with no increase in AEs observed.[43] These trials were uncontrolled, however. Therefore, Urowitz et al carried out a post hoc longitudinal propensity score (PS)-matched study comparing individual patients of the BLISS LTE trials (US patients only) to clinically and demographically similar patients in the Toronto lupus cohort.[44] A total of 17 clinical variables across four categories were used to estimate the PS. The study showed that belimumab significantly reduced organ damage progression (p≤0.001) over 5 years as well as slowing the rate of organ damage progression and also reduced the magnitude of year-on-year damage.

Professor Urowitz concluded by highlighting that damage can be caused by both disease and corticosteroids of the disease. This damage accrues and is associated with mortality. However, hydroxychloroquine treatment, from diagnosis, protects against damage accrual and belimumab also protects against damage accrual.

Strategies for minimising corticosteroid exposure in SLE. Zahir Amoura (France)

Professor Amoura's presentation focused on the central role of glucocorticoids (GCs) in the treatment of SLE, yet their long-term damaging effects mean physicians must develop treatment strategies for minimising exposure to GCs in SLE.

Professor Amoura began his presentation by highlighting that SLE is a chronic disease characterised by a fluctuating course and that GCs play a central role in treatment of SLE. However, there is broad agreement on the toxicity of high-dose GCs, and therefore a need to develop strategies for minimising GC exposure in SLE. Because SLE is a chronic disease, strategy for minimising GC exposure needs to be assessed over the long term, that is before beginning GCs, at GC initiation, tapering and maintenance and withdrawal (**Figure**). Professor Amoura outlined the treatment strategies at each step.

Figure. Step-by-Step Strategies for Minimising GC Exposure in SLE
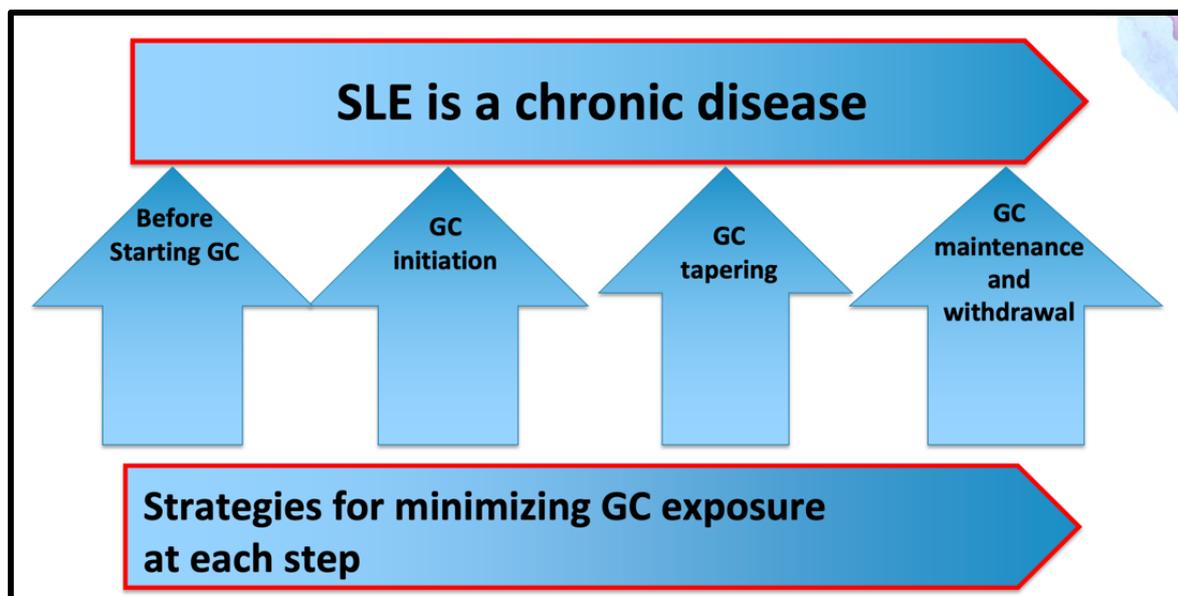
Step 1. Before Starting GCs

It is important to try treatments other than GCs as GCs are damaging and difficult to stop once started. According to the recent update of the EULAR guidelines, before starting GCs all patients should be given hydroxychloroquine (HCQ), unless contraindicated.[45] Patients with skin and joint manifestations should not be on GCs if they are not on HCQ too. Further evidence for this comes from the S2k guideline by Kuhn et al [46], which highlights that GCs are often not needed and lists alternative treatments such as HCQ 400 mg/d; methotrexate (MTX) 15-25 mg/week, thalidomide 50 mg/d, lenalidomide 10 mg/d. The same guidance applies to patients with lupus arthritis, which should first be treated with pain killers, HCQ, MTX or methylprednisolone pulses for rapid induction of remission.

Step 2. GC Initiation

When starting GCs it is important to use reduced doses according to organ involvement. Lupus nephritis (LN) should be treated with prednisone 0.5 mg/d, with higher induction doses. Indeed, MP pulses are underused in SLE and can enable a lower starting dose for GC induction therapy. Immunosuppression and biologics should be started as soon as possible after GCs. MMF and MPA also have evidence for control of lupus arthritis.

Step 3. GC Tapering

It is important to remember that the primary goal of treating SLE is to achieve and maintain clinical remission. Therefore, once remission is achieved, GCs should be tapered to 5–7.5 mg by Week 24 on an individual basis. Tapering may be done faster following MP pulses or immunosuppression.

Step 4. GC Maintenance and Withdrawal

The primary goal of remission is to maintain control of disease as flares directly correlate with long-term damage, therefore it is important to ensure effective long-term maintenance of remission. Currently, the withdrawal of GCs is at the discretion of the treating physician. Studies have shown that low-dose GCs prevents relapse in about 1/5 to 1/3 of patients, resulting in reintroduction of higher dose GCs, within a year of withdrawal. [47] Damage scores were the same in GC maintenance and withdrawal groups over one year. After 3 years of follow up however, there was an increase in damage in patients in the GC withdrawal group, due to reintroduction of higher dose steroids on relapse.

Professor Amoura concluded his presentation by highlighting that GCs are effective treatments for many clinical manifestations of SLE. Control of SLE in the short term, but also in the long term, should be the first objectives of treatment of SLE, a chronic disease. Finally, to preserve the long-term prognosis, there are now strategies to minimise GC exposure at each step of SLE treatment.

Targeting remission and low disease activity in SLE. Andrea Doria (Italy)

Professor Doria's presentation reviewed treat-to-target (T2T) goals and strategy, highlighting the major treatment targets in SLE, the importance of treating remission or low disease activity (LDA) and the role of biologics in achieving this.

Treat-to-target Goals

Professor Doria began his presentation by highlighting the overarching principles of T2T in SLE, recalling the success of this approach in other diseases as well as SLE,

noting that in SLE, remission and LDA are the principal treatment goals.[48] However, the concept of remission and LDA has not be elucidated yet, therefore in 2016 a task force set out to build a framework for remission in SLE.[49] This task force identified four domains that are critical for defining remission in SLE: disease activity, serological activity, treatment and duration, forming the DORIS definition of remission. The minimum requirement for fulfilling DORIS was defined as clinical remission on therapy based cSLEDAI-2K=0, PGA <0.5, prednisone ≤5 mg/d, and stable on background therapy (i.e. HCQ, IS or biologics). Since DORIS, other definitions of remission have been proposed, a notable difference in these definitions being DORIS is the only definition that includes the Physicans' Global Assessment (PGA). Saccron et al published a paper comparing the use of these clinical definitions in a large multicentre cohort, with all being considered regardless of serological findings or treatment.[50] cSLEDAI was the best forming measure, thus adding PGA or prednisone ≤5 mg to the definition did not improve its performance. A similar situation of various definitions of LDA has also developed.[49, 51-56] As with DORIS, the Lupus Low-Disease Activity Index (LLDAS) is the only definition that includes PGA. Professor Doria did, however, highlight that there are two major problems with the definition of LDA, firstly the LLDAS is not aligned with other definitions of remission, including DORIS; it is in fact based on SLEDAI-2K ≤4, unlike the DORIS definition, which is based on cSLEDAI2k=0. Because many patients with a SLEDAI2K ≤4 have a SLEDAI2K=0, there is, therefore, a large overlap of patients who may be in remission but recorded as having LDA. Moreover, a report by Zen et al, showed that 70–90% of patients in LLDAS were also in remission according to the DORIS definition; therefore, LLDAS cannot discriminate between patients in true LDA and those in remission.[57] This is also the case for all definition of LDA, because the SLEDAI is used, in some form in all LDA definitions and dose not accurately measure for LDA vs remission.

SLEDAS was developed to show a higher sensitivity for changes in disease activity compared with SLEDAI2k.[58] SLEDAS uses 17 weighted clinical and laboratory parameters attributed to SLE and is assessed at each outpatient visit, including two that are excluded from SLEDAI2k (i.e. lupus enteritis and haemolytic anaemia) as well as other slight differences. SLEDAS provides an accurate and practical global score to measure disease activity over time (sle-das.eu).

Treat-to-target Strategy
T2T is a stepwise strategy to achieve clinical remission or sustained LDA (**Figure**).[59]

Figure. T2T Strategy: A Stepwise Approach to Managing Lupus
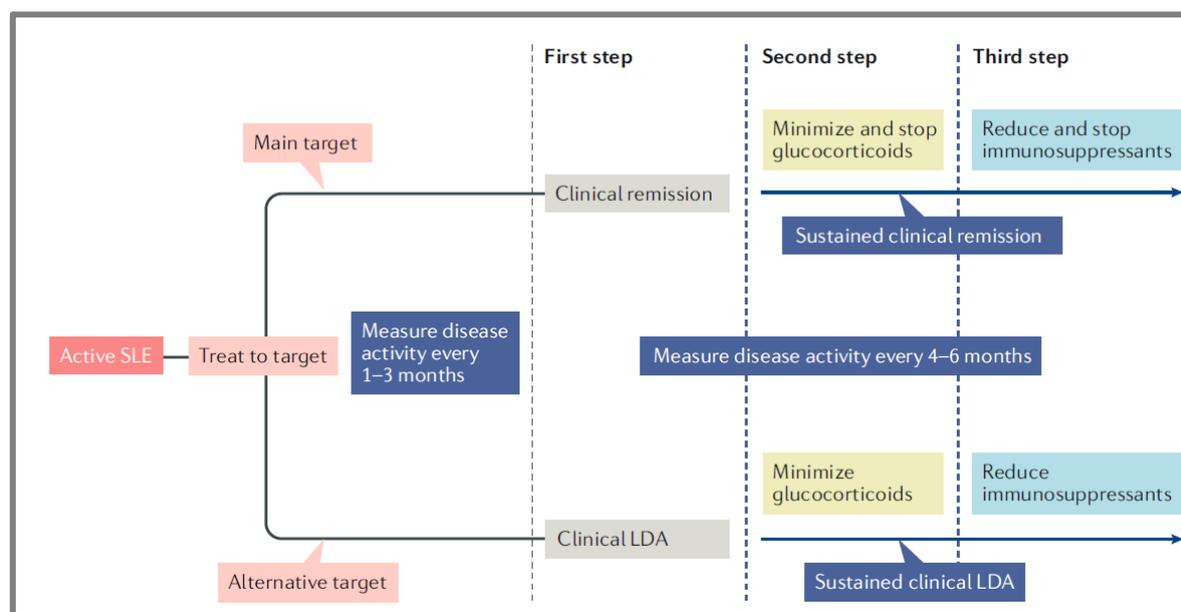
The first step and main target is achieving clinical remission or LDA, measuring disease activity every 1–3 months. Today, achieving remission or LDA are achievable, particularly in clinical trials; the problem is maintaining them.[57, 60] Moreover, the longer a patient remains in remission/LDA the lower the damage accrual.[57] The same situation is seen with LN, with failure to achieve EULAR/ER-EDTA response at one year being the greatest predictor of poor long-term renal outcomes.[61]

The second step is to reduce/stop GC when sustained clinical remission/LDA is achieved, measuring disease activity every 4–6 months. GC damage with prednisone ≤5mg/d is not always evident in the few years of remission, however in the long-term (≥5 years of remission) damage accrual becomes evident in those achieving clinical remission with prednisone compared with those who achieve clinical remission without.[60] The third step is to reduce/stop immunosuppression when sustained clinical remission/LDA is achieved. Stopping GC and immunosuppressants are predictive of long-term damage and should be reduced/stopped in patients achieving LDA/remission. Zen et al showed flare-free survival was much greater in patients who discontinued immunosuppression due to remission, than those who discontinued due to poor adherence.[62]

Professor Doria concluded, noting that the proportion of patients who can achieve remission and LDA largely depends on the definition used and that the definition of LDA is still challenging. The T2T strategy is a stepwise process, which can improve disease outcomes, especially damage accrual.

Lupus Treatment in the Next Decade: The Next Decade is Upon Us. Richard Furie (USA)

Professor Furie's presentation outlined the unmet needs in SLE treatment, before describing the biologic targets for SLE drug development and reviewing recent clinical trial results.

Professor Furie began his presentation noting that these are exciting times for lupus, with the advances seen in Rheumatology over 10 years ago now been seen in lupus research and clinical practice, with drug development activity being unprecedented. He noted that his presentation purposely avoids covering voclosporin and belimumab as they are presented elsewhere in the programme.

Unmet Needs in SLE
Professor Furie asked the audience how they were performing to address unmet needs in lupus, including disease activity, damage accrual, quality of life, steroid use and comorbidities. Reviewing SLE studies over the past 10 years, the majority of patients in the standard of care groups are not achieving a clinical index response, with steroids and mycophenolate mofetil (MMF), and the situation is worse for studies of patients with LN. Ranking unmet needs in lupus, Professor Furie, placed LN at the top, followed by severe extra-renal disease, damage prevention (flare and steroid/IM sparing), remission induction and quality of life.

SLE Drug Development
Professor Furie gave a review of the innate and adaptive immune system and provided a picture of the various therapeutic targets that reside there. Interferons are divided into three types/targets: Type I (IFN-α, -β, -ω, -ε, -κ), which bind to IFNAR; Type II (IFN-γ), which binds to IFNGR; and Type III (IFN-λ). Anifrolumab, a fully human monoclonal antibody binds to subunit 1 of the type I interferon receptor, blocking the activity of type I interferons. Professor Furie presented the effect sizes in SRI and BILCA for anifrolumab in the TULIP 1,2 and MUSE studies, highlighting the one anomaly in TULIP 1 where the effect size for SRI was smaller than for endpoints in other studies (**Table**). This discordance between SRI and BILCA in TULIP 1 remains unexplained. Other studies have generally shown good concordance between SRI and BICLA.[63-65]

Table. Improvement in Anifrolumab Studies

	SRI	BICLA
MUSE	22.4% (PE)	27.8*
TULIP 1**	3.9% (PE)	16.5%
TULIP 2**	18.2%	16.3% (PE)

* 300 mg at day 365 (without steroid taper requirement)

** post-hoc with amended medication rules

PE, primary endpoint; SRI, Systemic Lupus Responder Index; BICLA, British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment

Professor Furie then looked at other ways of targeting the IFN pathway, notably the plasmacytoid dendritic cell, which expresses BDCA2, a target for the compound BII059, which in itself, blocks production of proinflammatory cytokines, chemokines and Type I inteferon.[66] The Phase 2 dose ranging LILAC study of BII059 in patients with cutaneous LE (CLASI ≥8), resulted in a significant reduction in CLASI-A or 39–48% versus placebo, p<0.001.[67] LILAC A studied BII059 in patients with SLE and resulted in reduction in tender and swollen joints (-2.4; p=0.037) and improved SRI (57% vs. 30%, p=0.003) scores, versus placebo.[68]

Cellular targets for B-cell directed therapies include CD20, and also nuclear transcription factors and bruton tyrosine kinase, a target which hasn't been very successful in lupus yet. The anti-CD20 obinutuzumab has been used previously for chronic lymphocytic leukaemia and in SLE has been shown to result in greater B-cell depletion than rituximab in tissue and blood. Moreover, it has been shown to be superior to rituximab in head-to-head trials in B-cell malignancies [69-72] The Phase 2 104 week NOBILITY study of obinutuzumab in lupus found 85% B-cell depletion in year one, with an effect size of 12% (vs placebo + MMF) in year one and 20% in Year 2; a highly successful result.[73] Moving on from anti-CD20, Professor Furie highlighted the nuclear transcription factors IKZF1: Ikaros; IKZF3: Aiolos. Both are hematopoietic-specific transcription factors involved in the regulation of lymphocyte development Iberdomide binds cereblon and promotes proteosomal degradation of IKZF1 and IKZF3. Week 24 data from Phase 2 study of Iberdomide are promising, with a 20% effect size, with those having a high aiolos signature baseline having an effect size of 33%.

Professor Furie briefly mentioned the many treatment targets for SLE, including, targeting T cells, T – B cell interactions, and trafficking, with early studies of anti-CD40 ligand, antgi-CD28, sphingosine, mTOR pathway inhibition and CNIIs all underway. Key cytokine targets include IL-2 restoration and JAK/STAT inhibition, as well as other cytokine. Drugs are in development for many of these, some already approved for indications other than SLE and LN. Concluding, Professor Furie highlighted that that there is much optimism about the future for the treatment of SLE, with new targets, treatment strategies, more medicines, predicative biomarkers and improved outcome measures.

Hot Topics: The Role of Complement in SLE

Complement in SLE. John Atkinson (USA)

Professor Atkinson's presentation reviewed the role of complement in SLE, highlighting complement as a biomarker and recent advances in our understanding of how complement deficiency predisposes to SLE.

Professor Atkinson began his presentation by providing an overview of the history of complement in lupus and its origins dating from the 1920s, followed by studies in the 1940s and 1950s in lupus. Later metabolic studies and C3 turnover showed that complement activation was a problem, thereafter studies showed that complement deposit in skin and kidneys was mediating the adverse effects of lupus. The standard correlate of bad lupus is associated renal disease, DNA autoantibodies and low C3 and low C4. Moreover, studies in the 1960s showed that if the C3 and C4 levels returned to normal, the patient with lupus tended to do better; therefore, establishing low C3 and low C4 as a key biomarker in lupus.

Complement deficiencies follow a pathway beginning with C1Q, which binds to antibodies activating C1r/C1s proteases, which then cleave C4 and C2. Most patients with complete deficiencies in these would develop lupus.[74]

Goals of Complement Research

The goals of complement research over the past 30 years focus on two major areas: (1) Improving the sensitivity and specificity of biomarkers for disease activity, and (2) Immunopathogenesis: Why and how does C1, C4 or C2 deficiency lead to SLE? Weinstein et al provided a recent evaluation of new biomarkers in SLE, which highlights complement activation products, including plasma activation (slip) products and cell-bound complement activation products.[75] These multiple biomarkers (**Table**) have been studied by many groups. The main question is why are these biomarkers more widely used? That is, are fragments in plasma and on cells a better biomarker for SLE than antigenic levels of C4 and C3? The problem is that these biomarkers are complex, costly, have limited availability, interpretation is difficult, timing is an issue, wide range of normal values, handling issues (i.e., hospital ER), etc; however, their use in the future may be less problematic.

Table. Complement Biomarkers.

Type	Marker
Split Products	C3dg, iC3b, C4d or ratios C3dg/C3, iC3b/C3 C3a and C5a (anaphylatoxins), Bb, Ba. sC5b – 9 (MAC).
Cell Bound (CB)	Complement activation products (CAPS) CB-CAPS. C3d-covalently bound, C4d-covalently bound. C5b – 9 (membrane attached-MAC). Notably on B-cells, red blood cells and platelets.

How Does Complement Deficiency Result in Lupus?

Tam et al showed that intracellular sensing of complement C3 activates cell autonomous immunity.[76] Sensing of C3 in the cytosol activates MAVS-dependent signaling cascades and induces proinflammatory cytokine secretion. C3 also flags viruses for rapid proteasomal degradation, thereby preventing their replication. Thus, complement C3 allows cells to detect and disable pathogens that have invaded the cytosol. Another study by Sorbora et al showed that C3 activation and opsonization is an important part of the host response to infection, with C3 also being carried into cells by invasive bacteria, when autophagy-dependent restriction of the bacterium through an interaction with the autophagy protein ATG16L1 takes place.[77] A third study showed that C3 bound to dying cells can direct the intracellular route of the cargo and modulate the subsequent T-cell response to antigens displayed on dying cells. These results uncover a new role of C3 and have important implications for our understanding of the role of complement in health and disease.

Switching back to complement deficiency Professor Atkinson reviewed studies of the deletion of C4 genes (C4A [acidic] and C4B [basic]) in patients with SLE, whereby C4A binds best to amino groups, whilst C4B binds best to hydroxyl groups, predisposing patients to getting lupus. Linter et al found the same outcome, highlighting that the lupus is a result of the C4 deficiency alone, not an HLA4 association.[74] Kamitaki et al also studied the genetics of 1000s of patients and found that C4a protects against SLE and Sjogren's Syndrome, but too much is risk factor for schizophrenia.[78] Mouse models have also shown that C4a is involved in humoral autoimmunity. [79]

Before concluding, Professor Atkinson highlighted a reason why complement has becoming of interest to investigators and pharmaceutical companies alike. Rare genetic variants in complement regulators have been identified in aHUS and C3G and successfully treated with anti-C5 mAbs. This therapeutic development along with the discovery of rare variants in age-related macular degeneration have ignited the field of complement therapeutics.

The Role of Complement and Complement Inhibition in APS Pregnancy. Jane Salmon (USA)

Professor Salmon reviewed the risk factors, mediators and mechanisms for adverse pregnancy outcomes in patients with APS and described the potential targets to treat and prevent pregnancy complications in these patients.

Professor Salmon noted that one of the defining characteristics of APS is obstetric complications, including preeclampsia, foetal and neonatal death and foetal growth restriction, yet identifying women at risk of these complications is challenging and limits the physician's ability to counsel or care for them, whilst treatments to prevent poor pregnancy outcomes require an understanding of mechanisms of injury.

Pathogenesis of Pregnancy Complications APS

The classification of APS defines specific types of pregnancy complications, including:

1. One or more unexplained deaths of a morphologically normal foetus at ≥10 weeks' gestation, or
2. One or more premature births of a morphologically normal neonate before 34 weeks' gestation because of eclampsia, preeclampsia, or placental insufficiency, or
3. Three or more consecutive spontaneous pregnancy losses at <10 weeks' gestation, unexplained by chromosomal abnormalities or by maternal anatomic or hormonal causes

Complement and Pregnancy: Murine Models

The presence of lupus anticoagulant (LAC) is the strongest predictor of pregnancy complications in APS. Professor Salmon's group used a mouse model to detect the mechanisms and mediators of complications in the APS pregnancy. When injecting the mouse with antibodies from a healthy human, the pregnancy went normally, however, when injecting a mouse with antibodies from a patient with APS, the result was inflammation, resulting in turn in several non-viable/smaller foetuses. Thirdly, injection of both antibodies and drugs that block inflammation resulted in viable pregnancies. Interestingly, murine models of pregnancy complications induced by aPL antibodies implicate complement activation as an essential and causative factor in foetal loss and growth restriction.[80, 81] Blockade of the alternative pathway (factor B), C3, C5, or C5aR rescues foetal death and prevents growth restriction in APL-treated pregnant mice, therefore they are essential. In vitro studies have shown that heparin, a drug used in APS patients, works by blocking C3 and its downstream effects. [81] Notably, the effectiveness of heparins in the prevention of obstetric complications in women with APS may be due to their complement inhibitory effects, rather than their anticoagulant activities. The mouse models confirmed that C3 needs to be cleaved once APL antibodies bind to the placental cell surface, generating C3B deposition on the surface and activation of C5, cleaved to released C5A that in turn recruits and activates inflammatory cells. These inflammatory cells are essential for pregnancy outcomes; therefore, at the time of these studies, blocking C5 was not possible, therefore blocking the downstream inflammatory mediators (e.g. anti-TNF) was studied. [82]

Professor Salmon continued to review complement, not just in terms of foetal loss, but also preeclampsia. The first stage involves abnormal placental development due to a failure of remodeling of uterine spiral arteries into dilated, flaccid vessels in early pregnancy, leading to under perfusion of the placental intervillous space. This first stage is clinically silent, but factors toxic to the maternal endothelium are released, leading to the second stage. The second stage is a maternal systemic response to placental hypoperfusion, characterised by maternal hypertension, proteinuria, and

other end-organ manifestations attributed to widespread maternal endothelial dysfunction, mediated by placental secretion of anti-angiogenic factors. Professor Salmon's team used a BPH/5 mouse model to study preeclampsia-like syndrome in pregnancy.[83] They found that complement inhibition rescued BPJ/5 pregnancies and normalized spiral artery remodeling/placental development, thus improving outcomes in pregnancy. Concluding her overview of the mouse studies, Professor Salmon highlighted that complement blockade rescues pregnancies and normalizes placental development, prevents placental dysfunction, allows spiral artery remodeling, prevents angiogenic imbalance, attenuates fetal loss and attenuates fetal growth restriction.

Complement and Pregnancy: Humans
The evidence for complement activation in human pregnancy complications shows C4d is present at the foetal-maternal interface in placentas from women with preeclampsia. The activation of the alternative complement pathway, demonstrated by increased levels of the factor B fragment Bb, occurs in non-autoimmune women destined to develop PE. Complement and coagulation cascades activation are the main pathological pathways in severe early PE revealed by proteomics. Allelic variants of complement and complement-regulatory proteins are enriched in women to PE. [84-89]

In APS C4d and C5b-9 is present at the foetal-maternal interface in placentas from women with SLE and/or APS. Hypocomplementemia (low C3 and C4) is associated with poor pregnancy outcomes in APS patients, in some but not all studies. In aPL-positive patients, elevated levels of complement activation products are detectable early in pregnancy and are independently associated with adverse outcomes. Mutations of complement and complementregulatory proteins predispose to PE. [88, 90-96]

Before concluding, Professor Salmon provided an overview of the PROMISSE study looking at complement activation in APS pregnancy complications, which sought to find out if elevated levels of complement activation products affected outcomes. The study found that, in pregnant patients with SLE and/or aPL, increased Bb and sC5b-9 (detectable early in pregnancy) were strongly predictors or poor pregnancy outcomes, thus supporting the activation of complement as a contributor to these poor outcomes. In conclusion, complement therapeutics could include antibodies, small molecules, nucleic acid-based antisense oligo, RNAi and peptide blockers.

The Interface of the Complement and Coagulation Pathways. Edward Conway (Canada)
Professor Conway's presentation sought to review the cellular and molecular links between the complement and coagulation systems, the role of complement in

different diseases and explain the importance of delineating the relationship between complement and coagulation.

Professor Conway began with an overview of the interplay between the coagulation and complement systems in relation to injury, highlighting the thrombin and fibrin clot and initiation of immune response to injury. In recent decades, understanding of the molecular links between the two systems has led to the development of novel therapies. An example of this is the atypical haemolytic uremic syndrome (aHUS), which is associated with rapid progression, leading to 25% of patients dying in the first few weeks and 50% ending up in renal failure. aHUS's molecular mechanism involves hyperactivation of complement and is treated with anti-compliment C5.

Complement is similarly activated by three pathways that have distinct triggers and converge the transformation of C3 to C3b + the anaphylatoxin, C3a, by C3 convertase. This leads to formation of a C5 convertase which converts C5 to C5a + C5b, and the formation of the membrane attack complex from C6 through C9, destroying the pathogen (**Figure**).

Figure. Complement Activation Pathways.
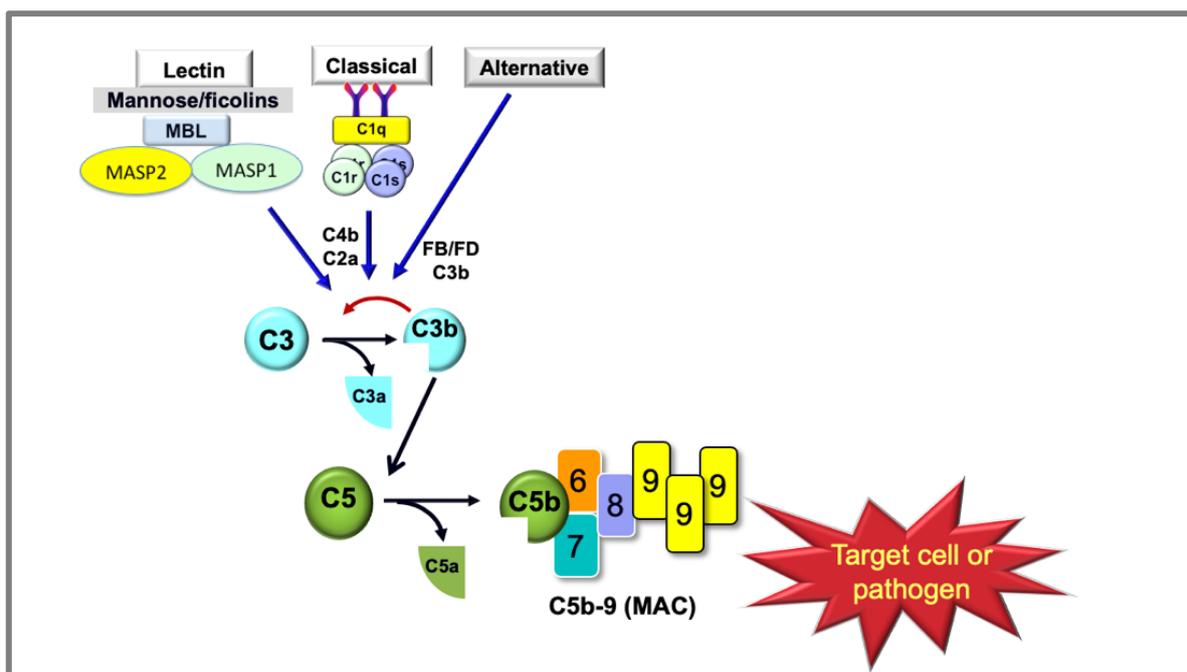
While coagulation serves to prevent bleeding, complement has protective properties, achieved via components along the way that serve to tag pathogens/damaged cells for immune destruction, recruit inflammatory/immune cells, recruits adaptive immunity and damage the membrane integrity of pathogens/damaged cells.

Professor Conway focused next on describing the classical and lectin complement activation pathways and the alternative pathway that have tight regulation at multiple steps to prevent excess activation of complement. If complement activation goes unregulated, this results in damage to host vasculature resulting in a procoagulant

endothelial surface, due to loss of factor H/thrombomodulin. There are many other mechanisms (e.g. MASPs C3, C3a, C5, C5a, C5b-9) associated with excess complement activation and together they set the stage for escalation of thrombosis.

Professor Conway concluded with a simplified explanation of the positive feedback loop involved in complement activation, highlighting that when exposed to an infection, someone with an underlying disorder such as a loss of function or gain of function mutation is left sensitive to hyperactivation of complement C5a and C5b-9, which affects different cells, including endothelial cells, platelets, leukocytes etc. resulting in thrombin generation, which feedback and further activates complement C5a and C5b-9 generation. Fortunately, there are treatments including anti-C5, RNAi and peptides entering the clinics and more in development, targeting multiple parts of the complement pathway.

Lessons learned from complement inhibition in ANCA vasculitis. David Jayne (UK)

Professor Jayne's presentation reviewed the role of complement in ANCA vasculitis pathogenesis and then reviewed the progress with complement inhibitor therapies in AAV, before considering the lessons we can learn for lupus.

Professor Jayne began his presentation by describing ANCA vasculitis as being pauci immune, with scant immune deposit compared with LN; however, complement fragments (Bb, C3d, C5b-9) are detected in the kidneys of patients with ANCA vasculitis. Most patients with AAV have normal levels of C4 and C4 in the blood, but those with low/normal levels do worse that those with high normal levels; lower C3, but not C4, levels associate with poor outcome. [97] In the urine of AAV patients, there is clear indication of complement activation taking place in the kidney, with Bb, C3a, C5a, C5b-9 elevated in active AAV, yet falling in remission.

The initial interest of looking at complement inhibition in ANCA vasculitis came from the ability of C5a in ANCA to activate neutrophils. In active vasculitis microparticles are released into the blood and are capable of converting C3a and C5a into their active products. [97-100] A mouse model has shown that the presence of an intact C5a receptor a crescentic nephritis occurs.[101] Knocking out this C5a receptor with avacopan, resolved the vasculitis. However, knocking out the C5L2 receptor resulted in more active disease, indicating that this receptor may have a more regulatory function.

Professor Jayne continued to review the role of complement inhibitors in ANCA vasculitis (**Figure**).

Figure. Targeting the Complement Pathway.
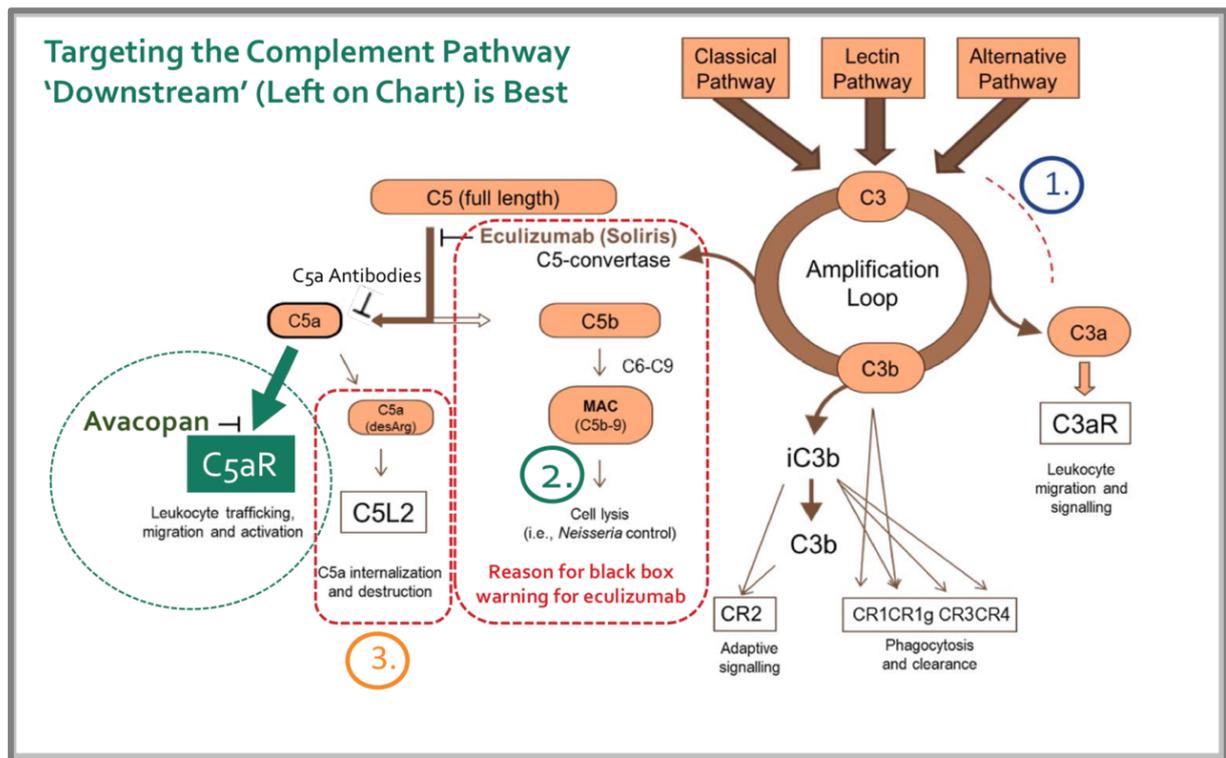
Avacopan was studied in the Phase II CLEAR study, a three-stage trial which looked at replacing steroids with avacopan.[102] This study showed non-inferiority for replacing steroids with avacopan, with a faster fall in disease activity with avacopan. Remarkably, there was a significant fall in proteinuria and improvement in QoL (EQ5D, SF-36) with avacopan. The Phase II ADVOCATE study also confirmed non-inferiority of avacopan versus steroids for remission at 6 months and superiority for remission at 12 months, with fewer relapses, greater improvement in GFR with avacopan versus steroids. [103]

Professor Jayne reviewed the lessons that can be learned for lupus, beginning with what aspect of the complement system should be targeted. ANCA focuses on the alternative, but lupus is more complex in that it also results from the classical pathway, typically reflected by a low C4 component. He then looked at what animal models can teach us about complement in lupus, with those in AAV providing the impetus for the clinical development programme. In lupus, targeting inflammation, NET formation and the role of complement in autoantibody formation as well as humanising animal models to test human therapeutics, (e.g. C5aR) can all be considered. In addition, it would be important to identify phenotypes or biomarkers that predict response, notably a neutrophil signature and nephritis.

In conclusion, Professor Jayne outlined goals for clinical studies, in that the role for complement is one of an anti-inflammatory agent looking to replace steroids by providing superior efficacy, perhaps in nephritis first. Early phase studies should

identify pharmacodynamic effects (e.g., neutrophil activation), the impact on varying aspects of disease pathogenesis, identify response predictors (e.g., neutrophil RNA signature) and assess any potentially harmful effects (e.g., apoptotic clearance).

Hot Topics: Highlighting Accomplishments in Lupus Research

Translational insights into the pathogenesis transforming SLE treatment. Thomas Dörner (Germany)

Professor Dörner's presentation reviewed the translational rationale and distinct mechanisms of action for novel therapeutic targets in SLE and also explained the significance of certain signalling pathways, specially Jak/Stat and BCR/TLR signalling as potential treatment targets in SLE.

Professor Dörner began his presentation outlining the pathogenic concept of SLE, outlining the impact of environmental factors on innate immunity that results in inflammation and organ damage (**Figure**).

Figure. Pathogenetic Concept in SLE Positive Feed Forward Loop of Activation.
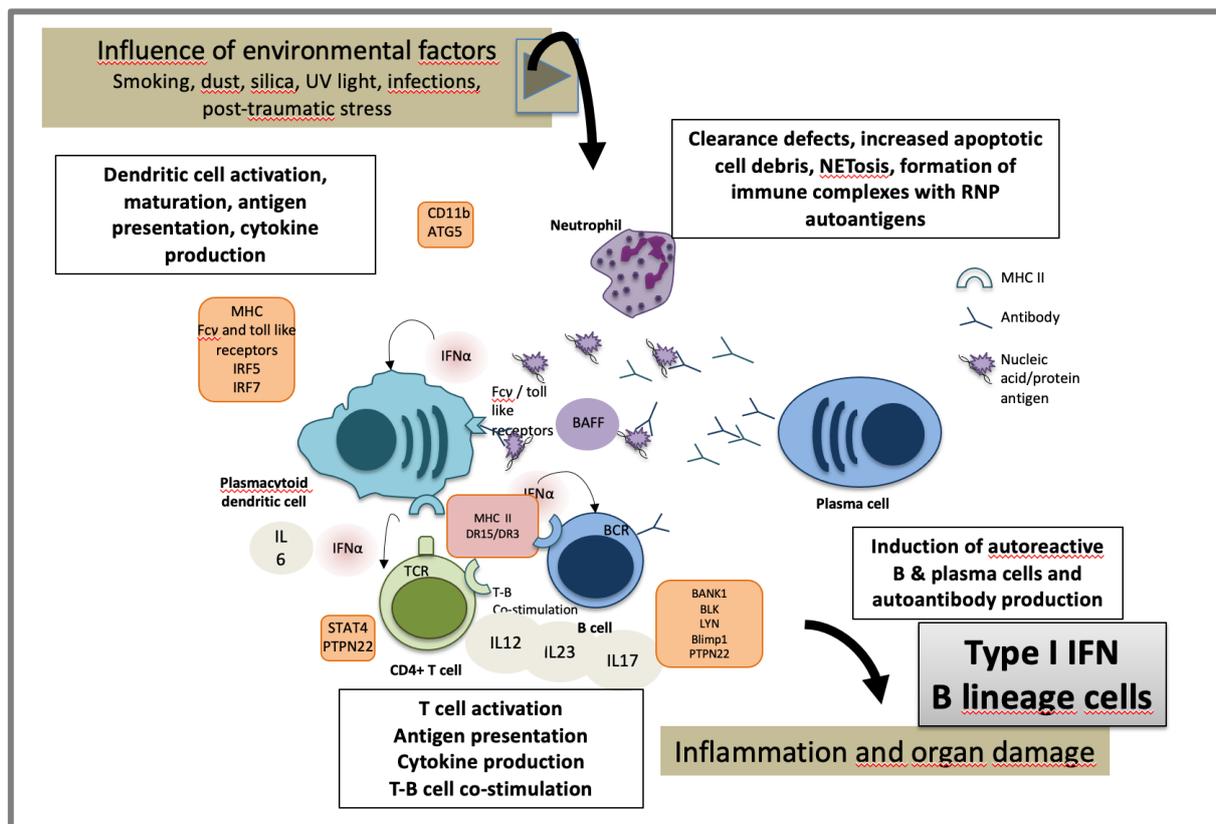
Professor Dörner then reviewed the similarities and differences of cytokines in COVID-19 versus SLE. A recent publication looked at abnormalities of the B-cell compartment in patients with COVID and SLE, finding that COVID-19 correlated with SLE-like

activation of the extrafollicular pathway.[104] Furthermore, another study has shown that in severe COVID-19, SARS-CoV-2 induces a chronic TGF-β-dominated adaptive immune response.[105] Although the immune reaction is initially controlled by interferon, IL-21 and TGF-β but later TGF-β dominates and drives B cells into terminal switching to IgA2. Continued immune reaction to SARS-CoV-2 does not contribute significantly to humoral immunity against the virus.[106] In SLE, IgA1 plasmablasts with a mucosal phenotype occur in peripheral blood not related to disease activity in contrast to IgG+ plasmablasts.[107]

Targeting Cytokines in SLE

There is a cytokine imbalance in SLE, with key cytokines grouped in type I and II IFN and BAFF. An important subset of pro-inflammatory SLE cytokines utilise JAK pathways. Clinical experience in patients with SLE has shown that increased STAT1 is characteristic of SLE lymphocytes and correlates with disease activity as measured by SLEDAI.[108, 109] In fact, in most SLE patients both STAT1 and 2 are expressed, simultaneously.[110] This was demonstrated in the Phase 2 baricitinib trials, which showed resolution of arthritis or rash (SLEDAI-2K) for baricitinib 2-mg or 4-mg versus placebo at Week 24, moreover the SRI-4 improvement effect size for baricitinib versus placebo was 16.8% .[111] Pharmacologically-induced changes in gene expression in response to baricitinib treatment results in reduction in STAT at Week 12.[110] The reduction in IFN gene expression did not correlate with the clinical response in SLEDAI-2K or SRI-4 at Weeks 12 or 24. Unlike IFN, changes in STAT-related genes were found to correlate with clinical improvement measured using SLEDAI-2K (FDR < 0.1). At Week 12, treatment with baricitinib 4-mg was shown to significantly decrease serum IL-12/23p40 and IL-6 cytokine levels.

Targeting B Cells in SLE

Professor Dörner then reviewed B-cell targets in SLE, reviewing naïve, memory and plasma cells. There are distinct effects of direct and indirect B cell-targeting drugs within lymphoid follicles.[112] The recent identification of anergic post-activated B cells (APA) require consideration as anti-CD22 treatment (epratuzumab) as well as the first studies evaluating BTK inhibitors in SLE (fenebrutinib, evobrutinib) did not achieve the primary endpoint.[113, 114] As CD40 appears to be a crucial controlling checkpoint molecule of APA B cells, this treatment strategy continues as potential therapeutic modality.[115] In conclusion, consideration of APA B cells in certain autoimmune diseases responding to CD40 activation may guide the development of successful new therapies in SLE and other diseases.

Clinical Science highlights that are transforming treatment. Bevra Hahn (USA)

Professor Hahn's presentation described the efficacy of novel treatment interventions and combinations in improving outcomes in patients with SLE/LN and discuss current unmet needs in the management of SLE/LN and how novel treatments may overcome these. In addition, she explains the need for the improving fast access to treatment, whilst minimizing costs and adverse treatment effects, and the importance of educating patients and caregivers about these.

Professor Hahn highlighted the transformative changes in the way SLE and LN are treated, noting that these are exciting times for the treatment of these diseases. Lupus nephritis studies have shown that achieving a robust, early clinical response improves outcomes in terms of both patients and kidney survival.[116] A recent study of belimumab showed that when added to low dose CYC or MMF 3 g qd, there was a good kidney response in (43% vs 32% p = 0.03) after 2 years. [17] Similar results were seen in a study of voclosporin, with SOC, where 59% did not have a good renal response at the end of year one. Despite these significant differences versus placebo, there is clearly a need to do better in the treatment of LN.

Unmet Needs

Professor Hahn highlighted the unmet needs in LN as highlighted by these clinical trials, including: the need for even better new treatment or combinations; identification of treatments most likely to work in any given patient; strategies to identify responders early during a treatment; optimization of background therapies; strategies to anticipate flares before they are clinically evident; earlier diagnosis and treatment; and better reduction of risk for damage and death.

New Treatments

New treatments are now numerous and entering late phase trials, Professor Hahn focused on several of these, including B-cells targeting obinutuzumab and telitacicept; the anti-CD40 compound, dapirolizumab; BIIB059 targeting pDC; stem cells and inhibition of pathways by cytokines, chemokines, TLR, and the JAK/STAT pathway. Obinutuzumab, now in Phase 3 trials, depletes B-cells more effectively than rituximab and is less immunogenic, with Phase 2 trials showing a 40% CRR vs 18% in placebo added to MMF + GC, (p = 0.007) at 52 weeks. A 24 Week trial of the BIIB059 mAb to BDCA2 showed SRI-4 response in 57% vs 35% on placebo in patients with non-renal SLE, with a 3.4 fold reduction in active joint count.[117] Baricitinib 4mg significantly improved the signs and symptoms of active SLE (skin and joint disease) in a 24 week study, with resolution of SLEDAI-2K arthritis or rash being achieved by 67% of patients receiving baricitinib 4 mg.[111] A Phase II trial of telitacicept showed that 75% of patients

achieved SRI-4 compared to 33% of those taking placebo; this iis now in Phase III fast track status at FDA. Lastly, in Phase 2 trial, dapirolizumab achieved improvement by BICLA in 57% vs 37% for placebo at 24 weeks; however, infections increased 24 vs 13%.

<u>Timely Diagnosis, Treatment, and Identifying Responders</u>

Professor Hahn also highlighted the importance of timely biopsy and treatment for LN. A delay in diagnosis of >3 months is associated with lower likelihood of remission[118], moreover a delay in biopsy >6 months results in >9x increased risk of kidney failure.[119] Therefore it is imperative that both diagnosis and treatment are carried out quickly. Goals for identifying treatment responders, and protect kidney function in LN, include targeting a proteinuria decrease of 25% by 3 months, a 50% decrease by 6 months and a UPCR target below 0.5–0.7 g/24h by 12 months.[23] This intervention reduces the risk for increasing serum creatinine by approximately 3 fold over 10 years. Clinical flares in SLE can be identified before they occur, but to date we do not have good widely available blood or urine biomarker panels that are better than changes in complement and titers of anti-DNA in predicting response or flares. Existing background therapies that help improve outcomes in SLE include hydroxychloroquine, which has been shown to improve outcomes in SLE, with a 35% reduction in mortality over 12 years for >80% of the time. Other medicines have been shown to prevent damage in SLE, with statins reducing mortality in those with hyperlipidemic SLE and bisphosphonates reduce vertebral fractures in steroid-induced osteoporosis.

Professor Hahn concluded by highlighting those new interventions improve SLE disease activity/damage in higher proportions of patients than achieved before now, but approximately 50–60% of patients with moderate to severe disease do not have good, sustained responses. Better treatments/combinations are therefore needed, including depletion/inactivation of B cells/plasma cells, regulation of cytokines, interruption of B/T signaling and others. In patients with lupus nephritis, declining proteinuria is a good predictor of response, and we should aim for a target of <0.7g/24h by 12 months. Although we do not have good widely available blood or urine biomarker panels that are better than changes in complement and titers of anti-DNA in predicting response or flares, it is likely we will in future. We should maximize "background" therapies (e.g. hydroxychloroquine) to be sure treatment is optimal. Importantly, delays in diagnosis, renal biopsy, and treatment substantially reduce chances of good outcomes, therefore education of the public and of healthcare givers in urgency of diagnosis and treatment is required.

PLENARY II: TREATMENT CHALLENGES

Treatment of CAPS: Which drugs and in which order? Marc Pineton de Chambrun (France)

Dr Pineton's presentation highlighted the importance of early treatment of CAPS, a severe complication of APS, describing why the combination of anticoagulation and corticosteroids is the cornerstone treatment of CAPS. It also, reviewed the the importance of continued anticoagulation in CAPS-related severe thrombocytopenia and explained why rituximab and eculizumab may be useful in refractory CAPS patients.

Dr Pineton began by defining catastrophic antiphospholipid syndrome (CAPS), which aims to describe evolving forms of APS responsible for organ failures, notably thrombotic episodes with multiple organ involvement, occurring over a short period with small vessel occlusion in patients with defined APS. CAPS affects about 1% of those with APS and is associated with high mortality, although this has decreased during the past 25 years with improvement in treatment (58% vs 23%). The CAPS classification criteria were published in 2003[120] and validated in 2005,, it is important to note these are not diagnostic criteria.[121]

Recommended treatment of CAPS is based on a very low level of evidence, weak recommendations as there are no prospective or controlled trials. Guidelines for CAPS emerge from expert opinion / consensus and evidence mainly relies on the publications of the CAPS Registry. Following this disclaimer, Dr Pineton provided an overview of CAPS treatment (**Figure**).

Figure. Overview of CAPS Treatment
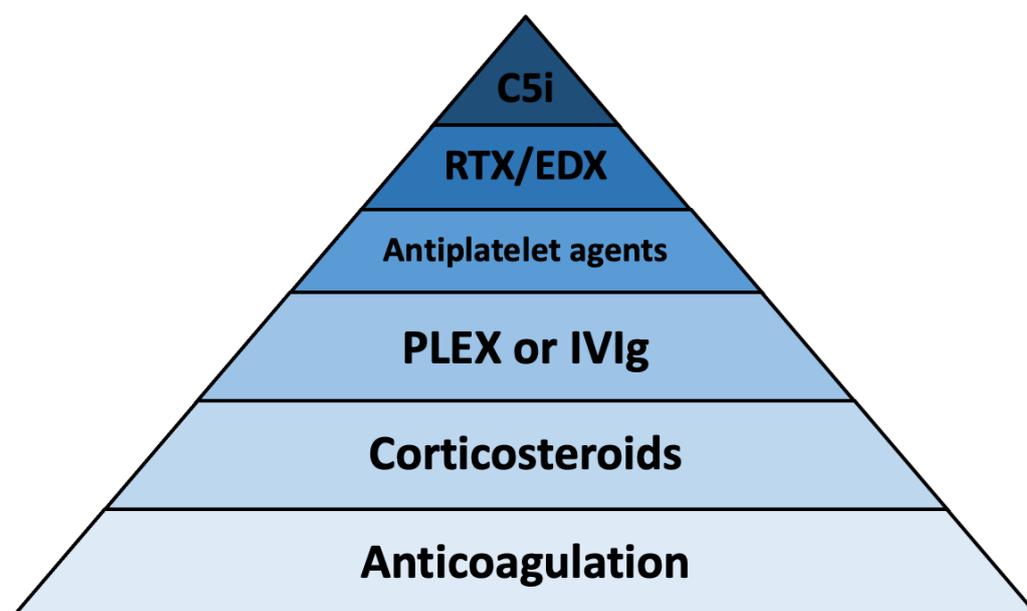
Generally, the CAPS patients should be managed in the ICU, with provision for organ failure, transfusion, and treatment of adrenal failure. Any infection should be treated, causative drugs withdrawn, pregnancy delivered and SLE flare treated.

Anticoagulation

Anticoagulation is the first and most important treatment, comprising LMWH or URN, heparinemia should be monitored and if thrombocytopenia occurs, anticoagulation should continue. Anticoagulation has the strongest level of evidence with a meta-analysis showing the effect of anticoagulation over mortality and also being independently associated with improved hospital survival.[122-124]

Corticosteroids

The combination of anticoagulation and corticosteroids should be used in every CAPS patient, with prednisone 0.5–1g pulse dosing for 3 days in a row, followed by 1 mg/kg/d, but there are no data on how to taper this [123, 125]. Although corticosteroids do have a positive effect on mortality, and in-hospital mortality, this effect is not statistically significant.[123, 124, 126]

PLEX or IVIg

Triple therapy with anticoagulation, corticosteroids and plasma exchange (PLEX) or intravenous immunoglobulin (IVIg), should be available to all CAPS patients, administered as IVIg 2g/kg over 2–5 days and PLEX 3–5 days. In the TMA patient PLEX should be used over IVIG and in the ITP patient IVIg over PLEX.[123, 125] In patients with primary APS, triple therapy remains unvalidated. The effect of triple-therapy versus other treatments over mortality is not significant.

Second-Line Treatments

When triple therapy has failed, aspirin 75–250 mg can be used, although there is no evidence to suggest this treatment improves mortality. RTX 375mg/m^2/week / cyclophosphamide 750mg/m^2/month can also be used, but no statistically significant improvements in mortality have been reported. The last treatment that can be tried is the complement C5 inhibitor, eculizumab. Complement activity is higher in CAPS, than in APS and SLE and its pathophysiology warrants the use of eculizumab in CAPS.[127] A small case series of 11 CAPS patients showed that eculizumab was very effective for the treatment of haematological failure.[128]

In summary, Dr Pineton noted that CAPS criteria are classification not diagnostic criteria. Treatment should be started early: in pre-CAPS/near-CAPS, with double

therapy being the cornerstone treatment of CAPS. Triple-therapy is recommended in first-line but low level of evidence. Second-line therapies should be used in patient's refractory to triple-therapy.

Refractory cutaneous lupus: Use of thalidomide or lenalidomide for refractory lupus skin disease. François Chasset (France)

Dr Chasset's presentation reviewed therapeutic strategy in CLE, explaining the mechanism of action and when to prescribe thalidomide and lenalidomide as well as discussion their safety profiles.

Dr Chasset gave an overview of the treatment of cutaneous lupus erythematosus (CLE), highlighting that it may present as a separate entity from SLE or manifest as one of the most common features of SLE, with lesions are classified as acute, subacute and discoid. The European expert consensus for CLE treatment recommends thalidomide and lenalidomide as third line treatments for selected refractor CLE patients, preferabily in addition to antimalarials,[46] whereas EULAR recommends that thalidomide should be considered only as a 'rescue' therapy in patients who have failed multiple previous agents [45] These opinions maybe because of the unfavorable risk benefit ratio or that they are expensive treatments. A major unmet need in CLE, is understating the important of considering CLE subtypes in the overall therapeutic strategy for CLE. Some CLE subtypes (i.e. discoid CLE and lupus panniculitis) are associated with extensive skin damage with major impact on QoL.

Thalidomide and Lenalidomide: MoA in CLE

Dr Chasset reviewed the general MoA of thalidomide and lenalidomide, mainly demonstrated in multiple myeloma. Specific to CLE it has been shown that CC220 can reduce CD4+ B cells as well as plasma dendric cells by 85%, increase IL-2 and decrease IL1β, TNFα and IL-6 levels. Thalidomide has also been shown to result in activation of CD4+ T helper > Th2 population and increase NK cells, inhibit NFκB by modulation of IRF4 in lymphocytes and inhibit mTOR by modulation of AMPK in keratinocytes. Patients with CLE treated with lenalidomide have also demonstrated clinical responses characterised by an increase in circulating Tregs, decreases pDC and decreased IFN-1 gene signature.

Thalidomide for the Treatment of CLE

Dr Chasset's systematic literature review included 21 studies, 548 patients and revealed that the thalidomide starting dose tended to decrease over time in publications, which was likely due to the need to decrease side effects.[129] Moreover,

overall response was 90% and complete response rate was 64%, with similar response rates seen between CLE subtypes and between starting doses of 50mg/day versus ≥100mg/day. A common problem with thalidomide is the relapses following withdrawal, with a relapse rate of 57% in DLE and only 20% of patients achieving long-term remission.[130] The metanalyses showed a 71% relapse rate following thioamide withdrawal, but on 34% with minimal maintenance dose.[129] Thalidomide withdrawal rates were related with adverse events in about 25% of patients, of which drowsiness, constipation and neuropathy were common. Interestingly, the daily thalidomide dose (>25 mg/d) was the main risk factor for neuropathy, regardless of treatment duration. Thromboembolic risk was 2.74 for 100 patient-years.

Lenalidomide for the Treatment of CLE

The thalidomide analogue lenalidomide is 100–2000 times more potent than those of thalidomide, particularly for TNFα inhibition. An open-label study of 5 patients with severe CLE (CLASI ≥20) showed 4/5 patients had significant improvement in CLASI activity score (>50% of baseline CLASI activity).[131] Another study of lenalidomide in CLE patients intolerant of thalidomide found an 88% improvement in CLASI with lenalidomide.[132, 133] The safety profile of lenalidomide is good with studies showing no cases of peripheral neuropathy, but a similar risk of thromboembolic events to thalidomide.[132]

Dr Chasset concluded his presentation noting that both thalidomide and lenalidomide are very effective treatments for SLE yet, unlike lenalidomide, thalidomide is associated with potentially severe AEs including peripheral neuropathy.

Osteonecrosis: Prevention and treatment. Bernardo Pons Estel (Argentina)

Professor Pons-Estel presentation gave an overview of the epidemiology and clinical presentations of osteonecrosis (ON) in patients with SLE and explained the modifiable risk factors, while highlighting the preventative measures and treatments for ON in patients with SLE.

Professor Pons-Estel highlighted that osteonecrosis (ON) is an ischemic, aseptic, and atraumatic bone necrosis, prevalent in the younger populations and is a well-known component of damage accrual and frequently causes disability and affects the patients QoL. [36, 134, 135] The prevalence of symptomatic ON is only 3–15% in SLE, with 29% being symptomatic, 40% being symptomatic and silent and multifocal being as high as 47%. In fact, the GLADEL inception cohort highlights musculoskeletal manifestations as one of the most common in SLE.[136] Other than genetic predisposition, the pathophysiology of ON comprises several modifiable risk factors,

including alcohol intake, cigarette smoking, high triglyceride levels, and heavy physical work [137-141]

The use of corticosteroids (CS) has also been recognized as a major risk factor for the development of ON, with studies showing high dose, total cumulative dose and pulse therapy being associated with ON.[138] Moreover, other clinical manifestations (i.e., arthritis, NPSLE, paynaud's, vasculitis, serositis, hypertension, renal disease and SLEDAI >8), laboratory parameters (anti-CL IgM) and medications (i.e. CS and cyclophosphamide) are directly correlated with increased ON incidence.[138] Antiphospholipid score has also been shown to be a novel risk factor for ON in SLE patients. [142]

Clinical Presentation and Diagnosis of ON

The clinical presentation of ON is variable, being related to the size and location of the affected bone(s).[140] It may be clinically silent or present with pain of gradual onset that can progress to severe pain, bone collapse and joint damage. The hip and knee are the most frequently affected joints followed by ankle and shoulder (**Figure**). Multifocal ON has been reported in up to half of patients with SLE.

Figure. Joints Most Affected by ON in Patients with SLE.
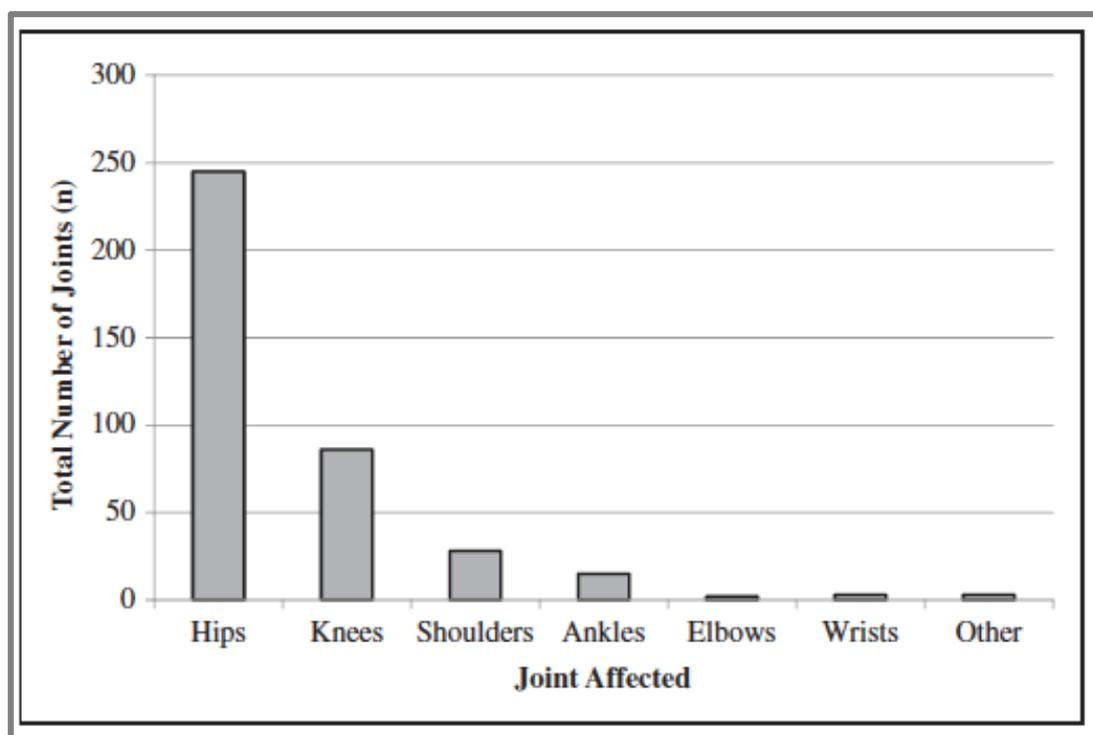
The early diagnosis of ON is challenging because it frequently occurs silently; there is often a time lag between the development of ON and the onset of symptoms. Diagnosis typically involves clinical history and physical examination and imaging: X-

ray, skeletal scintigraphy and MRI, which may be used to detect a very early stage of ON with greater sensitivity and specificity.

Prevention and Treatment of ON

The early diagnosis of ON is challenging (time lag between the development of ON and the onset of symptoms). Prevention involves reducing the modifiable risk factors (smoking, alcohol intake, heavy works). Importantly, physicians should be alert of ON in all lupus patients receiving corticosteroids, which should be prescribed at the lowest dose and for the shortest period of time.[139] **More conservative use of corticosteroid** use, even in **lupus nephritis** is now possible (rituxilup, belimumab, voclosporin) and **tacrolimus**, has been associated with a lower rate of ON after renal transplantation. In addition, w**arfarin** and **statins**, may reduce the incidence of corticosteroid-induced ON. **Generally, individual risk assessment** for ON development should be made prior to and during treatment for SLE.

Non-operative treatments for ON in SLE include immobilization. For small lesions that will spontaneously heal and electrical stimulation, which could be indicated as an adjunct to other therapies. Some medications have been used anecdotally, with some benefit, including lipid-lowering drugs, anticoagulants, vasodilators, and bisphosphonates. Stem cell treatment of femoral head ON has been reported as useful therapy; however, this therapeutic approach has not been standardized and will need to be studied further.

Surgical intervention is based on the severity of joint damage. For early ON, core decompression and percutaneous debridement and drilling is recommended. For ON lesions prior to bone collapse, bone grafting and osteotomies are also a possibility. Once subchondral fracture collapse is evident, bone grafting, hemi-resurfacing and total hip arthroplasty are the treatment options.

Professor Pons-Estel concluded his presentation by summarising that ON could be silent and multifocal in many patients. MRI should be used to detect early ON, allowing prevention strategies and modifiable risk factors to be implemented as soon as possible. Corticosteroids should be used at a low dose and for a short period and treatment strategies should consider both the joint and extent of injury caused by ON.

Alveolar hemorrage. Ricard Cervera (Spain)

Professor Cervera' presentation reviewed the main challenges in the differential diagnosis of alveolar haemorrhage in SLE, its treatment options and also the new research trends in this area.

Professor Cervera described diffuse alveolar hemorrhage (DAH) as a real nightmare, highlighting that diffuse alveolar hemorrhage (DAH) has been described in a number of systemic autoimmune diseases, including systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), Behçet's disease, microscopic polyarteritis, cryoglobulinaemic granulomatous vasculitis and others.

Diagnosis and Clinical Characteristics of DAH

Diffuse alveolar hemorrhage syndromes are notoriously difficult to diagnose, with the majority of cases exhibiting little or no haemoptysis, even with large volume intra-alveolar bleeding. Diagnosis is based on new infiltrates on the chest X ray or CT, an acute decrease in hemoglobin without any other bleeding source and either hemoptysis, hypoxemia, bronchoscopic or biopsy evidence of pulmonary hemorrage or increased diffusion capacity of the lung. Differential diagnosis includes: pulmonary infections; acute lupus pneumonitis; pulmonary embolism; uremic pneumonitis; bleeding from coagulopathies; and cardiogenic or noncardiogenic pulmonary edema.[143]

The main causes of DAH include systemic autoimmune diseases, accounting for 30–40%.[143] Mirouse et al reported data from 104 patients with DAH showing that 76% of patients presented with vasculitis and 25% with SLE or APS.[144] Professor Cervera then presented a case series of 47 with CAPS, 69% of whom had pulmonary involvement and 21% with acute respiratory disease,[145] before outlining the pathology of DAH in APS, where most patients present with pulmonary capillaritis or microvascular thrombosis (**Figure**).[146]

Figure. Presentation of DAH in APS: Histopathology.
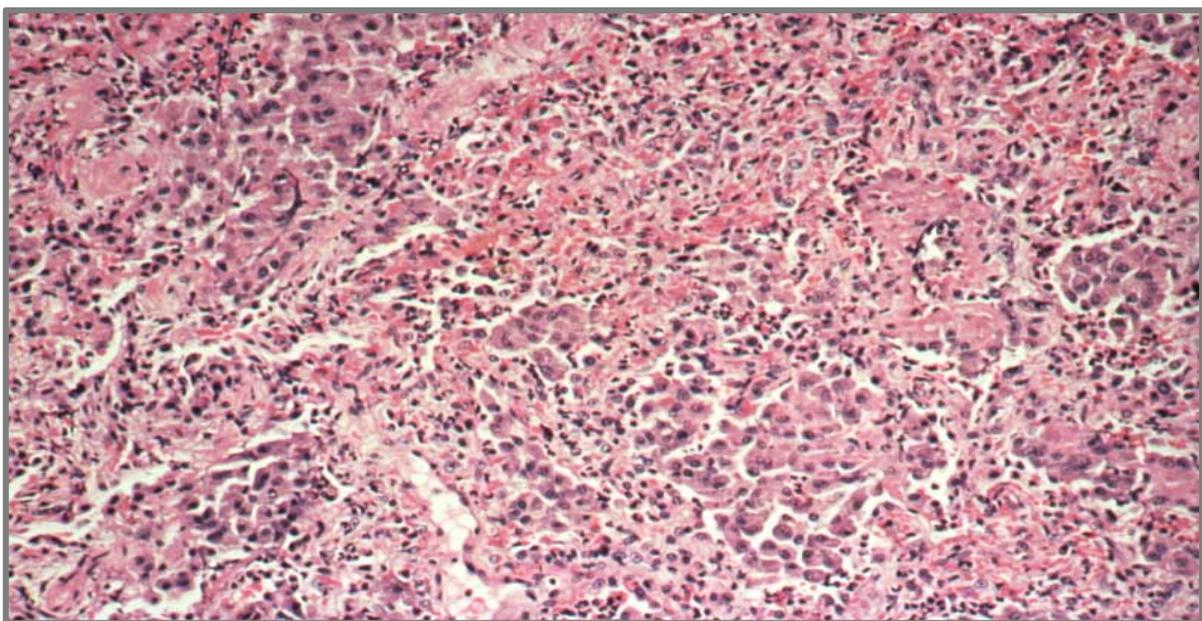
Returning to the data from Mirouse et al, Professor Cervera noted DAH most commonly affects middle-aged women and 50% of lupus patients first present with pulmonary manifestations compared with 80% of vasculitis patients. Likewise, about half of lupus patients present with renal involvement compared to about 90% of vasculitis patients.[144] Patients with lupus and DAH are typically admitted to ICU within a day of hospital admission, whereas those with vasculitis take about 6 days. Patients with APS usually also presented with thrombocytopenia, unlike those with vasculitis, who usually presented with renal failure. Those with lupus and APS usually presented with high levels of LDH.

Treatment of DAH

Treatment of DAH comprises ICU management, corticosteroids, immunosuppression, plasma exchange and rituximab. Mirouse et al found more pateints with vasculitis (62%) than with SLE (24%) required renal replacement therapy, moreover requirement for time on ventilation was short for patients with SLE. [144] Significantly more patients with vasculitis required immunosuppressive therapy for DAH than those with lupus. In terms of outcomes, a higher number of vasculitis patients (17%) died as a result of DAH compared with lupus patients (12%) and significantly more had a bacterial infection (34% vs 12%). Twenty-two (47%) patients had a lung CT-scan evaluation during follow-up showing lung fibrosis in 8 (36%) patients. Pulmonary function testing was performed in 15 (32%) patients and showed a restrictive pulmonary disorder in 6 (40%) cases. Therefore the long-term outcome for these patients is not good.

Professor Cervera concluded his presentation by highlighting that alveolar hemorrhage has been described in several systemic autoimmune diseases, including SLE, APS – mainly CAPS -and systemic vasculitis. The radiological signs are florid but often highly non-specific. Bronchoalveolar lavage to exclude infection is the pivotal investigation. In general, in treated autoimmune diseases, infiltrative lung disorders can, for practical therapeutic purposes, be divided broadly into opportunistic infection, which demands specific antimicrobial therapy and a reduction in immunosuppression, and a wide range of immunologically mediated processes, which demand the opposite approach: Intensification of immunosuppressive therapy. Therefore, active steps must be taken to diagnose alveolar hemorrhage.

References

1. Ravindran A, Casal Moura M, Fervenza FC, *et al.* In Patients with Membranous Lupus Nephritis, Exostosin-Positivity and Exostosin-Negativity Represent Two Different Phenotypes. *J Am Soc Nephrol*. 2021;32(3):695-706.
2. Anders HJ, Saxena R, Zhao MH, *et al.* Lupus nephritis. *Nat Rev Dis Primers*. 2020;6(1):7.
3. Dall'Era M, Cisternas MG, Smilek DE, *et al.* Predictors of long-term renal outcome in lupus nephritis trials: lessons learned from the Euro-Lupus Nephritis cohort. *Arthritis Rheumatol*. 2015;67(5):1305-13.
4. ReBioLup: http://rebiolup.com (Accessed 20 October 2021).
5. De Rosa M, Azzato F, Toblli JE, *et al.* A prospective observational cohort study highlights kidney biopsy findings of lupus nephritis patients in remission who flare following withdrawal of maintenance therapy. *Kidney Int*. 2018;94(4):788-94.
6. Anders HJ**.** Re-biopsy in lupus nephritis. *Ann Transl Med*. 2018;6(Suppl 1):S41.
7. Chen TK, Estrella MM, Fine DM**.** Predictors of kidney biopsy complication among patients with systemic lupus erythematosus. *Lupus*. 2012;21(8):848-54.
8. Narváez J, Ricse M, Gomà M, *et al.* The value of repeat biopsy in lupus nephritis flares. *Medicine (Baltimore)*. 2017;96(24):e7099.
9. Anders HJ, Huber TB, Isermann B, Schiffer M**.** CKD in diabetes: diabetic kidney disease versus nondiabetic kidney disease. *Nat Rev Nephrol*. 2018;14(6):361-77.
10. Boumpas DT, Austin HA, 3rd, Vaughn EM, *et al.* Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis. *Lancet*. 1992;340(8822):741-5.
11. Chan TM, Li FK, Tang CS, *et al.* Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. Hong Kong-Guangzhou Nephrology Study Group. *N Engl J Med*. 2000;343(16):1156-62.
12. Houssiau FA, Vasconcelos C, D'Cruz D, *et al.* Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. *Arthritis Rheum*. 2002;46(8):2121-31.
13. Houssiau FA, Vasconcelos C, D'Cruz D, *et al.* Early response to immunosuppressive therapy predicts good renal outcome in lupus nephritis: lessons from long-term followup of patients in the Euro-Lupus Nephritis Trial. *Arthritis Rheum*. 2004;50(12):3934-40.
14. Tektonidou MG, Dasgupta A, Ward MM**.** Risk of End-Stage Renal Disease in Patients With Lupus Nephritis, 1971-2015: A Systematic Review and Bayesian Meta-Analysis. *Arthritis Rheumatol*. 2016;68(6):1432-41.
15. Bultink IEM, de Vries F, van Vollenhoven RF, Lalmohamed A**.** Mortality, causes of death and influence of medication use in patients with systemic lupus erythematosus vs matched controls. *Rheumatology (Oxford)*. 2021;60(1):207-16.
16. Rovin BH, Solomons N, Pendergraft WF, 3rd, *et al.* A randomized, controlled double-blind study comparing the efficacy and safety of dose-ranging voclosporin with placebo in achieving remission in patients with active lupus nephritis. *Kidney Int*. 2019;95(1):219-31.
17. Furie R, Rovin BH, Houssiau F, *et al.* Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis. *N Engl J Med*. 2020;383(12):1117-28.
18. Rovin BH, Teng YKO, Ginzler EM, *et al.* Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet*. 2021;397(10289):2070-80.
19. Singh JA, Hossain A, Kotb A, Wells G**.** Risk of serious infections with immunosuppressive drugs and glucocorticoids for lupus nephritis: a systematic review and network meta-analysis. *BMC Med*. 2016;14(1):137.
20. Illei GG, Takada K, Parkin D, *et al.* Renal flares are common in patients with severe proliferative lupus nephritis treated with pulse immunosuppressive therapy: long-term followup of a cohort of 145 patients participating in randomized controlled studies. *Arthritis Rheum*. 2002;46(4):995-1002.
21. Mok CC, Ho LY, Ying SKY, *et al.* Long-term outcome of a randomised controlled trial comparing tacrolimus with mycophenolate mofetil as induction therapy for active lupus nephritis. *Ann Rheum Dis*. 2020;79(8):1070-6.

22. Teng YKO, Bruce IN, Diamond B*, et al.* Phase III, multicentre, randomised, double-blind, placebo-controlled, 104-week study of subcutaneous belimumab administered in combination with rituximab in adults with systemic lupus erythematosus (SLE): BLISS-BELIEVE study protocol. *BMJ Open*. 2019;9(3):e025687.

23. Fanouriakis A, Kostopoulou M, Cheema K*, et al.* 2019 Update of the Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of lupus nephritis. *Ann Rheum Dis*. 2020;79(6):713-23.

24. Austin HA, 3rd, Klippel JH, Balow JE*, et al.* Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. *N Engl J Med*. 1986;314(10):614-9.

25. Grootscholten C, Ligtenberg G, Hagen EC*, et al.* Azathioprine/methylprednisolone versus cyclophosphamide in proliferative lupus nephritis. A randomized controlled trial. *Kidney Int*. 2006;70(4):732-42.

26. Touma Z, Urowitz MB, Ibañez D, Gladman DD**.** Time to recovery from proteinuria in patients with lupus nephritis receiving standard treatment. *J Rheumatol*. 2014;41(4):688-97.

27. Petri MA, van Vollenhoven RF, Buyon J*, et al.* Baseline predictors of systemic lupus erythematosus flares: data from the combined placebo groups in the phase III belimumab trials. *Arthritis Rheum*. 2013;65(8):2143-53.

28. Inês L, Duarte C, Silva RS*, et al.* Identification of clinical predictors of flare in systemic lupus erythematosus patients: a 24-month prospective cohort study. *Rheumatology (Oxford)*. 2014;53(1):85-9.

29. Petri M, Singh S, Tesfasyone H, Malik A**.** Prevalence of flare and influence of demographic and serologic factors on flare risk in systemic lupus erythematosus: a prospective study. *J Rheumatol*. 2009;36(11):2476-80.

30. Nikpour M, Urowitz MB, Ibañez D, Gladman DD**.** Frequency and determinants of flare and persistently active disease in systemic lupus erythematosus. *Arthritis Rheum*. 2009;61(9):1152-8.

31. Conti F, Ceccarelli F, Perricone C*, et al.* Flare, persistently active disease, and serologically active clinically quiescent disease in systemic lupus erythematosus: a 2-year follow-up study. *PLoS One*. 2012;7(9):e45934.

32. Palmer SC, Tunnicliffe DJ, Singh-Grewal D*, et al.* Induction and Maintenance Immunosuppression Treatment of Proliferative Lupus Nephritis: A Network Meta-analysis of Randomized Trials. *Am J Kidney Dis*. 2017;70(3):324-36.

33. Atisha-Fregoso Y, Malkiel S, Harris KM*, et al.* Phase II Randomized Trial of Rituximab Plus Cyclophosphamide Followed by Belimumab for the Treatment of Lupus Nephritis. *Arthritis Rheumatol*. 2021;73(1):121-31.

34. Rovin BH, Furie R, Latinis K*, et al.* Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. *Arthritis Rheum*. 2012;64(4):1215-26.

35. Condon MB, Ashby D, Pepper RJ*, et al.* Prospective observational single-centre cohort study to evaluate the effectiveness of treating lupus nephritis with rituximab and mycophenolate mofetil but no oral steroids. *Ann Rheum Dis*. 2013;72(8):1280-6.

36. Gladman D, Ginzler E, Goldsmith C*, et al.* The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. *Arthritis Rheum*. 1996;39(3):363-9.

37. Gladman DD, Urowitz MB, Rahman P, Ibañez D, Tam LS**.** Accrual of organ damage over time in patients with systemic lupus erythematosus. *J Rheumatol*. 2003;30(9):1955-9.

38. Petri M, Purvey S, Fang H, Magder LS**.** Predictors of organ damage in systemic lupus erythematosus: the Hopkins Lupus Cohort. *Arthritis Rheum*. 2012;64(12):4021-8.

39. Rahman P, Gladman DD, Urowitz MB, Hallett D, Tam LS**.** Early damage as measured by the SLICC/ACR damage index is a predictor of mortality in systemic lupus erythematosus. *Lupus*. 2001;10(2):93-6.

40. Ruiz-Arruza I, Gladman D, Ibanez D, Urowitz M**.** Antimalarials protect systemic lupus erythematosus patients from damage accrual during the first five years of the disease. *Arthritis Rheum*. 2012;64:S611.

41. Furie R, Petri M, Zamani O*, et al.* A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. *Arthritis Rheum*. 2011;63(12):3918-30.

42. Navarra SV, Guzmán RM, Gallacher AE*, et al.* Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. *Lancet*. 2011;377(9767):721-31.

43. Bruce IN, Urowitz M, van Vollenhoven R*, et al.* Long-term organ damage accrual and safety in patients with SLE treated with belimumab plus standard of care. *Lupus*. 2016;25(7):699-709.

44. Urowitz MB, Ohsfeldt RL, Wielage RC*, et al.* Organ damage in patients treated with belimumab versus standard of care: a propensity score-matched comparative analysis. *Ann Rheum Dis*. 2019;78(3):372-9.

45. Fanouriakis A, Kostopoulou M, Alunno A*, et al.* 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis*. 2019;78(6):736-45.

46. Kuhn A, Aberer E, Bata-Csörgő Z*, et al.* S2k guideline for treatment of cutaneous lupus erythematosus - guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV). *J Eur Acad Dermatol Venereol*. 2017;31(3):389-404.

47. Mathian A, Pha M, Haroche J*, et al.* Withdrawal of low-dose prednisone in SLE patients with a clinically quiescent disease for more than 1 year: a randomised clinical trial. *Ann Rheum Dis*. 2020;79(3):339-46.

48. van Vollenhoven RF, Mosca M, Bertsias G*, et al.* Treat-to-target in systemic lupus erythematosus: recommendations from an international task force. *Ann Rheum Dis*. 2014;73(6):958-67.

49. van Vollenhoven R, Voskuyl A, Bertsias G*, et al.* A framework for remission in SLE: consensus findings from a large international task force on definitions of remission in SLE (DORIS). *Ann Rheum Dis*. 2017;76(3):554-61.

50. Saccon F, Zen M, Gatto M*, et al.* Remission in systemic lupus erythematosus: testing different definitions in a large multicentre cohort. *Ann Rheum Dis*. 2020;79(7):943-50.

51. Zen M, Iaccarino L, Gatto M*, et al.* Prolonged remission in Caucasian patients with SLE: prevalence and outcomes. *Ann Rheum Dis*. 2015;74(12):2117-22.

52. Bardin T, Keenan RT, Khanna PP*, et al.* Lesinurad in combination with allopurinol: a randomised, double-blind, placebo-controlled study in patients with gout with inadequate response to standard of care (the multinational CLEAR 2 study). *Ann Rheum Dis*. 2017;76(5):811-20.

53. Polachek A, Gladman DD, Su J, Urowitz MB**.** Defining Low Disease Activity in Systemic Lupus Erythematosus. *Arthritis Care Res (Hoboken)*. 2017;69(7):997-1003.

54. Tselios K, Gladman DD, Touma Z*, et al.* Clinical Remission and Low Disease Activity Outcomes Over 10 Years in Systemic Lupus Erythematosus. *Arthritis Care Res (Hoboken)*. 2019;71(6):822-8.

55. Alarcón GS, Ugarte-Gil MF, Pons-Estel G*, et al.* Remission and low disease activity state (LDAS) are protective of intermediate and long-term outcomes in SLE patients. Results from LUMINA (LXXVIII), a multiethnic, multicenter US cohort. *Lupus*. 2019;28(3):423-6.

56. Franklyn K, Lau CS, Navarra SV*, et al.* Definition and initial validation of a Lupus Low Disease Activity State (LLDAS). *Ann Rheum Dis*. 2016;75(9):1615-21.

57. Zen M, Iaccarino L, Gatto M*, et al.* Lupus low disease activity state is associated with a decrease in damage progression in Caucasian patients with SLE, but overlaps with remission. *Ann Rheum Dis*. 2018;77(1):104-10.

58. Jesus D, Matos A, Henriques C*, et al.* Derivation and validation of the SLE Disease Activity Score (SLE-DAS): a new SLE continuous measure with high sensitivity for changes in disease activity. *Ann Rheum Dis*. 2019;78(3):365-71.

59. Gatto M, Zen M, Iaccarino L, Doria A**.** New therapeutic strategies in systemic lupus erythematosus management. *Nat Rev Rheumatol*. 2019;15(1):30-48.

60. Zen M, Iaccarino L, Gatto M*, et al.* The effect of different durations of remission on damage accrual: results from a prospective monocentric cohort of Caucasian patients. *Ann Rheum Dis*. 2017;76(3):562-5.

61. Moroni G, Gatto M, Tamborini F*, et al.* Lack of EULAR/ERA-EDTA response at 1 year predicts poor long-term renal outcome in patients with lupus nephritis. *Ann Rheum Dis*. 2020;79(8):1077-83.
62. Zen M, Saccon F, Gatto M*, et al.* Prevalence and predictors of flare after immunosuppressant discontinuation in patients with systemic lupus erythematosus in remission. *Rheumatology (Oxford)*. 2020;59(7):1591-8.
63. Morand EF, Furie R, Tanaka Y*, et al.* Trial of Anifrolumab in Active Systemic Lupus Erythematosus. *N Engl J Med*. 2020;382(3):211-21.
64. Furie R, Khamashta M, Merrill JT*, et al.* Anifrolumab, an Anti-Interferon-α Receptor Monoclonal Antibody, in Moderate-to-Severe Systemic Lupus Erythematosus. *Arthritis Rheumatol*. 2017;69(2):376-86.
65. Furie RA, Morand EF, Bruce IN*, et al.* Type I interferon inhibitor anifrolumab in active systemic lupus erythematosus (TULIP-1): a randomised, controlled, phase 3 trial. *The Lancet Rheumatology*. 2019;1(4):e208-e19.
66. Pellerin A, Otero K, Czerkowicz JM*, et al.* Anti-BDCA2 monoclonal antibody inhibits plasmacytoid dendritic cell activation through Fc-dependent and Fc-independent mechanisms. *EMBO Mol Med*. 2015;7(4):464-76.
67. Werth V, Furie R, Romero-Diaz J*, et al.* OP0193 BIIB059, A HUMANIZED MONOCLONAL ANTIBODY TARGETING BDCA2 ON PLASMACYTOID DENDRITIC CELLS (PDC), SHOWS DOSE-RELATED EFFICACY IN THE PHASE 2 LILAC STUDY IN PATIENTS (PTS) WITH ACTIVE CUTANEOUS LUPUS ERYTHEMATOSUS (CLE). *Annals of the Rheumatic Diseases*. 2020;79(Suppl 1):120.
68. Furie R vVR, Kalunian K, Navarra S, Romero-Díaz J, Werth V, Huang X, Carroll H, Meyers A, Musselli C, Barbey C, Franchimont N. . Arthritis Rheumatol. 2020; 72 (suppl 10). **.** Efficacy and Safety Results from a Phase 2, Randomized, Double-Blind Trial of BIIB059, an Anti-Blood Dendritic Cell Antigen 2 Antibody, in SLE [abstract]. *Arthritis Rheumatol*. 2020;72
69. Marcus R, Davies A, Ando K*, et al.* Obinutuzumab for the First-Line Treatment of Follicular Lymphoma. (1533-4406 (Electronic)).
70. Goede V, Fischer K Fau - Busch R, Busch R Fau - Engelke A*, et al.* Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. (1533-4406 (Electronic)).
71. Reddy V, Klein C, Isenberg DA*, et al.* Obinutuzumab induces superior B-cell cytotoxicity to rituximab in rheumatoid arthritis and systemic lupus erythematosus patient samples. (1462-0332 (Electronic)).
72. Mössner E, Brünker P Fau - Moser S, Moser S Fau - Püntener U*, et al.* Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell-mediated B-cell cytotoxicity. (1528-0020 (Electronic)).
73. Furie R, Aroca G, Alvarez A*, et al.* Two-Year Results from a Randomized, Controlled Study of Obinutuzumab for Proliferative Lupus Nephritis [abstract]. *Arthritis Rheumatol*. 2020;72.
74. Lintner KE, Wu YL, Yang Y*, et al.* Early Components of the Complement Classical Activation Pathway in Human Systemic Autoimmune Diseases. (1664-3224 (Print)).
75. Weinstein AA-O, Alexander RV, Zack DJ**.** A Review of Complement Activation in SLE. (1534-6307 (Electronic)).
76. Tam JC, Bidgood SR, McEwan WA, James LC**.** Intracellular sensing of complement C3 activates cell autonomous immunity. (1095-9203 (Electronic)).
77. Sorbara MT, Foerster EG, Tsalikis J*, et al.* Complement C3 Drives Autophagy-Dependent Restriction of Cyto-invasive Bacteria. (1934-6069 (Electronic)).
78. Kamitaki NA-O, Sekar A, Handsaker RA-O*, et al.* Complement genes contribute sex-biased vulnerability in diverse disorders. (1476-4687 (Electronic)).
79. Simoni L, Presumey J, van der Poel CE*, et al.* Complement C4A Regulates Autoreactive B Cells in Murine Lupus. (2211-1247 (Electronic)).
80. Girardi G, Berman J Fau - Redecha P, Redecha P Fau - Spruce L*, et al.* Complement C5a receptors and neutrophils mediate fetal injury in the antiphospholipid syndrome. (0021-9738 (Print)).
81. Girardi G, Redecha P Fau - Salmon JE, Salmon JE**.** Heparin prevents antiphospholipid antibody-induced fetal loss by inhibiting complement activation. (1078-8956 (Print)).

82. Berman J, Girardi G Fau - Salmon JE, Salmon JE. TNF-alpha is a critical effector and a target for therapy in antiphospholipid antibody-induced pregnancy loss. (0022-1767 (Print)).

83. Gelber SE, Brent E, Redecha P, *et al.* Prevention of Defective Placentation and Pregnancy Loss by Blocking Innate Immune Pathways in a Syngeneic Model of Placental Insufficiency. *J Immunol*. 2015;195(3):1129-38.

84. Banadakoppa M, Balakrishnan M, Yallampalli C. Common variants of fetal and maternal complement genes in preeclampsia: pregnancy specific complotype. *Sci Rep*. 2020;10(1):4811.

85. Bazzan M, Todros T, Tedeschi S, *et al.* Genetic and molecular evidence for complement dysregulation in patients with HELLP syndrome. *Thromb Res*. 2020;196:167-74.

86. Youssef L, Miranda J, Blasco M, *et al.* Complement and coagulation cascades activation is the main pathophysiological pathway in early-onset severe preeclampsia revealed by maternal proteomics. *Sci Rep*. 2021;11(1):3048.

87. Lynch AM, Murphy JR, Byers T, *et al.* Alternative complement pathway activation fragment Bb in early pregnancy as a predictor of preeclampsia. *Am J Obstet Gynecol*. 2008;198(4):385.e1-9.

88. Viall CA, Chamley LW. Histopathology in the placentae of women with antiphospholipid antibodies: A systematic review of the literature. *Autoimmun Rev*. 2015;14(5):446-71.

89. Buurma A, Cohen D, Veraar K, *et al.* Preeclampsia is characterized by placental complement dysregulation. *Hypertension*. 2012;60(5):1332-7.

90. Shamonki JM, Salmon JE, Hyjek E, Baergen RN. Excessive complement activation is associated with placental injury in patients with antiphospholipid antibodies. *Am J Obstet Gynecol*. 2007;196(2):167.e1-5.

91. Cohen D, Buurma A, Goemaere NN, *et al.* Classical complement activation as a footprint for murine and human antiphospholipid antibody-induced fetal loss. *J Pathol*. 2011;225(4):502-11.

92. Chighizola CB, Lonati PA, Trespidi L, Meroni PL, Tedesco F. The Complement System in the Pathophysiology of Pregnancy and in Systemic Autoimmune Rheumatic Diseases During Pregnancy. *Front Immunol*. 2020;11:2084.

93. Kim MY, Guerra MM, Kaplowitz E, *et al.* Complement activation predicts adverse pregnancy outcome in patients with systemic lupus erythematosus and/or antiphospholipid antibodies. *Ann Rheum Dis*. 2018;77(4):549-55.

94. Scambi C, Ugolini S, Tonello M, *et al.* Complement activation in the plasma and placentas of women with different subsets of antiphospholipid syndrome. *Am J Reprod Immunol*. 2019;82(6):e13185.

95. Salmon JE, Heuser C, Triebwasser M, *et al.* Mutations in complement regulatory proteins predispose to preeclampsia: a genetic analysis of the PROMISSE cohort. *PLoS Med*. 2011;8(3):e1001013.

96. Tedesco F, Borghi MO, Gerosa M, *et al.* Pathogenic Role of Complement in Antiphospholipid Syndrome and Therapeutic Implications. *Front Immunol*. 2018;9:1388.

97. Augusto JF, Langs V, Demiselle J, *et al.* Low Serum Complement C3 Levels at Diagnosis of Renal ANCA-Associated Vasculitis Is Associated with Poor Prognosis. *PLoS One*. 2016;11(7):e0158871.

98. Schreiber A, Xiao H, Jennette JC, *et al.* C5a receptor mediates neutrophil activation and ANCA-induced glomerulonephritis. *J Am Soc Nephrol*. 2009;20(2):289-98.

99. Ohlsson S, Holm L, Hansson C, *et al.* Neutrophils from ANCA-associated vasculitis patients show an increased capacity to activate the complement system via the alternative pathway after ANCA stimulation. *PLoS One*. 2019;14(6):e0218272.

100. Antovic A, Mobarrez F, Manojlovic M, *et al.* Microparticles Expressing Myeloperoxidase and Complement C3a and C5a as Markers of Renal Involvement in Antineutrophil Cytoplasmic Antibody-associated Vasculitis. *J Rheumatol*. 2020;47(5):714-21.

101. Xiao H, Dairaghi DJ, Powers JP, *et al.* C5a receptor (CD88) blockade protects against MPO-ANCA GN. *J Am Soc Nephrol*. 2014;25(2):225-31.

102. Jayne DRW, Bruchfeld AN, Harper L, *et al.* Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA-Associated Vasculitis. *J Am Soc Nephrol*. 2017;28(9):2756-67.

103. Jayne DRW, Merkel PA, Schall TJ, Bekker P. Avacopan for the Treatment of ANCA-Associated Vasculitis. *N Engl J Med*. 2021;384(7):599-609.

104. Woodruff MC, Ramonell RP, Nguyen DC, *et al.* Extrafollicular B cell responses correlate with neutralizing antibodies and morbidity in COVID-19. *Nat Immunol*. 2020;21(12):1506-16.

105. Ferreira-Gomes M, Kruglov A, Durek P, *et al.* SARS-CoV-2 in severe COVID-19 induces a TGF-β-dominated chronic immune response that does not target itself. *Nat Commun*. 2021;12(1):1961.

106. Lorenz M, Jung S, Radbruch A. Switch transcripts in immunoglobulin class switching. *Science*. 1995;267(5205):1825-8.

107. Mei HE, Hahne S, Redlin A, *et al.* Plasmablasts With a Mucosal Phenotype Contribute to Plasmacytosis in Systemic Lupus Erythematosus. *Arthritis Rheumatol*. 2017;69(10):2018-28.

108. Aue A, Szelinski F, Weißenberg SY, *et al.* Elevated STAT1 expression but not phosphorylation in lupus B cells correlates with disease activity and increased plasmablast susceptibility. *Rheumatology (Oxford)*. 2020;59(11):3435-42.

109. Goropevšek A, Gorenjak M, Gradišnik S, *et al.* Increased Levels of STAT1 Protein in Blood CD4 T Cells from Systemic Lupus Erythematosus Patients Are Associated with Perturbed Homeostasis of Activated CD45RA(-)FOXP3(hi) Regulatory Subset and Follow-Up Disease Severity. *J Interferon Cytokine Res*. 2017;37(6):254-68.

110. Dörner T, Tanaka Y, Petri MA, *et al.* Baricitinib-associated changes in global gene expression during a 24-week phase II clinical systemic lupus erythematosus trial implicates a mechanism of action through multiple immune-related pathways. *Lupus Sci Med*. 2020;7(1).

111. Wallace DJ, Furie RA, Tanaka Y, *et al.* Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet*. 2018;392(10143):222-31.

112. Dörner T, Lipsky PE. B cells: depletion or functional modulation in rheumatic diseases. *Curr Opin Rheumatol*. 2014;26(2):228-36.

113. S H. Phase 1b/2a Trial of Tofacitinib, an Oral Janus Kinase Inhibitor, in Systemic Lupus Erythematosus. 13th World Congress on SLE, San Francisco April 3rd, 2019. Oral presentation.

114. Dörner T, Szelinski F, Lino AC, Lipsky PE. Therapeutic implications of the anergic/postactivated status of B cells in systemic lupus erythematosus. *RMD Open*. 2020;6(2).

115. Weißenberg SY, Szelinski F, Schrezenmeier E, *et al.* Identification and Characterization of Post-activated B Cells in Systemic Autoimmune Diseases. *Front Immunol*. 2019;10:2136.

116. Chen YE, Korbet SM, Katz RS, Schwartz MM, Lewis EJ. Value of a complete or partial remission in severe lupus nephritis. *Clin J Am Soc Nephrol*. 2008;3(1):46-53.

117. Furie R, Aroca G, Alvarez A, *et al.* A Phase II Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Obinutuzumab or Placebo in Combination with Mycophenolate Mofetil in Patients with Active Class III or IV Lupus Nephritis [abstract]. *Arthritis Rheumatol*. 2019;71.

118. Ioannidis JP, Boki KA, Katsorida ME, *et al.* Remission, relapse, and re-remission of proliferative lupus nephritis treated with cyclophosphamide. *Kidney Int*. 2000;57(1):258-64.

119. Faurschou M, Starklint H, Halberg P, Jacobsen S. Prognostic factors in lupus nephritis: diagnostic and therapeutic delay increases the risk of terminal renal failure. *J Rheumatol*. 2006;33(8):1563-9.

120. Asherson RA, Cervera R, de Groot PG, *et al.* Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. *Lupus*. 2003;12(7):530-4.

121. Cervera R, Font J, Gómez-Puerta JA, *et al.* Validation of the preliminary criteria for the classification of catastrophic antiphospholipid syndrome. *Ann Rheum Dis*. 2005;64(8):1205-9.

122. Asherson RA, Piette JC. The catastrophic antiphospholipid syndrome 1996: acute multi-organ failure associated with antiphospholipid antibodies: a review of 31 patients. *Lupus*. 1996;5(5):414-7.

123. Legault K, Schunemann H, Hillis C, *et al.* McMaster RARE-Bestpractices clinical practice guideline on diagnosis and management of the catastrophic antiphospholipid syndrome. *J Thromb Haemost*. 2018.

124. Pineton de Chambrun M, Larcher R, Pène F, *et al.* In-Hospital Mortality-Associated Factors in Patients With Thrombotic Antiphospholipid Syndrome Requiring ICU Admission. *Chest*. 2020;157(5):1158-66.

125. Cervera R, Rodríguez-Pintó I, Colafrancesco S, *et al.* 14th International Congress on Antiphospholipid Antibodies Task Force Report on Catastrophic Antiphospholipid Syndrome. *Autoimmun Rev*. 2014;13(7):699-707.

126. Cervera R, Bucciarelli S, Plasín MA, *et al.* Catastrophic antiphospholipid syndrome (CAPS): descriptive analysis of a series of 280 patients from the "CAPS Registry". *J Autoimmun*. 2009;32(3-4):240-5.

127. Chaturvedi S, Braunstein EM, Yuan X, *et al.* Complement activity and complement regulatory gene mutations are associated with thrombosis in APS and CAPS. *Blood*. 2020;135(4):239-51.

128. Yelnik CM, Miranda S, Mékinian A, *et al.* Patients with refractory catastrophic antiphospholipid syndrome respond inconsistently to eculizumab. *Blood*. 2020;136(21):2473-7.

129. Chasset F, Tounsi T, Cesbron E, *et al.* Efficacy and tolerance profile of thalidomide in cutaneous lupus erythematosus: A systematic review and meta-analysis. *J Am Acad Dermatol*. 2018;78(2):342-50.e4.

130. Cortés-Hernández J, Torres-Salido M, Castro-Marrero J, Vilardell-Tarres M, Ordi-Ros J**.** Thalidomide in the treatment of refractory cutaneous lupus erythematosus: prognostic factors of clinical outcome. *Br J Dermatol*. 2012;166(3):616-23.

131. Braunstein I, Goodman NG, Rosenbach M, *et al.* Lenalidomide therapy in treatment-refractory cutaneous lupus erythematosus: histologic and circulating leukocyte profile and potential risk of a systemic lupus flare. *J Am Acad Dermatol*. 2012;66(4):571-82.

132. Aitmehdi R, Arnaud L, Francès C, *et al.* Long-term efficacy and safety outcomes of lenalidomide for cutaneous lupus erythematosus: A multicenter retrospective observational study of 40 patients. *J Am Acad Dermatol*. 2021;84(4):1171-4.

133. Fennira F, Chasset F, Soubrier M, *et al.* Lenalidomide for refractory chronic and subacute cutaneous lupus erythematosus: 16 patients. *J Am Acad Dermatol*. 2016;74(6):1248-51.

134. Gladman DD, Chaudhry-Ahluwalia V, Ibañez D, Bogoch E, Urowitz MB**.** Outcomes of symptomatic osteonecrosis in 95 patients with systemic lupus erythematosus. *J Rheumatol*. 2001;28(10):2226-9.

135. Prasad R, Ibanez D, Gladman D, Urowitz M**.** The role of non-corticosteroid related factors in osteonecrosis (ON) in systemic lupus erythematosus: a nested case-control study of inception patients. *Lupus*. 2007;16(3):157-62.

136. Pons-Estel BA, Catoggio LJ, Cardiel MH, *et al.* The GLADEL multinational Latin American prospective inception cohort of 1,214 patients with systemic lupus erythematosus: ethnic and disease heterogeneity among "Hispanics". *Medicine (Baltimore)*. 2004;83(1):1-17.

137. Kallas R, Li J, Petri M**.** Predictors of osteonecrosis in systemic lupus erythematosus: A prospective cohort study. *Arthritis Care Res (Hoboken)*. 2020.

138. Hussein S, Suitner M, Béland-Bonenfant S, *et al.* Monitoring of Osteonecrosis in Systemic Lupus Erythematosus: A Systematic Review and Metaanalysis. *J Rheumatol*. 2018;45(10):1462-76.

139. Nawata K, Nakamura J, Ikeda K, *et al.* Transitional changes in the incidence of osteonecrosis in systemic lupus erythematosus patients: focus on immunosuppressant agents and glucocorticoids. *Rheumatology (Oxford)*. 2018;57(5):844-9.

140. Gladman DD, Dhillon N, Su J, Urowitz MB**.** Osteonecrosis in SLE: prevalence, patterns, outcomes and predictors. *Lupus*. 2018;27(1):76-81.

141. Gurion R, Tangpricha V, Yow E, *et al.* Avascular necrosis in pediatric systemic lupus erythematosus: a brief report and review of the literature. *Pediatr Rheumatol Online J*. 2015;13:13.

142. Hisada R, Kato M, Ohnishi N, *et al.* Antiphospholipid score is a novel risk factor for idiopathic osteonecrosis of the femoral head in patients with systemic lupus erythematosus. *Rheumatology (Oxford)*. 2019;58(4):645-9.

143. Martínez-Martínez MU, Oostdam DAH, Abud-Mendoza C**.** Diffuse Alveolar Hemorrhage in Autoimmune Diseases. *Curr Rheumatol Rep*. 2017;19(5):27.

144. Mirouse A, Parrot A, Audigier V*, et al.* Severe diffuse alveolar hemorrhage related to autoimmune disease: a multicenter study. *Crit Care*. 2020;24(1):231.

145. Bucciarelli S, Espinosa G, Asherson RA*, et al.* The acute respiratory distress syndrome in catastrophic antiphospholipid syndrome: analysis of a series of 47 patients. *Ann Rheum Dis*. 2006;65(1):81-6.

146. Stoots SA, Lief L, Erkan D**.** Clinical Insights into Diffuse Alveolar Hemorrhage in Antiphospholipid Syndrome. *Curr Rheumatol Rep*. 2019;21(10):56.