Discussion points

- Identify patients at higher risk to develop nephritis and look for renal disease -especially when active- by urinalysis
- Do not underestimate hematuria-especially if active serology and extrarenal lupus. Best to do a biopsy irrespective of the presence or not of proteinuria
- Have a low threshold for renal biopsy. If you think about it, just do it (unless contraindicated)
- Look for crescents/fibrinoid necrosis and tubular atrophy and interstitial fibrosis in the biopsy report
- Stratify according to severity (histologic and clinical factors) and treat accordingly. For most patients mycophenolate mofetil (MMF) is the drug for initial choice based upon its lack of gonadal toxicity
- In patients with chronic disease and scarring in the kidney, or those with nephrotic range proteinuria, may need to wait longer for proteinuria to subside
- Proteinuria is a good prognostic factor (if below 0.7 mg/dl) irrespective of hematuria
- Hematuria/active urine sediment are reliable indicators for activity and flare but not for prognosis

Case 3: 25-year-old woman with arthritis, photosensitive rashes, leukopenia and thrombocytopenia and positive lupus serologies

A 25-year-old woman presents with arthritis, photosensitive rashes, leukopenia and thrombocytopenia and positive lupus serologies. Her proteinuria is 1.3 gm/day and she has hematuria, normal serum creatinine and albumin 3.2g/day. Renal biopsy showed focal proliferative lupus nephritis (Class IIIa with AI 7 and CI 0). She was treated with MMF and then with azathioprine because of contemplation of pregnancy reaching remission. Two years later she has nephrotic range proteinuria, increased creatinine to 1.4 mg/dl, and a biopsy consistent with pure membranous lupus nephropathy. No chronicity.

Discussion points

- Membranous nephropathy has a more benign course. Histologic transition may be observed
- Patients with nephrotic range proteinuria and impaired renal function are at greater risk for end stage renal disease and require more aggressive therapy
- Anticoagulant treatment in cases of nephrotic syndrome with serum albumin <20 g/L, presence of antiphospholipid antibodies or other pro-thrombotic conditions

Learning objectives

- Recognise, document and treat renal disease in SLE
- Explain how membranous disease differs from proliferative disease?
- Describe the targets of therapy
- Describe treatment of refractory disease

State-of-the-art Lecture: Measuring Outcomes

01 T2T, LLDAS AND REMISSION: OPERATIONAL DEFINITIONS MEET REALITY?

Andrea Doria. University of Padova, Italy

10.1136/lupus-2019-la.12

In the wake of the effect of the treat-to-target (T2T) approach in rheumatoid arthritis and other rheumatic conditions,

remission and low disease activity (LDA) have recently been the objective of a number of studies in systemic lupus erythematosus (SLE), where the validity of some definitions for their effect on organ damage were tested.

Remission An agreement on the principles that should guide the development of the definition of remission was published in 2017,¹ and some new definitions of remission have been proposed.¹⁻³

All definitions distinguish two subtypes of remission, namely complete (no serological and clinical activity) and clinical (serologically active clinical quiescent disease). They differ in terms of allowed therapies and disease activity indices used. To be defined as a therapeutic goal, a potential target should be achievable by a significant proportion of patients. Prolonged remission was rarely reported in the past, but in the last few years it has been shown that durable remission might be not anymore rare in SLE.³⁻⁶ Discrepancy can be due to the application of definitions of remission different from those used in the past, together with improved knowledge and management of the disease.

All the aforementioned definitions of remission succeeded in identifying patients with a better disease outcome.

DORIS and Zen definitions are close on several aspects,^{1 3} with the substantial difference of excluding the physician global assessment (PGA) by Zen *et al.* PGA has the known limitation of having relevant inter-observer variability⁷ and, moreover, a significant difference between pre-laboratory and post-laboratory PGA was highlighted.⁸

Interestingly, comparable results in terms of prevalence of remission and of protective effect on damage progression were obtained using either Zen's^{3 4} or DORIS' definition,^{2 4} suggesting that exclusion of PGA might not alter the ability to identify patients with better prognosis and that achievement of clinical SLE disease activity index (SLEDAI)-2K equal to zero is probably the main driver of the protective effect of remission.

Low disease activity

The concept of LDA has recently been proposed in SLE and preliminary data suggest that patients achieving LDA have better outcomes.^{2 9-11}

Three definitions of LDA have recently been set up: Those by Franklyn *et al.*⁹ (10) and Ugarte *et al.*² are similar, although the latter does not consider PGA. These definitions were tested in different cohorts with promising results, with patients in LDA having lower damage progression than those without LDA.

The definition by Polachek *et al.* is quite different, with the cut off for definition being a clinical SLEDAI-2K ≤2, and antimalarials the only medications allowed.¹⁰ This definition was associated with improved outcomes in the original cohort, but it has not been validated in other cohorts.

Notably, measurement of disease activity should be continuous for defining LDA and not categorical (item present/absent) as SLEDAI is, being thus inadequate to capture low-intermediate activity in each single organ domain. In fact, LDA should not only correspond to milder lupus manifestations, but it should identify patients with low activity irrespective of the type of manifestations (e.g. low persistent proteinuria, low-active arthritis). Thus, SLEDAI is not adequate to define LDA and to separate remission from LDA on a continuum. In this regard, PGA, which is indeed a continuous index, could be helpful in complementing SLEDAI; however, PGA does not include objective measure of disease activity and, as mentioned above, it has a number of substantial limitations.

A new disease activity index named SLE-DAS ('<http://sle-das.eu/>') has recently been proposed and validated,¹² which is a continuous disease activity index with a higher sensitivity to

change than SLEDAI. This new index is very promising in the evaluation of a treatment response and in discriminating LDA from remission.

Learning objectives

- Describe definitions of remission in SLE
- Identify patients who can achieve SLE remission
- Identify patients who can achieve SLE LDA

REFERENCES

1. 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.
2. Ugarte-Gil MF, Wojdyla D, Pons-Estel GJ, et al. Remission and Low Disease Activity Status (LDAS) protect lupus patients from damage occurrence: data from a multiethnic, multinational Latin American Lupus Cohort (GLADEL). *Annals of the Rheumatic Diseases* 2017;**76**(12):2071–74.
3. Zen M, Iaccarino L, Gatto M, et al. Prolonged remission in Caucasian patients with SLE: prevalence and outcomes. *Annals of the Rheumatic Diseases* 2015;**74**(12):2117–22.
4. Mok CC, Ho LY, Tse SM, et al. Prevalence of remission and its effect on damage and quality of life in Chinese patients with systemic lupus erythematosus. *Ann Rheum Dis* 2017;**76**(8):1420–25.
5. Tsang ASMW, Bultink IE, Heslinga M, et al. Both prolonged remission and Lupus Low Disease Activity State are associated with reduced damage accrual in systemic lupus erythematosus. *Rheumatology (Oxford, England)* 2017;**56**(1):121–28.
6. 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. *Annals of the Rheumatic Diseases* 2016;**75**(3):562–65.
7. Isenberg DA, Allen E, Farewell V, et al. An assessment of disease flare in patients with systemic lupus erythematosus: a comparison of BILAG 2004 and the flare version of SELENA. *Ann Rheum Dis* 2011;**70**(1):54–9.
8. Aranow C. A pilot study to determine the optimal timing of the Physician Global Assessment (PGA) in patients with systemic lupus erythematosus. *Immunologic Research* 2015;**63**(1–3):167–69.
9. Franklyn K, Lau CS, Navarra SV, et al. Definition and initial validation of a Lupus Low Disease Activity State (LLDAS). *Annals of the Rheumatic Diseases* 2015;**75**(9):1615–21.
10. Polachek A, Gladman DD, Su J, et al. Defining Low Disease Activity in Systemic Lupus Erythematosus. *Arthritis care & research* 2017;**69**(7):997–1003.
11. 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.
12. 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.

Plenary II: Novel Therapeutic Approaches to Improve Clinical Outcomes

01 TARGETING TYPE I INTERFERONS

Richard Furie. *Hofstra Northwell School of Medicine, New York, USA*

10.1136/lupus-2019-la.13

Evidence that the type I interferon pathway plays an important role in the pathogenesis of SLE has been mounting over the last several decades.^{1–3} Therefore, it was only natural that this pathway be the target of therapeutic interventions in systemic lupus erythematosus (SLE). Although rontalizumab and sifalimumab, the first two monoclonal antibodies directed against interferon alpha to be evaluated in clinical trials, yielded negative and modest clinical trial results, respectively, other pursuits were undertaken that initially proved more successful. Phase II SLE clinical trial data were quite robust with anifrolumab, an antibody to the type I interferon receptor that inhibits all five subtypes of type I interferons.⁴ These results reaffirmed the clinical significance of type I interferons.

This presentation will review various strategies being pursued in order to block the interferon pathway.⁵

Learning objectives

- Describe the role of the type I interferon pathway in the pathogenesis of SLE
- Discuss strategies for inhibiting the type I interferon pathway
- Analyse results of clinical trials in SLE of interferon inhibitors

REFERENCES

1. Bengtsson AA, Rönnblom L. Role of interferons in SLE. *Best Practice & Research Clinical Rheumatology* 2017;**31**(3):415–28.
2. Crow MK, Rönnblom L. Report of the inaugural Interferon Research Summit: interferon in inflammatory diseases. *Lupus Sci Med* 2018;**5**(1):e000276.
3. Crow MK, Rönnblom L. Type I interferons in host defence and inflammatory diseases. *Lupus Sci Med* 2019;**6**(1):e000336.
4. Furie R, Khamashta M, Merrill JT, et al. Anifrolumab, an Anti-Interferon- α Receptor Monoclonal Antibody, in Moderate-to-Severe Systemic Lupus Erythematosus. *Arthritis & Rheumatology* 2017;**69**(2):376–86.
5. Furie R, Werth VP, Merola JF, et al. Monoclonal antibody targeting BDCA2 ameliorates skin lesions in systemic lupus erythematosus. *Journal of Clinical Investigation* 2019;**129**(3):1359–71.

02 TARGETING B CELLS AND PLASMA CELLS

David Isenberg. *University College London, UK*

10.1136/lupus-2019-la.14

It is almost 20 years since B-cell depletion using rituximab [anti CD20] was introduced for the treatment of systemic lupus erythematosus (SLE).¹ Despite the failure of two major clinical trials² both the ACR and EULAR guidelines recommend rituximab for the treatment of lupus nephritis and NHS England permits its use more widely.

Well over 50,000 SLE patients worldwide have been treated with rituximab and it seems to be very effective for many haematological, musculoskeletal, dermatological and renal aspects of lupus.³ Increased risk of infection and hypogammaglobinaemia remain concerns.⁴ Newer fully-humanized anti-CD20 monoclonal antibodies (e.g. ofatumumab) offer a way forward for those who become allergic to rituximab, which is 20% murine. Research indicates that there are at least two types of anti-CD20 antibodies.

In contrast, anti-plasma cell therapies have been much less widely utilized. Some studies using bortezomib (anti-proteasome) have been reported⁵ and studies with experimental anti CD19 monoclonals are under way. Although significant reductions in autoantibodies (and immunoglobulins) and a rise in serum complement have been noted, precursor B-cells and T-cells largely remain unaffected resulting in a rapid re-population of short-lived plasma cells. This result suggests that this approach will need to be combined with other B-cell therapies.

Learning objectives

- Describe the role anti-CD20 antibodies in the treatment of SLE
- Explain the benefits of rituximab and ofatumumab for patients with SLE
- Discuss utilization of proteasome inhibitors, such as bortezomib, for the treatment of SLE

REFERENCES

1. Leandro MJ, Edwards JC, Cambridge G, et al. An open study of B lymphocyte depletion in systemic lupus erythematosus. *Arthritis & Rheumatism* 2002;**46**(10):2673–77.