Lupus Nephritis UHL Renal Guideline

University Hospitals of Leicester NHS
NHS Trust

RRCV CMG
Renal and Transplant Service
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1. Introduction

This guidance has been produced to facilitate standardisation of the management of patients with lupus nephritis presenting to the Renal Department at UHL.

Lupus nephritis (LN) affects approximately 60% of patients with systemic lupus erythematosus (SLE) and is associated with adverse outcomes. Survival at 5 and 10 years with SLE is 95% and 92% respectively and this falls to 88% at 10 years in the presence of nephritis. LN is more common and more severe in patients of African or Asian descent. Nephritis is apparent in 50% of patients with SLE at presentation and 10-30% of patients develop established renal failure within 15 years. Without treatment, survival is 20-25%.

Treatment should be guided by kidney histology and common indications for initial biopsy are:

- Proteinuria > 50mg/mmol +/- haematuria
- Nephritic syndrome
- Nephrotic syndrome

Less commonly, a kidney biopsy may be required to investigate patients with SLE and unexplained renal impairment with bland urine, isolated non-visible haematuria and unexplained pyuria. Repeat biopsy can be helpful in a number of patients. There are national and international guidelines of situations where a repeat biopsy is indicated – relapse / flare, refractoriness to treatment, failure to decrease PCR by ≥ 50% at 1 year, failure to achieve complete remission in 1-2 years.

Abnormal GFR is associated with chronic change, so other markers of “disease activity” should be sought in patents with eGFR < 30 mL/min/1.72m2 before proceeding with a biopsy. The aim of this guideline is to provide concise advice on the management of patients with lupus nephritis.

2. Scope

The guideline is applicable to all clinical staff involved in the care of patients with lupus nephritis.

3. Recommendations, Standards and Procedural Statements

Management of patients presenting with possible or confirmed Lupus Nephritis should be in conjunction with one of the consultants who deliver the vasculitis/lupus

clinic. Management will follow latest national and international guidelines (the European League against Rheumatism (EULAR), KDIGO, British Society of Rheumatology and the American College of Rheumatology). Patients presenting with LN should be offered recruitment into clinical trials where appropriate. Please discuss with the renal vasculitis/lupus clinic team as soon as possible.

Treatment is guided by the histological class and the patient's other medical history and history of previous treatment regimens. Treatment aims to preserve kidney function, prevent flares, improve disease control and improve survival while minimising adverse effects of treatment.

Most often treatment involves Corticosteroids and Mycophenolate. Other therapeutic options include Cyclophosphamide, Azathioprine, Calcineurin inhibitors and Biologics Rituximab and Belimumab as per NHSE commissioning guidelines. Supportive treatments for CKD (including ACE inhibitors, Angiotensin receptor blockers, SGLT2 inhibitors) and cardiovascular risk protection should always be considered.

Information leaflets about the above treatments are available from the renal vasculitis/lupus clinic or from the Lupus UK website (www.lupusuk.org.uk).

Failure to improve within 6 months, to achieve a partial response within 6-12 months or complete response within 2 years should prompt consideration of repeat renal biopsy and switching to alternative agent.

4. General guidance and preparation for treatment

4.1 Informed consent

Patients should be given information about all proposed treatments and discussion about risks and benefits documented in the medical notes. For treatment with Cyclophosphamide or Rituximab, written consent on UHL consent form or electronically on Concentric should be obtained. Information leaflets about medications used to treat LN are available on www.lupusuk.org.uk and www.versusarthritis.org

- Substantial benefits include:
  - Improved survival
  - Disease control
  - Prevention / amelioration of permanent organ damage

Information regarding the prescribing, side effects, and risk of serious complications related to treatment with Cyclophosphamide, Rituximab and corticosteroids can be found in the Renal Vasculitis UHL guideline C2/2008.

- Provide information

- Consider referral to the Rheumatology team and Rheumatology Lupus specialist nurse for counselling

- Information on how and when to seek advice:
    - Signpost to Lupus UK website www.lupusuk.org.uk
    - Immunosuppression medication booklets, steroid card
    - Patients Know Best access
    - Daily oral inspection for candidiasis
    - Annual eye test if on HCQ, and ophthalmology referral after 5 years.

Vaccination/screening advice:

- Follow the national vaccination schedule and refer to the Green Book for the most current advice
- Live vaccinations should be avoided until ≥ 3 months after stopping immunosuppression
- Vaccinations should be completed before treatment if feasible (aim 4 weeks before). Otherwise, they should be postponed until after induction therapy completed (at least 4 weeks after rituximab)
- Annual inactivated influenza vaccination
- COVID-19 vaccination
- Pneumococcal vaccination (every 5 years)
- Shingles Vaccination (Shingrix is recommended as it is a recombinant subunit vaccine) where appropriate
- HPV vaccination where appropriate
- Cervical screening following cyclophosphamide where appropriate
    - Annual for 3 years
    - Every 3 years thereafter
- Sun exposure protection

Contraception and pregnancy planning:

- Women of childbearing potential should have advice on the optimal time to conceive in relation to disease activity and medication
- Offer advice on contraception
- Women with lupus at risk of thromboembolism (e.g. severe nephrotic syndrome, antiphospholipid syndrome or active systemic SLE) should be advised to avoid oestrogen-based contraception

4.2 Baseline Investigations

- Assess disease activity through history taking, clinical examination and disease severity scores (e.g. BILAG, SLEDAI-6K).
- FBC, U+E, LFT, CRP, CK. Serum Glucose, lipids.
- Immunology: dsDNA levels, ENA, ANA, C3, C4, IgG, IgA, IgM and SPEP.
- Lupus anticoagulant, anticardiolipin and β2 microglobulin antibodies.
    - If positive repeat after 12 weeks to confirm positive result.
    - Anticoagulation will interfere with result of LA.
- Urine dip, urine PCR/ACR.
- HIV, Hepatitis B surface Ag, Hepatitis B core Ab, Hepatitis C Abs
    - If positive, refer to infectious diseases

    - Refer to UK systemic anti-cancer board guidelines for prevention of Hepatitis B reactivation.
        - https://www.uksactboard.org/position-statements

- CXR, QuantiFERON test
    - Refer to TB team if positive or suspicion of TB
- Assessment of health status and quality of life recommended by the BSR guideline (SF-36 / HRQOL – at 0, 3, 6 and 12 months, then annually).

4.3 Prophylaxis and Adjunctive Treatment

4.3.1 Pneumocystis Jiroveci Pneumonia

- Co-trimoxazole 480mg daily PO.
- For patients who are intolerant or allergic to co-trimoxazole, alternatives include dapsone 100mg od (2nd line), atovaquone 750mg bd (3rd line), or discuss with microbiologist.

Duration:

- Continuously while on oral Cyclophosphamide
- For patients receiving oral mycophenolate who are considered at high risk of PJP infection e.g. frail, chronic respiratory or cardiac disease, pulmonary involvement
- From start of therapy to 4 weeks post IV Cyclophosphamide
- From start of therapy to 6 months post Rituximab
- Any other immunosuppressive used in conjunction with ≥ Prednisolone 20mg daily.

4.3.2 Gastric Protection

- For initial 6 months of therapy or for duration of steroid treatment (stop at steroid withdrawal).
- Lansoprazole 30mg daily or equivalent PPI.

4.3.3 Fungal Infection

- All patients receiving induction therapy with Cyclophosphamide.
    - Nystatin 1ml qds PO.

4.3.4 Osteoporosis (see Leicestershire Osteoporosis Group guidelines)

- Adcal D3 chewable, 2 tablets daily (or equivalent) while on steroids unless contra-indicated.
- Assess fracture risk (FRAX score).
- Correct vitamin D deficiency where present.
- If expectant long-term steroid therapy, consider DEXA at baseline and then at the recommended intervals for consideration of bisphosphonates.

- Consider Alendronate 70mg weekly in all patients on long-term steroids unless contra-indicated (bisphosphonates are contra-indicated if eGFR<30 ml/min or planning pregnancy – refer to the metabolic bone clinic).
- Bisphosphonate drug holiday after 3-5 years.

4.3.5 Thromboembolic Disease

- VTE prophylaxis is warranted during any period of immobility or hospital admission unless contraindicated.
- Anticoagulate for Antiphospholipid Syndrome.
- Consider anticoagulation if nephrotic with albumin < 20 g/L or significant oedema.

4.3.6 Cardiovascular risk reduction and Renoprotection

- Optimise blood pressure and anti-proteinuric therapy (RASi).
- Consider SGLT2i (wait until around 3 months after starting induction therapy)
- Smoking cessation
- Lipid management according to CVD risk

4.3.7 Ovarian protection during IV cyclophosphamide therapy (for women who may wish to consider pregnancy in the future)

- Induction:
  - 0 hours Leuprorelin 3.75mg SC or IM injection.
  - 6 hours Ganirelix 0.25mg SC injection (Day 1) and to continue 0.25mg ganirelix. SC injection daily (until day 5-7).
- Cyclophosphamide can be given after 4th dose of ganirelix.
- Maintenance:
  - Repeat Leuprorelin 3.75mg SC or IM every 4 weeks until Cyclophosphamide is completed.

5. Treatment by LN Class

LN $3_{A/C}$, LN $4_{A/C}$ (+/- LN 5):

- Steroid plus
  - Mycophenolate (preferred for side effect profile and ease of use) or
  - Low dose IV Cyclophosphamide or
  - Azathioprine – selected cases only (intolerance of CyP or MMF, no adverse prognostic factors).
  - +/- CNI (e.g. Voclosporin)
  - +/- Belimumab

LN $3_{A/C}$, LN $4_{A/C}$ (+/- LN 5) with adverse histological features (crescents / necrosis):

- Steroid plus
  - Mycophenolate or
  - Low dose IV Cyclophosphamide or

- High dose IV Cyclophosphamide or
- Oral Cyclophosphamide
- +/- CNI
- +/- Belimumab

LN 5 and Nephrotic:

Note:
- 20% have fall in GFR, 8-12% ESKD over 10 years.
- VTE occurs in 13-23%.

- Steroid plus:
  - Mycophenolate or
  - IV Cyclophosphamide
  - +/- CNI or
  - Rituximab.

LN 5 and non-nephrotic proteinuria:
- RASi
- Corticosteroid +/- Azathioprine

LN 2 with PCR > 100 despite RASi:
- Corticosteroid +/- Azathioprine.

LN2 with PCR < 100:
- Treat as per extra-renal disease

LN1 or 2 with podocytopathy (heavy proteinuria):
- Treat as per minimal change
- Treat as per extra-renal disease

TIN
- Corticosteroid +/- Azathioprine 1.5-2mg/kg/day

APS-associated Nephropathy
- Can be present in absence of serological markers
- Microangiopathy, fibrous intimal hyperplasia, organising thrombi, focal cortical atrophy, fibrous occlusions of arteries/arterioles
  - Hydroxychloroquine
  - Antiplatelet / anticoagulant
  - Immunosuppression if LN present

5.1 Hydroxychloroquine
- Assess renal and liver function (adjust dose if impaired).
- Ask patient about visual impairment (not corrected by glasses). If impairment or eye disease present, assessment by an optometrist is advised and any abnormality should be referred to an ophthalmologist.

- Initiate hydroxychloroquine treatment if no abnormality detected.
    - 200mg daily if <60kg, 400mg daily if >60kg.
    - Maximum dose 6.5 mg/kg actual body weight up to a maximum of 400mg daily.
- Patient should immediately report any visual disturbances, including abnormal colour vision, or pigmentary changes.
- Annual eye test, and ophthalmology referral after 5 years.

5.2 Voclosporin

- Voclosporin is a novel calcineurin inhibitor, and is approved by NHSE as a treatment option in adults with active class III, IV, or V lupus nephritis in combination with mycophenolate mofetil
- Use of voclosporin allows a more rapid steroid taper, and the regimen used in the AURORA-1 trial is recommended
- Note that MDT discussion and completion of Blueteq form is required

6. Biologic Therapies

Rituximab and/or Belimumab may be considered in accordance with NICE and NHSE commissioning guidelines and after documented discussion by two consultants preferably at the vasculitis/lupus MDT (http://www.england.nhs.uk/wp-content/uploads/2013/09/a13- psa.pdf, http://www.england.nhs.uk/wp-content/uploads/2013/09/a13-psa.pdf). Rituximab administration and monitoring guideline are detailed in the Renal Vasculitis UHL guideline C2/2008.

IV Ig and plasmapheresis may be considered in discussion with haematology for patients with refractory cytopenias, TTP, rapidly deteriorating acute confusion or catastrophic variant of APS. If IVIg is considered, early discussion with immunology consultant is required.

6.1 Belimumab

- Belimumab is a monoclonal antibody that inhibits B cell activating factor (BAFF), and is approved by NICE as an option as add-on treatment for active autoantibody-positive SLE in people with high disease activity despite standard treatment, only if:
    - high disease activity is defined as at least 1 serological biomarker (positive anti-double-stranded DNA or low complement) and a SELENA-SLEDAI score of greater than or equal to 10
    - treatment is continued beyond 24 weeks only if the SELENA-SLEDAI score has improved by 4 points or more
- Note that MDT discussion and completion of Blueteq form is required
- Subcutaneous (weekly) or intravenous (monthly) formulations are available
    - Intravenous may be preferable if adherence is a concern
- Patients should provide written consent on UHL consent form or electronically via Concentric
    - Common side effects are: nausea, diarrhoea, fever, stuffy or runny nose and sore throat, cough, trouble sleeping, leg or arm pain,

depression, headache, and pain, redness, itching, or swelling at the site of injection (when given subcutaneously

- Serious side effects include:
  - Serious infection or sepsis
  - Allergic (hypersensitivity) reactions
  - Depression, suicide, self-injury
  - Progressive Multifocal Leucoencephalopathy (PML)
  - Cancer (risk is unknown but any medicine affecting the immune system may increase risk of cancer)
- Assess patients for risk of depression or suicide before starting belimumab
  - Advise patients to promptly seek medical attention if they develop new or worsening depression, suicidal ideation or thoughts about injuring themselves.

7. Monitoring of lupus patients on a regular basis for disease manifestations, drug toxicity and comorbidities

- Patients with active disease to be reviewed at least every 1-3 months.
- Patients with stable low disease activity or in remission to be monitored less frequently e.g. 6 to 12 monthly.
- Measurement of disease activity and damage using standardized SLE assessment tools.
- Assessment of health status and quality of life annually.
- Re-evaluation of aPL prior to pregnancy or surgery and in the presence of a new severe manifestation or a vascular event.
- Anti-Ro and La antibodies status to be assessed prior to pregnancy.
- Assessment of co-morbidities, such as atherosclerotic disease, osteoporosis, avascular necrosis, malignancy and infection with annual review of modifiable risk factors (i.e. hypertension, dyslipidaemia, diabetes, high body mass index and smoking).

8. Withdrawal of Immunosuppression

In remission for ≥ 3-5 years and in the absence of disease activity (achieved CR and absence of extra-renal disease, withdrawal of immunosuppression can be considered.

- Glucocorticoids can gradually be withdrawn over 6-12 months.
- Patient remains well during taper and after 6 months steroid-free.
- Decide whether to continue, decrease or taper/withdraw other immunosuppressive agent over 6 months.
- The total process takes 18-24 months.

Patients should be cautioned regarding risk of relapse and remain vigilant for symptoms/signs that warrant immediate review.

Routine OPD required every 3 months during withdrawal and for ≥ 1 year afterwards.

Lifelong monitoring and management required for:

- Disease activity
- Organ damage
- Treatment complications
- Follow-up required even when immunosuppression-free

9. Treatment – Flare

Incidence is 27-66%. Minor “flare” occurring during taper/withdrawal of immunosuppression should be managed by escalating immunosuppression to previous effective level.

There should be a low threshold to restage disease with a further biopsy. Significant relapses should be treated with same initial therapy that worked initially, unless cumulative cyclophosphamide exposure is a concern.

10. Monitoring and Audit Criteria

Key Performance Indicator	Method of Assessment	Frequency	Lead
Use of Rituximab in accordance with NHSE policy	Annual Rituximab audit	Annual	MDT
Supportive therapy for prevention of long-term complications	Annual Vasculitis/Lupus clinic audit	Annual	MDT

11. Legal Liability Guideline Statement

See section 6.4 of the UHL Policy for Policies for details of the Trust Legal Liability statement for Guidance documents

12. Supporting Documents and Key References

- Gordon C, Amissah-Arthur MB, Gayed M, et al. The British Society for Rheumatology guideline for the management of systemic lupus erythematosus in adults. Rheumatology (Oxford). 2018;57(1):e1-e45.

- Kidney Disease: Improving Global Outcomes (KDIGO) Lupus Nephritis Work Group. KDIGO 2024 Clinical Practice Guideline for the management of Lupus Nephritis. Kidney Int. 2024;105(1S):S1-S69.

- Fanouriakis A, Kostopoulou M, Andersen J, et al. EULAR recommendations for the management of systemic lupus erythematosus: 2023 update. Ann Rheum Dis. 2024;83(1):15-29.

13. Key Words

Lupus Nephritis, Cyclophosphamide, Rituximab, Mycophenolate, BILAG.

~~This table is used to track the development and approval and dissemination of the~~ document and any changes made on revised / reviewed versions.

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