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 needs to be guided by kidney histology and common indications for initial biopsy are:

1. Proteinuria > 50mg/mmol +/- haematuria
2. Nephritic syndrome
3. Nephrotic syndrome

Less commonly, 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 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 done 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 renal 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 the NHSE commissioning guidelines. Supportive treatment with ACE inhibitors, Angiotensin receptor blockers and cardiovascular risk protection should always be considered.

Information leaflets about all above treatments is available from the renal vasculitis/lupus clinic or printable from 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 requires consideration of repeat renal biopsy and switching to alternative agent.

3.1 General guidance and preparation for treatment

3.1.1 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 forms should be obtained. Information leaflets about medications used to treat LN are available on www.lupusuk.org.uk and www.arthritisresearchuk.org

- Substantial benefits include:
    - Improved survival.
    - Disease control.
    - Prevention / amelioration of permanent organ damage.
- Serious complications and concerns related to treatment with Cyclophosphamide:
    - Infection.
    - Infertility, early menopause (circa 50%).
        - Dependent on cumulative dose and age.
        - Teratogenicity – contraceptive advise as appropriate.
        - Malignancy
            - Related to cumulative dose of cyclophosphamide > 25g (this dose is unlikely to be used in modern treatment regimens).
            - Lymphoma 4-11 fold increase.

        - Skin cancer 4-10 fold increase.
        - Bladder cancer 4-33 fold increase, 3% at 10 years.

    - Hair loss.
    - GI upset.

- Steroid side effects:

    - Mood disturbance, insomnia, change in appearance, weight gain.
    - Diabetes mellitus, bone disease, infection, GI disease.
    - Secondary hypoadrenalism.

3.1.2 Provide information

- Consider referral to the Lupus specialist nurse for counselling and provide Lupus Helpline number (01708 731251).

- Information on how and when to seek advise:

    - Daily oral inspection for candidiasis.
    - Monitoring booklets, steroid card.
    - Renal Patient View access.
    - LUPUS UK website www.lupusuk.org.uk
    - Annual eye test with HCQ and ophthalmology referral after 5 years.

- Vaccination/screening advice:

    - Live vaccinations should be avoided until ≥ 3 months after stopping immunosuppression.
    - Vaccinations should be completed before treatment if feasible. Otherwise they should be postponed until after induction therapy completed (≥ 4 months after rituximab).
    - Annual inactivated influenza vaccination.
    - Pneumococcal vaccination.
    - HPV vaccination.
    - Cervical screening following cyclophosphamide.

        - Annual for 3 years.
        - Every 3 years thereafter.

    - Sun exposure protection.

- Contraception and pregnancy planning:

    - All women of child bearing age should have advice on optimal time to conceive in relation to disease activity and medication.
    - Offer advice on contraception.

- Women with lupus at risk of thromboembolism (e.g antiphospholipis disease or active systemic SLE) should be advised to avoid oestrogen containing contraception.
- Women with severe nephrotic syndrome should avoid oestrogen based contraception.

3.1.3 Baseline Investigations

- Assess disease activity through history taking, clinical examination and disease severity scores (BILAG,SLEDAI-6K).
- FBC, U+E, LFT, CRP, ESR, CK, TPMT level. Serum Glucose, lipids.
- Immunology: dsDNA levels, ENA, ANA, C3, C4, IgG, IgA, IgM and PEP.
- Lupus anticoagulant, anticardiolipin and B2 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 and C serology, VZV antibodies.
- CXR – BTS guidance regarding latent TB treatment.
- Quantiferon IGRA test.
- Assessment of health status and quality of life recommended by the BSR guideline (SF-36 / HRQOL – at 0, 3, 6 and 12 month, then annually).

3.2 Prophylaxis and Adjunctive Treatment

3.2.1 Pneumocystis Jiroveci Pneumonia

- Co-trimoxazole 480mg daily or 960mg thrice weekly.

- Alternatives:

    - Dapsone 100mg daily.
    - Pentamidine 300mg nebulised monthly.
    - Atoquavone (750 mg BD).

- Duration:

    - Continuously while on oral Cyclophosphamide.
    - For patients receiving oral mycophenolate who are considered at high risk of 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.

3.2.2 Gastric Protection

- For initial 6 months of therapy or for duration of steroid treatment (stop at steroid withdrawal).

- Ranitidine 150mg twice daily or Omeprazole 20mg daily.

3.2.3 Fungal Infection

- All patients receiving induction therapy, on Cyclophosphamide or Prednisolone ≥ 15mg daily.

    - Nystatin 1ml qds or Fluconazole 50mg daily.

3.2.4 Osteoporosis (see GIO prevention guideline on Insite)

- Adcal D3, 2 tablets daily (or equivalent) 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 2 yearly regular intervals for considerations of bisphosphonates.
- Consider Alendronate 70mg weekly in all patients unless contra-indicated (bisphosphonates contra-indicated if eGFR<30 ml/min or planning pregnancy).

    - Drug holiday after 3-5 years.

3.2.5 Thromboembolic Disease

- VTE prophylaxis warranted during any period of immobility or hospital admission unless contra-indicated.
- Anticoagulate with Antiphospholipid Syndrome.
- Consider anticoagulation if nephrotic with albumin < 20 or significant oedema.

3.2.6 Cardiovascular risk reduction and Renoprotection

- Optimise blood pressure and anti-proteinuric therapy (RAASi).
- Smoking cessation.
- Statin (target cholesterol <4).
- Aspirin.

3.2.7 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.
- Record near visual acuity of each eye (with glasses where appropriate) using a standard reading chart.
- Initiate hydroxychloroquine treatment if no abnormality detected.
- 200mg daily if <60kg, 200mg twice 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, pigmentary.

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

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.

3.3 Treatment by LN Class

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

- Steroid plus
    - Mycophenolate (preferred for SE profile and ease of use) or
    - low dose IV Cyclophosphamide or
    - Azathioprine – selected cases only (intolerance of CY or MPA, no adverse prognostic factors).

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.

LN 5 and Nephrotic:

- 20% have fall in GFR, 8-12% ERF over 10 years.
- VTE 13-23%.
- Steroid plus:
    - Mycophenolate High dose IV Cyclophosphamide or
    - CNI or
    - Rituximab.

LN 5 and non-nephrotic proteinuria:

- RAASi.
- Corticosteroid plus Azathioprine.

LN 2 with PCR > 100 despite RAASi:

- 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.

Biological Therapies

Rituximab and/or Belimumab may be considered in accordance with NICE and NHSE commissioning guidelines and after documented discussion by 2 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 is detailed in the guideline 'IV Rituximab for patients with vasculitis and renal involvement' available on INSITE. UHL Guideline and prescription for Belimumab are under development.

IVIg 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.

3.4 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 with assessments above and those below.
- 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, dyslipidemia, diabetes, high body mass index and smoking).

3.5 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.

1. Glucocorticoids can gradually be withdrawn over 6-12 months.
2. Patient remains well during taper and after 6 months steroid-free.
    a. Decide whether to continue, decrease or taper/withdraw other immunosuppressive agent over 6 months.

    b. The total process takes 18-24 months.

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

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

5. Lifelong monitoring and management required for:

    1. disease activity.
    2. organ damage.
    3. treatment complications.
    4. follow-up required even when immunosuppression-free.

3.6 Treatment – Flare

Incidence is 27-66%. Minor “flare” occurring during taper/withdrawal of immunosuppression should be managed be 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.

5. Monitoring and Audit Criteria

Key Performance Indicator	Method of Assessment	Frequency	Lead

Use of Rituximab in accordance with NHSE policy	Annual Rituximab audit	Annual	Reem Al-Jayyousi/ Rupert Major
Supportive therapy for prevention of long term complications	Annual Vasculitis/Lupus clinic audit	Annual	Reem al-Jayyousi

6. 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

7. Supporting Documents and Key References

- The British Society for Rheumatology guideline for the management of systemic lupus erythematosus in adults https://doi.org/10.1093/rheumatology/kex286.

- KDIGO Clinical Practice Guideline for Glomerulonephritis.
- KI, 2012, Vol2 , Suppl 2.

- Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis 2012;71:1771–1782.

- American College of Rheumatology Guidelines for Screening, Treatment, and Management of Lupus Nephritis.
  Arthritis Care & Research, Vol. 64, No. 6, June 2012, pp 797–808

8. Key Words

Lupus Nephritis, Cyclophosphamide, Rituximab, Mycophenolate, BILAG.

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