Management of lupus nephritis

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INTRODUCTION

- In the US, approximately 35% of adults with SLE have clinical evidence of nephritis at the time of diagnosis, with an estimated total of 50–60% developing nephritis during the first 10 years of disease

survival

- Overall survival in patients with SLE is approximately 95% at 5 years after diagnosis and 92% at 10 years after diagnosis
- The presence of lupus nephritis (LN) significantly reduces survival to approximately 88% at 10 years, with even lower survival in African Americans

I. Case Definition for LN

- LN is defined as clinical and laboratory manifestations that meet ACR criteria (persistent proteinuria > 0.5 gm per day or greater than 3+ by dipstick, and/or cellular casts including [RBCs], hemoglobin, granular, tubular, or mixed)

I. Case Definition for LN

- A spot urine protein/cr ratio of > 0.5 can be substituted for the 24-hr protein, and "active urinary sediment" (>5 RBCs/ [hpf], >5 [WBCs]/hpf in the absence of infection, or cellular casts limited to RBC or WBC casts) can be substituted for cellular casts
- An additional, perhaps optimal, criterion is a renal biopsy sample demonstrating IC–mediated GN compatible with LN

Indications for renal biopsy in patients with SLE

- Increasing serum creatinine without compelling alternative causes (such as sepsis, hypovolemia, or medication)
- Confirmed proteinuria of 1.0 gm per 24 hours (either 24-hour urine or spot protein/creatinine ratios are acceptable)
- Combinations of the following, assuming the findings are confirmed in at least 2 tests done within a short period of time and in the absence of alternative causes:

a. Proteinuria 0.5 gm per 24 hours plus hematuria, defined as 5 RBCs per hpf

b. Proteinuria 0.5 gm per 24 hours plus cellular casts

Table 1. International Society of Nephrology Renal Pathology Society 2003 classification of LN*

- Class I Minimal mesangial LN
- Class II Mesangial proliferative LN
- Class III Focal LN (<50% of glomeruli)
- Class IV Diffuse LN (>50% glomeruli)
- Class V Membranous LN
- Class VI Advanced sclerosing LN (>90% globally sclerosed glomeruli without residual activity)

Lupus Nephritis

(Goals of treatment)

- Preventing evolution to ESRD and reducing mortality by:
  - « Early induction of remission
  - « Sustaining long-term remission
  - « Lowest possible toxicity

Lupus Nephritis

(Treatment strategy)

- Adjunctive therapies
- Induction to remission
  - « Treatment of resistant cases
- Maintenance of remission
  - « Treatment of relapses and flares
- Novel therapies
- Renal replacement therapy

Lupus Nephritis

(Adjunctive therapies)

- Goals:
  - « Treat concomitant risk factors for the progression to chronic renal disease
- More importance in membranous LN
- Include:
  - « Conservative therapies
  - « Non-immunosuppressive treatments

Lupus Nephritis

(Adjunctive therapies)

- Aggressive treatment of hypertension
  - « Goal BP: less than 130/80 mmHg
  - « Recommended drugs: ACE inhibitors, diuretics, Calcium channel antagonists, beta-blockers
- Angiotensin inhibition
  - « Reduce the rate of disease progression by lowering intraglomerular pressure
  - « Recommended in proteinuria > 500 mg/24 hours
  - « Goal: reduction of protein excretion from the baseline value (optimally < 500-1000 mg/day)
  - « ACE inhibitors and AR blockers

Lupus Nephritis

(Adjunctive therapies)

- Lipid lowering
  - « Goal: LDL cholesterol < 100 mg/dL
  - « Recommended drugs: Statins
  - « Slowing the progression of renal disease?
- Anticoagulation
  - « Notably in membranous with nephrotic syndrome
  - « Prophylactic use in high risk patients (massive proteinuria with serum albumin < 2.5g/dL)
- Osteoporesis prevention and treatment
  - « Recommended drugs: Calcium, Vitamin D, biphosphonates,

Lupus Nephritis

(Adjunctive therapies)

- Prevention and treatment of infections
  - « UTI (E. Coli); Pneumonia (Pneumocystis Carinii)
  - « Vaccines: Influenza/year, pneumococcal/5 years, Herpes zoster in those > 60-year old
- Nutritional recommendations
  - « Salt or protein restrictions (0.3-0.6 g/kg daily)
- Antimalaric drugs (Hydroxychloroquine)
  - « Protective effect on renal damage
    Decreased flare of lupus
    Reduce the risk of clotting events in SLE

Lupus Nephritis
(Adjunctive therapies)

- Increased Atherosclerosis due to:
- High BP Goal decrease BP to<130/80
- High LDL >100 mg/dl
- GFR lower than 60 ml/1.73 m2/min = creatinine >1.5 gm/dl
- SLE itself is also an independent risk factor for accelerated atherosclerosis

Lupus Nephritis

(Treatment strategy)

- Induction to remission

Lupus Nephritis

(Induction therapy)

- Goals:
  - « Rapid reduction of glomerular inflammation
  - « Control of immunologic activity
  - « Improvement of renal function
- Appropriate treatment response by:
  - « An effective immunosuppressive regimen
- Duration:
  - « 3 to 12 months (mean: 6 months)

Induction therapy

(Treatment strategy)

- Immunosuppressive treatment
  - « Proliferative (focal or diffuse)
  - « Membranous
    - Ø Severe nephrotic syndrome
    - Ø Elevates serum creatinine
    - Ø Concurrent proliferative disease
- No or mild immunosuppression
  - « Mesangial
  - « Pure membranous

Induction therapy

(Standard immunosuppressive treatment)

NIH Protocol

- I.V. Pulse Cyclophosphamide (CYC)
  - « 0.5 – 1 g/m2 body surface monthly for 6 months
- Oral prednisolone
  - « 0.5 mg/kg body weight daily in divided doses

Induction therapy

(Alternative treatments)

Euro-Lupus Regimen

- I.V. Cyclophosphamide
  - « Six fixed low dose pulses (500 mg) every 2 weeks
- Glucocorticoid
  - « I.V. Methylprednisolone: 3 daily pulses of 750 mg
  - « Oral Prednisolone: 0.5 mg/kg daily for four weeks

- There are 2 regimens of IV CYC recommended by the Task Force Panel:
- 1) low-dose “Euro-Lupus” CYC (500 mg IV once every 2 weeks for a total of 6 doses), followed by maintenance therapy with daily oral (AZA) or daily oral MMF , and
- 2) high-dose CYC (500–1,000 mg/m2 IV once a month for 6 doses), followed by maintenance treatment with MMF or AZA

Induction therapy

(Alternative treatments)

Mycophenolate mofetil

- Equivalent (not superior) to Cyclophosphamide
  - « Lower rate of complications
- Dose
  - « 0.5 g bd in first week, 1.0 g bd in second week, 1.5 g bd or 1.0 g tds thereafter
  - « Oral Prednisolone 60 mg daily, tapered gradually (every 2 weeks by 10 mg/day, to 40 mg daily)

Induction therapy

(Mycophenolate mofetil)

- Higher response rate in black & Latino patients

  Isenberg et al, *Rheumatology* 2010
- Not considered as an alternative first-line agent for pure membranous type till 2012

MMF became first line therapy in membranous type

- MMF (2–3 gm total daily orally) or (IV) CYC along with glucocorticoids are considered equivalent based on recent high-quality studies, a meta-analysis, and expert opinion
- Asians compared to non-Asians might require lower doses(2 gm MMF per day in Asians has similar efficacy as 3 gm per day in non-A.

Induction therapy

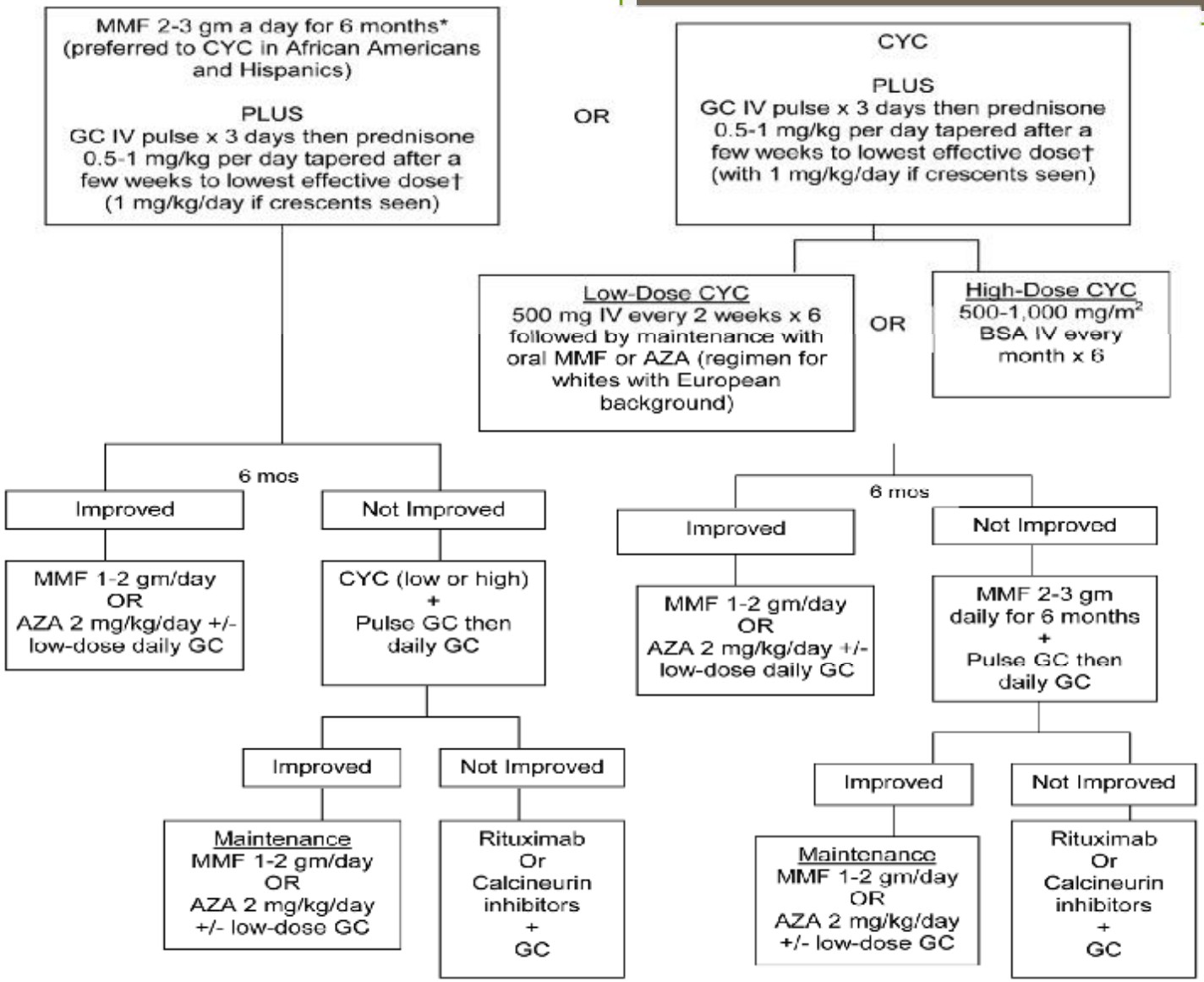
(Alternative treatments)

- Oral Cyclophosphamide
  - « 1-1.5 mg/kg daily for 2 to 4 months
  - « Higher rate of hemorrhagic cystitis, bladder carcinoma, bone marrow suppression
- Azathioprine
  - « More relapses & renal failure in 5-6 year follow-up
  - « Only in mild cases refuse to risk the side effects of more effective drugs
- Leflunomide
  - « 1 mg/kg/day for 3 days, followed by 30 mg daily

Induction therapy

(Alternative treatments)

- Cyclosporine
  - « 5 mg/kg daily in 2 divided dose
  - « Alternative first-line drug in pure membranous LN
  - « More relapses
  - « Women of child bearing age
- Chorambucil
  - « In membranous LN
- Plasmaphresis
  - « No added benefit to immunosuppressive drugs
  - « Higher side effects (serious infections) and death
  - « Only in severe crescentic forms (with ANCA) or proliferative LN with TTP and APLA


MMF 2-3 gm a day for 6 months*
(preferred to CYC in African Americans and Hispanics)
PLUS
GC IV pulse x 3 days then prednisone 0.5-1 mg/kg per day tapered after a few weeks to lowest effective dose†
(1 mg/kg/day if crescents seen)
OR
CYC
PLUS
GC IV pulse x 3 days then prednisone 0.5-1 mg/kg per day tapered after a few weeks to lowest effective dose†
(with 1 mg/kg/day if crescents seen)
Low-Dose CYC
500 mg IV every 2 weeks x 6 followed by maintenance with oral MMF or AZA (regimen for whites with European background)
OR
High-Dose CYC
500-1,000 mg/m² BSA IV every month x 6
6 mos
Improved
Not Improved
MMF 1-2 gm/day
OR
AZA 2 mg/kg/day +/- low-dose daily GC
CYC (low or high)
+
Pulse GC then daily GC
Improved
Not Improved
Maintenance
MMF 1-2 gm/day
OR
AZA 2 mg/kg/day
+/- low-dose GC
Rituximab
Or
Calcineurin inhibitors
+
GC
6 mos
Improved
Not Improved
MMF 1-2 gm/day
OR
AZA 2 mg/kg/day +/- low-dose daily GC
MMF 2-3 gm daily for 6 months
+
Pulse GC then daily GC
Improved
Not Improved
Maintenance
MMF 1-2 gm/day
OR
AZA 2 mg/kg/day
+/- low-dose GC
Rituximab
Or
Calcineurin inhibitors
+
GC

Induction therapy

(Type of remission)

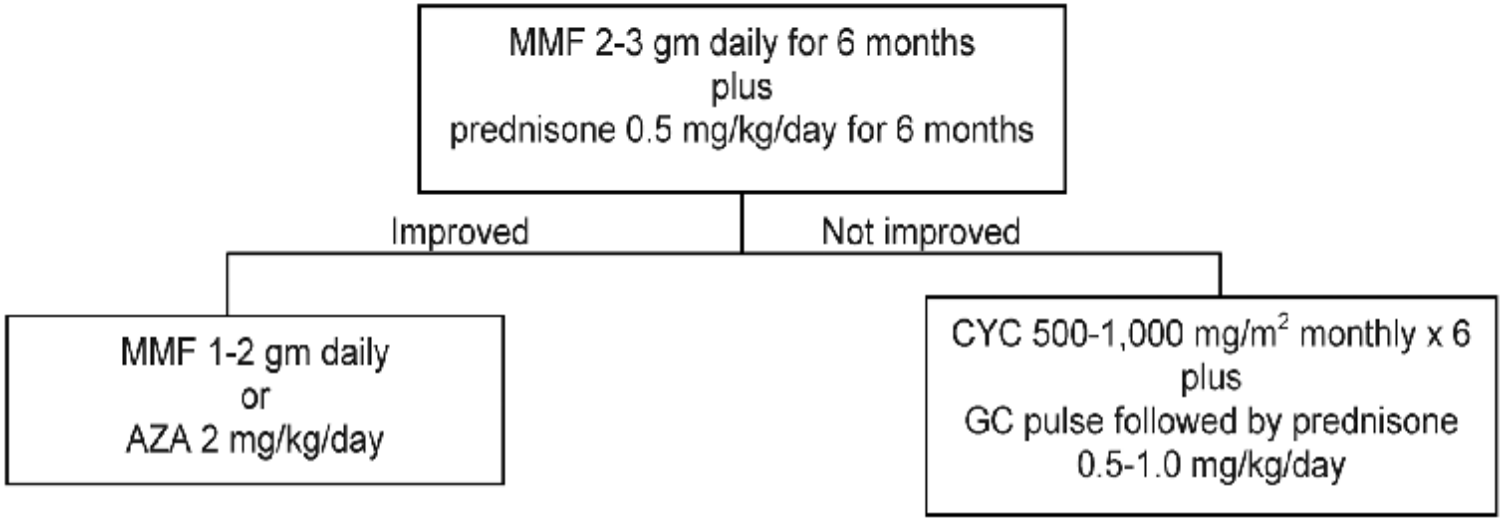
- Complete
  - Inactive urine sediment
  - Serum creatinine ≤ 1.4 mg/dL
  - Proteinuria ≤ 330 mg/day
- Partial
  - Stable serum creatinine
  - 50% reduction in proteinuria to < 1.5 g/day

Lupus Nephritis

(Prognosis in different classes)

	5 yr survival (%)
Class I	80-90
Class II	68
Class III	40-80
Class IV	25-40
Class V	60-80

Treatment of class V without proliferative changes and with nephrotic range proteinuria (3 gm/24 hours).



Lupus Nephritis

(Treatment strategy)

- Induction to remission
- Maintenance of remission

Lupus Nephritis

(Relapse)

- More than 50% in proliferative type
- Usually within 5 years after remission
  - « Mean of 8 in 100 patients per year
- Higher with partial remission
- Depending on induction therapy

Lupus Nephritis

(Maintenance therapy)

- Goals:
  - « Maintenance of remission
  - « Prevention of flares and relapse
  - « Decrease risk of end-stage renal disease
- Appropriate treatment response by:
  - « An effective regimen with lower side-effects and more convenient for patients
- Duration:
  - « At least 18 to 24 months (even 5 years)

Maintenance therapy

(Immunosuppressive treatments)

- I.V. pulse Cyclophosphamide
  - « In NIH protocol
  - « 0.5 – 1 g/m2 every 3 months for 2 years
  - « Prevention of ESRD ≥ 90% in 10-12 year follow-up
  - « Higher rate of infections & gonadal suppression
- Azathioprine
  - « After pulse cyclophosphamide induction therapy
  - « Preferred in women wanting to become pregnant
  - « Dose: 2 mg/kg (maximum 150-200 mg) daily
  - « Starting 2-4 weeks after last pulse if WBC>4000 and PMN>1500

Hossrau et al, *Ann Rheum Dis* 2010

Maintenance therapy

(Immunosuppressive treatments)

- Mycophenolate Mofetil
  - « After MMF induction therapy
  - « Daily dose: 1500 mg in first year, 1000-1250 mg in second year, 500-1000 mg in third year
- Cyclosporine
  - « Third choice in proliferative LN, but more indicated in membranous type
  - « Preferred in women wanting to become pregnant

Maintenance therapy

(Glucocorticoid therapy)

- Tapering gradually to minimum required dose
  - « 0.05-0.2 mg/kg daily
- Alternate day therapy is not recommended
  - « Due to aches and pain on the off days

Lupus Nephritis

(Treatment strategy)

- Adjunct therapies
- Induction to remission
- Maintenance of remission
- Novel therapies

Treatment Failure

- Switch of the immunosuppressive agent from either CYC to MMF, or from MMF to CYC, with these changes accompanied by IV pulses of glucocorticoids for 3 days
- Rituximab can be used in patients whose nephritis fails to improve or worsens after 6 months of one induction therapy, or after the patient has failed both CYC and MMF treatments .

Novel therapies

(B-cell targeted therapies)

- Rituximab
  - « Anti-CD20 chimeric monoclonal antibody
  - « LUNAR study showed no significant benefit in proliferative LN
  - « Same effect in membranous LN
  - « Reported infectious complications and progressive multifocal leukoencephalopathy
  - « Clinical & histologically improvement reported in refractory cases
- Abetimus (LJP 394; Riquent)
  - « Anti-dsDNA surface immunoglobulin receptors
- Belimumab
  - « Human anti-BLyS monoclonal antibody

Lupus Nephritis

(Novel therapies)

- T-cell targeted and co-stimulatory blockade
  - « Abatecept (CTLA4-Ig)
  - « Calcineurin inhibitors (Cyclosporine, Tacrolimus)
- Anti-cytokines
  - « No effect with anti-TNF, IL-1 receptor antagonists
- Non-specific immunologic therapies
  - « Intravenous immunoglobulin (IVIg)
    - Ø High dose for induction therapy: > 2 g/kg
    - Ø Low dose for maintenance therapy: 1 g/m2
  - « Stem cell transplantation
    - Ø Autologous hematopoietic or mesenchymal
    - Ø In refractory cases

Lupus Nephritis

(Definition of resistant cases)

- No consensus on the optimal definition
- A minimum of 3-12 months of induction therapy
- Not achieving goals for remission:
  - « Resolution of hematuria, pyuria & cellular casts
  - « Resolution or reduction of proteinuria (1 g/day)
  - « Reduction or stabilization of serum creatinine
  - « Improvement of biomarkers of immunologic activities (serum complement, anti-dsDNA antibody titers)
- Repeated kidney biopsy?
  - « Detecting non-immunologic irreversible lesions or progressive glomerulosclerosis

Treatment of resistant cases

(Proliferative Lupus Nephritis)

- Cyclophosphamide resistance: MMF
- MMF resistance: Cyclophosphamide
- Cyclophosphamide and MMF resistance:
  - « Rituximab
    - Ø No RCTs
    - Ø Limited data for resistance to both drugs
- Alternative agents:
  - « Cyclosporine
    - Ø In rare cases with marginal BM reserve
  - « Tacrolimus
    - Ø Resistant to MMF

- tacrolimus was equivalent to high-dose IV CYC in inducing complete and partial remissions of LN over a 6-month period.

- In another 4-year–long prospective trial , cyclosporine was similar to AZA in preventing renal flares in patients receiving maintenance therapy.

Treatment of resistant cases

(Membranous Lupus Nephritis)

- Cyclosporine resistance:
  - « Pulse Cyclophosphamide
  - « Repeated Cyclosporine
- Cyclophosphamide resistance:
  - « Cyclosporine

Treatment of LN in Patients Who Are Pregnant

- In patients with prior LN but no current evidence of systemic or renal disease activity, no nephritis medications are necessary.

- Patients with mild systemic activity may be treated with HCQ;

Treatment of LN in Patients Who Are Pregnant

- If clinically active nephritis is present, or there is substantial extrarenal disease activity, the clinician may prescribe glucocorticoids at doses necessary to control disease activity, and if necessary AZA can be added

Treatment of LN in Patients Who Are Pregnant

- High-dose glucocorticoid therapy in patients with SLE is associated with a high risk of maternal complications such as hypertension and diabetes mellitus .
- MMF, CYC, and methotrexate should be avoided because they are teratogenic in humans

Lupus Nephritis

(Treatment strategy)

- Adjunct therapies
- Induction to remission
- Maintenance of remission
- Novel therapies
- Renal replacement therapy

Lupus Nephritis

(End stage renal disease)

- In 10-30% of proliferative lupus nephritis
  - less in pure membranous lupus nephritis
- Depending on:
  - Severity of disease
  - Ancestral and socio-economic factors
  - Response to initial treatment
- Associated with gradual complete or partial resolution of the extra-renal and serologic manifestations of lupus

Lupus Nephritis

(Renal replacement therapy)

- Dialysis
  - « Hemodialysis
  - « Continuous ambulatory peritoneal dialysis
- Renal transplantation

Renal replacement therapy

(Renal transplantation)

- Survival the same as other causes of ESRD
- Clinical relapse rate: 2-30%
- Recommended dialysis duration before renal transplantation: 3-6 months
- Higher rate of recurrent rejection (≥ 4)