Baseline Evaluation, Initial Treatment and Assessment of Response in Lupus Nephritis

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Case Definition

- Persistent proteinuria: >0.5 gm per day/ >3+ by dipstick/UPCR >50 mg/mmoL

- and/or active urinary sediment (>5 RBCs/hpf, >5 WBCs/hpf in the absence of infection, or cellular casts limited to RBC or WBC casts), or acanthocytes ≥ 2/hpf

Major Sections

Baseline evaluation

Initial treatment

Assessment of response

Baseline Evaluation

When Do We Suspect?

- Appearance of edema
- Urinary abnormalities on routine testing

How Do We Establish?

Urine RE

UTP/UPCR, CCr

Not known lupus: ANA, anti-ds-DNA

Pre-treatment Clinical Evaluation

- Features of involvement of other organs/systems
- Clinical evidences of infections, malignancies, CLD, heart failure, lung diseases etc.
- Vaccination status
- Risk factors for osteoporosis and fractures

Other Lab Tests Before Therapy

CBC

BT, CT, prothrombin time, APTT

SGPT, electrolytes

Chest X-ray

HBsAg

Serum C3, C4

Plasma albumin

OGTT

Fasting lipid profile

Abdominal USG

Kidney biopsy

Selectively Required

CS: urine, blood

Anti-phospholipid antibodies

Anti-HCV ab

Echocardiography

Other investigations dictated by CF

Initial Treatment

Initial Treatment

Adjunctive treatment

Induction of remission

ADJUNCTIVE TREATMENT

Adjunctive Treatment…

- Hydroxychloroquine:
  - reduces flare, damage, thrombosis
- RAS blockade:
  - Reduces proteinuria by 30%
  - Delays rise of creatinine
  - Superior to CCBs and diuretics
- Reduction of BP to $\leq$140/90
- Statin: estimate 10-year CVD riskX1.5

Adjunctive Treatment

- Infection prevention:
  - Vaccination: infliuenza virus and pneumococcus
  - *Pneumocystis jirovecii* prophylaxis
  - Activity and exercise
- Contraception
- Prevention and treatment of GIOP
- Nutrition
- Anticoagulant treatment in nephrotic syndrome with serum albumin <20 g/L

  (specially if persistent or in the presence of aPL)

INDUCTION OF REMISSION

Class-wise Recommendations

- Class I and many with class II don’t require treatment
- Class III and IV require aggressive therapy
- Class V requires aggressive therapy when features of class III or IV are present
- Class VI requires preparation for renal replacement rather than immunosuppression

Induction of Remission

- Glucocorticoids
- Glucocorticoid sparing agents (GSAs)
  - Cyclophosphamide
  - Mycophenolate mofetil (MMF)

Glucocorticoids

Dosing of Glucocorticoid…

- Pulse methylprednisolone 500-1000 mg over 30 minutes daily for three days) prior to initiation of oral glucocorticoids (GC)
- There is no consensus about the best oral GC regimen
- There are no data suggesting that one regimen is superior to another

Dosing of Glucocorticoid…

- Oral prednisone is started @ 1 mg/kg/day & continued for 4 wks
- Tapered by 10 to 20% at 1 to 2-wk intervals on the basis of clinical improvement

(Ellen, M. et al, Mycophenolate Mofetil or Intravenous Cyclophosphamide for Lupus Nephritis, NEJM, vol. 353, no. 21, pp. 2219-28)

- Low-dose prednisolone (5-7.5 mg/day) is continued throughout the maintenance phase

Glucocorticoid Sparing Agents

Cyclo Regimen: Dose

- Monthly IV pulse
  - — 500 to 1000 mg/m^2 IV monthly for 6 mo

Monitoring…

- Urine RE: hematuria
- Full Blood Count (FBC)
- Serum creatinine
- Serum electrolytes
- Transaminases

Monitoring of WBC Count….

Check FBC on day of pulse or previous day

- If WBC prior to pulse $<4x10^9/l$, then postpone until WBC $>4x10^9/l$, checking WBC at least weekly
- Reduce dose of pulse by 25 %
- With any further episodes of leucopenia, reduce by further 25%

Monitoring of WBC Count

Check FBC between 10 and 14 after a pulse

- If the leukocyte nadir is $<3x10^9/l$, even if the WBC just previous to the next pulse is $>4x10^9/l$, then reduce next dose:

  a. leucocyte nadir $2\text{-}3x10^9/l$ reduce CYC dose of the last pulse by 20% of previous dose

  b. leucocyte nadir $1\text{-}2x10^9/l$ reduce CYC dose of the last pulse by 40% of previous dose

  c. If $<1x10^{9/L}$, stop CYC

CYC: Hepatic Impairment

- Serum bilirubin 3.1 to 5 mg/dL or transaminases >3 times ULN: Administer 75% of dose
- Serum bilirubin >5 mg/dL: Avoid use

CYC: Renal Impairment

- Cl_{cr} ≥10 mL/minute: No dosage adjustment required.
- Cl_{cr} <10 mL/minute: Administer 75% of normal dose.
- Hemodialysis: Moderately dialyzable (20% to 50%); administer 50% of normal dose; administer after hemodialysis
- Continuous ambulatory peritoneal dialysis (CAPD): Administer 75% of normal dose

MMF Dosing

- 500 mg bd for 1 wk followed by
  - 1000 mg bd
  - Induction dose 6 months

MMF vs. MPA

- Evidences not enough
- MMF may cause more nausea and diarrhea
- MPA : in those with MMF intolerance
- 1440 – 2160 mg MPA ≡ 2000 – 3000 mg MMF

Indications for Treatment of Class V

- Nephrotic proteinuria: ≥ 3.5 g/day
- Progressively rising creatinine
- Concomitant proliferative changes

Treatment of Class V LN

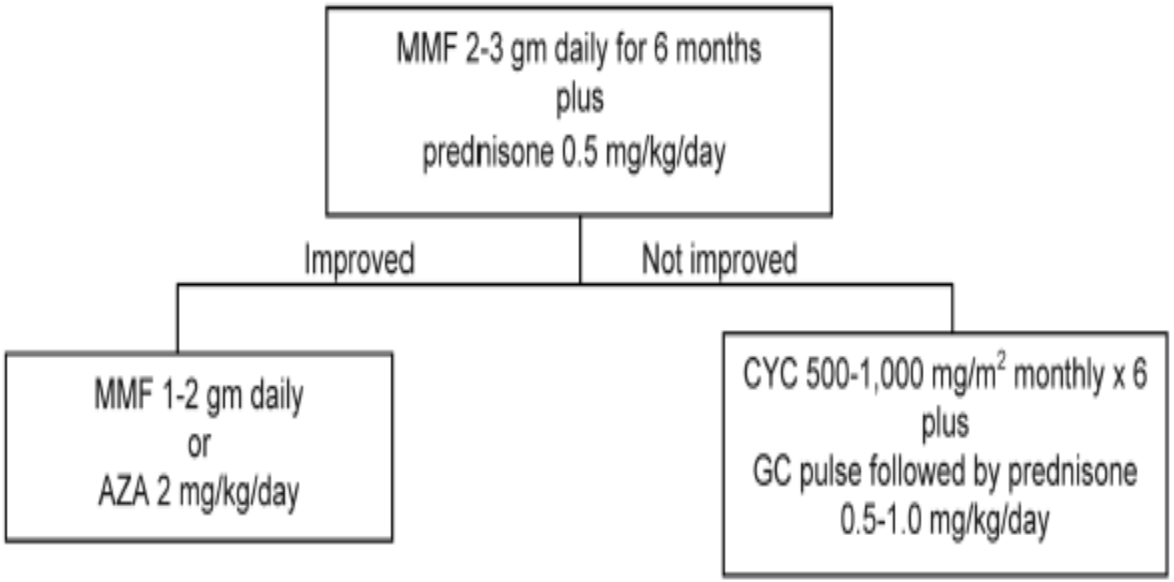


Figure 3. Treatment of class V without proliferative changes and with nephrotic range proteinuria (>3 gm/24 hours). Recommended background therapies for most patients are discussed in section III in the text. MMF = mycophenolate mofetil; AZA = azathioprine; CYC = cyclophosphamide; GC = glucocorticoids.

When to Treat Class II Lupus Nephritis with Immunosuppresives

- Class II LN with proteinuria >1 g/24 h despite RAS blockade specially in the presence of glomerular hematuria
  - EULAR recommends prednisolone 0.25–0.5 mg/kg/day alone or in combination with AZA (1–2 mg/kg/day), as a glucocorticoid sparing agent

Assessment of Response

Definition of Remission

- Inactive urinary sediment defined as:
  - ≤5 red blood cells per high-power field
  - ≤5 white blood cells per high-power field
  - Reading of 0 to 1+ on the urine dipstick for heme
  - No RBC/WBC casts
- Normal or near normal GFR
- Protein excretion <500 mg/day

Appel GB. J Am Soc Nephrol. 2009;20(5):1103.

Difficulties in Defining Remission

- Serum creatinine may not normalize:
  - Irreversible renal injury
    - A better alternative: stabilization
- Proteinuria:
  - May not normalize: glomerulosclerosis
  - May take long time
    - Reduction continues despite treatment tapering
- Hematuria: CYC bladder toxicity
  - Dysmorphic RBC: needs expertise

Timing of Response Assessment

- In drug-induced membranous GN, time to resolution of proteinuria: 1 yr after withdrawal
  - in some patients 3 yrs
- Proteinuria 1–1.6 g/day after 6 mo induction in those with eventually satisfactory outcome
  - In severe LN, response to treatment:
    - 50% at 6 mo, 65—80% between 12-254 mo

Timing of Response Assessment (EULAR Recommendations)

- Treatment should aim for complete renal response, defined as UPCR <50 mg/mmol & normal or near normal GFR (within 10% of normal GFR if previously abnormal)
  - To be achieved by the end of 2 yrs following treatment initiation
- Partial renal response, defined as ≥50% reduction in proteinuria to subnephrotic levels and normal or near-normal GFR, should be achieved preferably by 6 mo and no later than 12 mo following treatment initiation

Predictors of Continued Improvement from Partial Remission Despite Treatment Down-stepping

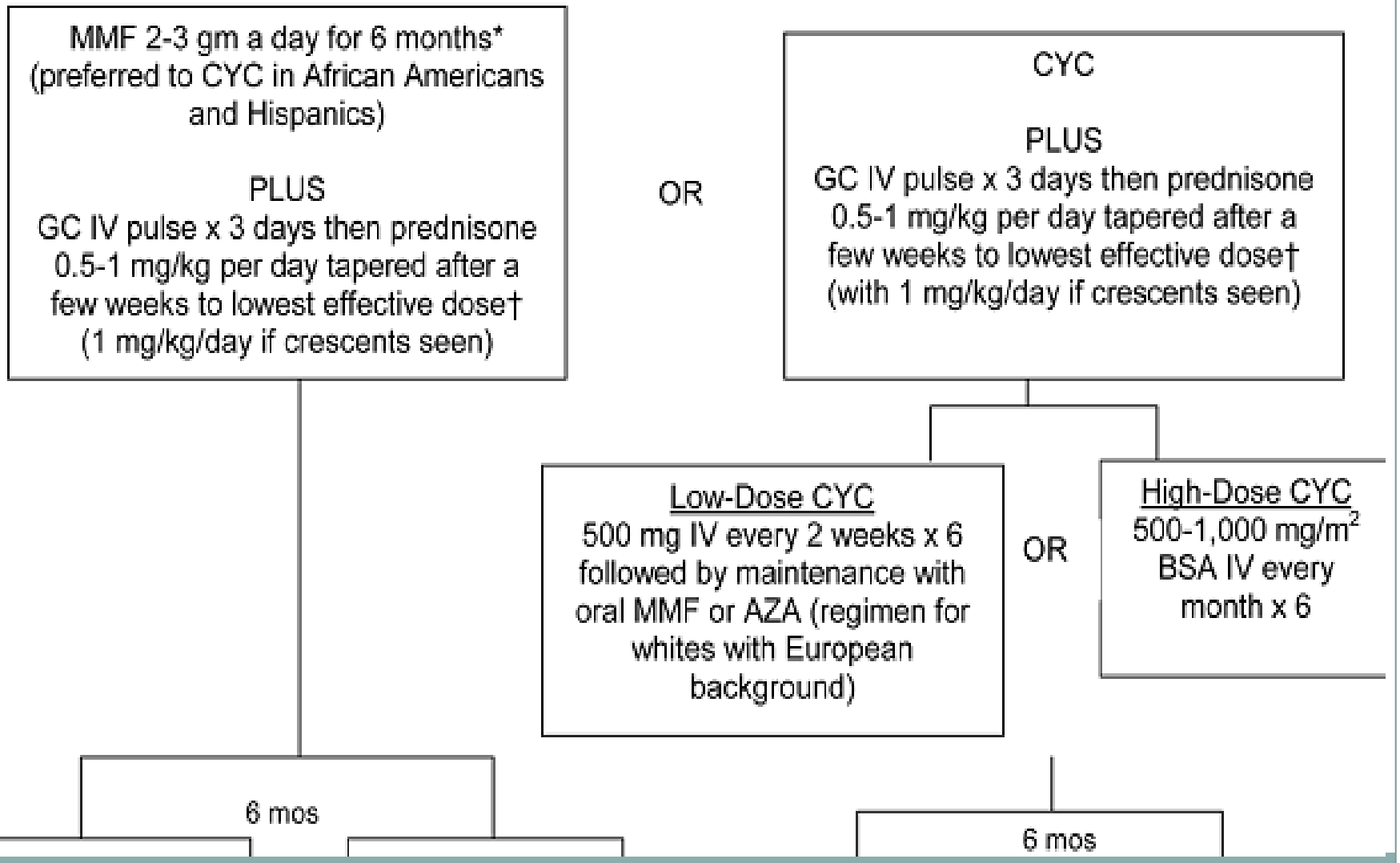
- 8 wk after initiation of induction:
  - ≥25% reduction in proteinuria
  - Normalization of serum C3 and or C4
- 6 mo after initiation:
  - Decrease in S. Creatinine
  - Decrease in UTP to <1 g/24 hr

Ginzler EM. N Engl J Med. 2005;353(21):2219.

ACR 2012 Statement

- Patients with severe LN on induction with CYC/MMF should be assessed after 6 mo except unequivocal evidence of worsening at 3 month:
  - ≥50% increase in proteinuria
  - ≥ 50% increase in serum creatinine

ACR 2012: Assessment Interval



Conclusions

- No universally effective strategy
- Cyclo or MMF with HDGC have reasonably good records
- Treatment has to be holistic with attention to infection prevention, RAS blockade, BP control, lipid control, maintenance of optimum functioning, etc
- Formal assessment of response is essential
- Patience is often rewarding, must be guarded by prompt identification of worsening

Thank you

Table 2. Indications for renal biopsy in patients with systemic lupus erythematosus*

	Level of evidence
Increasing serum creatinine without compelling alternative causes (such as sepsis, hypovolemia, or medication)	C
Confirmed proteinuria of ≥1.0 gm per 24 hours (either 24-hour urine specimens or spot protein/creatinine ratios are acceptable)	C
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:	C
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	

* RBCs = red blood cells; hpf = high-power field.

DD of LN Histology

- DDs:
  - Endocarditis
  - HIV
  - Hepatitis C
  - Portosystemic shunt
  - Poststreptococcal glomerulonephritis
- The full house immunofluorescence pattern may also be seen

Histopathologic Features Highly Characteristic of LN

- Glomerular deposits that stain dominantly for IgG and contain co-deposits of IgA, IgM, C3, and C1q, the so-called "full house" immunofluorescence pattern
- Glomerular deposits simultaneously seen in the mesangial, subendothelial, and subepithelial locations
- Extraglomerular immune-type deposits within tubular basement membranes, the interstitium, vessel walls
- Tubuloreticular inclusions in the glomerular endothelial cells