Lupus Nephritis: Filtering the New Data

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Conflict of Interest Disclosure

The speaker has no actual or potential conflict of interest in relation to this presentation.

Objectives

- Identify medications available for the treatment of lupus nephritis (LN)
- Review optimal treatment regimens based on patient-specific parameters

Epidemiology

- Manifestation of systemic lupus erythematosus (SLE) in kidneys[1]
- Prevalence in SLE patients: 25 – 75%[2]
- More than 60% have renal involvement[1,2]
- Most develop nephritis early in their disease[2]

Clinical Presentation[2]

- Progressive renal insufficiency
- Symptoms:
  - Tea-colored urine
  - Malaise
  - Anorexia
  - Low-grade fever
  - Migratory polyarthropathy
- Urinalysis:
  - Hematuria
  - Erythrocyte casts
  - Proteinuria
- Immunologic markers:
  - Antinuclear antibodies (ANA)
  - Anti-dsDNA
  - Anti-α-actinin antibodies

Pathophysiology[3]

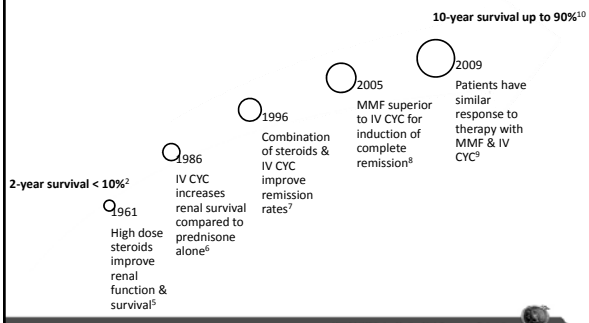
- Hallmark feature: dysregulated production of antibodies against multiple antigens present in the body
- Formation & deposition of immune complexes
- Autoantibodies induce inflammatory response by activating macrophages & neutrophils
- Self-stimulating pathway leads to progressive renal dysfunction

ISN/RPS Classification System[4]

Class	Designation	Description	Treatment
I	Normal	Minimal mesangial immune deposits	No immunosuppression
II	Mesangial nephritis	Mesangial hypercellularity, proliferation, or matrix expansion	No immunosuppression
III	Focal proliferative nephritis	Lesions in <50% of glomeruli with immune deposits or endocapillary proliferation	CYC 500mg IV every two weeks **OR** CYC 500 – 1000mg/m^2 IV every month **OR** oral MMF 2 – 3g/day **PLUS** Pulse IV glucocorticoids
IV	Diffuse proliferative nephritis	Lesions in >50% of glomeruli involving endo- and extracapillary proliferation	CYC 500mg IV every two weeks **OR** CYC 500 – 1000mg/m^2 IV every month **OR** oral MMF 2 – 3g/day **PLUS** Pulse IV glucocorticoids
V	Lupus membranous nephropathy	Subepithelial immune deposits and membranous thickening of glomerular capillaries	Prednisone 0.5mg/kg/day **PLUS** MMF 2 – 3g/day
IV	Advanced sclerosing nephritis	Sclerosis of >90% of glomeruli	Preparation for renal replacement therapy

ISN: International Society of Nephrology RPS: Renal Pathology Society CYC: cyclophosphamide MMF: mycophenolate mofetil

Advances in Induction Therapy



CYC: cyclophosphamide MMF: mycophenolate mofetil

Goals of Induction Therapy[1]

- Achievement of renal remission
- Disappearance of active urinary sediment
- Improvement in serum creatinine
- Decrease in urinary protein excretion
- Avoidance of renal flares
- Avoidance of chronic renal impairment
- Minimization of treatment toxicity

Mycophenolate Mofetil or Intravenous Cyclophosphamide for Lupus Nephritis

Ellen M. Ginzler, M.D., M.P.H., Mary Anne Dooley, M.D., M.P.H., Cynthia Aranow, M.D., Mimi Y. Kim, Sc.D., Jill Buyon, M.D., Joan T. Merrill, M.D., Michelle Petri, M.D., M.P.H., Gary S. Gilkeson, M.D., Daniel J. Wallace, M.D., Michael H. Weisman, M.D., and Gerald B. Appel, M.D.

Study Population[8] (n = 140)	Regimen	Endpoints	Outcomes	Adverse Effects
Age: 32 years Class: III – 15% IV – 55% V – 20% Mixed – 11% Race: Black 56% Hispanic 13% White 10% Asian 6%	IV CYC 0.5 – 1 g/m^2 monthly MMF 3g/day (goal dose) All patients received prednisone 1mg/kg/day, tapered as tolerated	Complete remission: · Scr ±10% normal value · proteinuria ± 10% normal value · urine sediment ± 10% normal value Partial remission: · 50% improvement in all abnormal renal measurements	Complete remission: CYC 5.8% vs MMF 22.5% (p = 0.005) Partial remission: CYC 24.6% vs MMF 29.6% Treatment failure: CYC 30.4% vs MMF 52.1% (p = 0.009)	Overall events: CYC 75 vs MMF 83 Severe infections: CYC 6 vs MMF 1 Diarrhea: CYC 2 vs MMF 15 New onset lymphopenia: CYC 28 vs MMF 18 Irreversible amenorrhea: CYC 2 vs MMF 0 Alopecia: CYC 8 vs MMF 0

CYC: cyclophosphamide MMF: mycophenolate mofetil

Mycophenolate Mofetil *versus* Cyclophosphamide for Induction Treatment of Lupus Nephritis

Gerald B. Appel,* Gabriel Contreras,† Mary Anne Dooley,‡ Ellen M. Ginzler,§ David Isenberg,¶ David Jayne,‖ Lei-Shi Li,** Eduardo Mysler,†† Jorge Sánchez-Guerrero,‡‡ Neil Solomons,§§ David Wofsy,¶¶ and the Aspreva Lupus Management Study Group

Study Population[9] (n = 370)	Regimen	Endpoints	Outcomes	Adverse Effects
Age: 32 years Class: III ±V – 16% IV ±V – 68% V – 16% Race: White 40% Asian 33% Other 27% Hispanic 35%	IV CYC 0.5 – 1 g/m^2 monthly MMF 3g/day (goal dose) All patients received prednisone 60mg/day, tapered as tolerated	Response to therapy: · decrease in urine/protein ratio · stabilization or improvement in Scr Partial remission: · improvement of 50% in all abnormal renal	Response to therapy: CYC 53% vs MMF 56% (p = 0.58) Normal Scr: CYC 68% vs MMF 70%	Proportion with adverse events: CYC 95% vs MMF 96% Infections: CYC 62% vs MMF 69% GI disorders: CYC 67% vs MMF 61% Mortality: CYC 3% vs MMF 5% Alopecia: CYC 36% vs MMF 11%

CYC: cyclophosphamide MMF: mycophenolate mofetil

Comparison of Induction Trials

Ginzler et al. [8]

- MMF superior to CYC
- Black patients made up 55% of study population
- Exclusion of patients with poor prognostic factors including elevated Scr

Appel et al. [9]

- MMF not superior to CYC
- Non-Caucasian/non-Asian constituted 30% of patients
- 27% of patients had baseline GFR < 30mL/min

Conclusions

- Blacks/Hispanics will likely respond better to MMF
- Patients with severe disease should receive CYC

CYC: cyclophosphamide MMF: mycophenolate mofetil

Patient Case

21YO African-American female with SLE and anemia who is admitted for low-grade fevers.

Findings:

Scr 1.1 (baseline 0.5)

Proteinuria

Hematuria

Biopsy: Class IV LN

Goals of Maintenance Therapy[1]

- Sustain the achieved renal remission
- Avoid renal relapse
- Minimize drug toxicities

Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: results from the MAINTAIN Nephritis Trial

Frédéric A Houssiau,[1] David D' Cruz,[2] Shirish Sangle,[2] Philippe Remy,[3] Carlos Vasconcelos,[4] Badmila Petrovic,[5] Christoph Fiehn,[6] Enrique de Ramon Garrido,[7] Inge-Magrethe Gilbe,[8] Maria Tektonidou,[9] Daniel Blockmans,[10] Isabelle Ravelingien,[11] Véronique le Guern,[12] Geneviève Depresseux,[1] Loïc Guillevin,[12] Ricard Cervera,[13] the MAINTAIN Nephritis Trial Group

Study Population[11] (n = 105)	Regimen	Endpoints	Outcomes	Adverse Effects
Age: 33 years Class: III – 31% IV – 58% V – 10% Race: White 79% Black 12% Asian 9%	AZA 2mg/kg/d MMF 2g/d (goal dose) All patients received steroid taper as tolerated	Time to renal flare: · nephrotic syndrome · Scr > 33% from baseline · 3-fold in proteinuria & hematuria # of severe systemic & benign flares # of patients withdrawing steroids # of patients achieving renal remission	Time to renal flare: AZA 25% vs MMF 19% (p = 0.486) Severe/benign flares: no difference Steroid withdrawal: no difference Renal remission: no difference	Overall events: AZA 73 vs MMF 60 Hematologic cytopenias: AZA 14 vs MMF 2 Time to 1st cytopenia: AZA, HR 4.54 (p = 0.03)

AZA: azathioprine MMF: mycophenolate mofetil HR: hazard ratio

Mycophenolate versus Azathioprine as Maintenance Therapy for Lupus Nephritis

Mary Anne Dooley, M.D., M.P.H., David Jayne, M.D., Ellen M. Ginzler, M.D., M.P.H., David Isenberg, M.D., Nancy J. Olsen, M.D., David Wofsy, M.D., Frank Eitner, M.D., Gerald B. Appel, M.D., Gabriel Contreras, M.D., M.P.H., Laura Lisk, B.Sc., and Neil Solomons, M.D., for the ALMS Group*

Study Population[12] (n = 227)	Regimen	Endpoints	Outcomes	Adverse Effects
Age: 31 years Class: III ± V – 13% IV ± V – 72% V – 15% Race: White 44% Asian 33% Black 10% Other 13% Hispanic 34%	AZA 2mg/kg/d MMF 2g/d (goal dose) Max prednisone dose: 10mg/d	Time to treatment failure: · death · ESRD · sustained doubling of Scr · renal flare · need for rescue therapy	Time to treatment failure: MMF, HR 0.44 (p = 0.003) Treatment failure: AZA 32% vs MMF 16% Renal flare: AZA 23% vs MMF 13% Time to rescue therapy: MMF, HR 0.39 (p = 0.02)	Overall events: AZA 97% vs MMF 98% Serious infections: AZA 12% vs MMF 10% Leukopenia: AZA 4% vs MMF 0% AE leading to drug withdrawal: AZA 40% vs MMF 25% (p = 0.02)

AZA: azathioprine MMF: mycophenolate mofetil HR: hazard ratio

Comparison of Maintenance Trials

MAINTAIN Trial[11]

- No statistical difference between AZA & MMF
- Largely Caucasian population
- Did not require renal response with induction

ALMS Group[12]

- MMF superior to AZA
- More racially diverse group
- Required clinical response after 6 months of induction
- Larger sample size
- Composite endpoint

Conclusions

- MMF & AZA are both reasonable options for maintenance therapy
- Race, adverse effects, and costs should be considered when selecting an agent

AZA: azathioprine MMF: mycophenolate mofetil

Patient Case

After achieving a response to induction therapy, the patient must decide what regimen to continue for her maintenance therapy.

What would you recommend? Why?

Clinical Pearls

- CYC and MMF are effective for induction therapy in LN
- AZA and MMF are effective agents for maintenance therapy in LN
- Selection of agents should include an evaluation of patient demographics, disease severity, cost, and potential adverse effects

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Post-Test

1. _____ is an appropriate regimen for induction therapy.

    a. IV cyclophosphamide with steroids
    b. PO azathioprine with steroids
    c. PO mycophenolate without steroids
    d. IV rituximab without steroids

2. A 22 year old African-American female with newly diagnosed Class III lupus nephritis is being evaluated for induction therapy. Which of the following should be considered for this patient?

    a. Age because she is too young to receive mycophenolate mofetil.
    b. Gender because cyclophosphamide is more effective in women.
    c. Lupus nephritis classification because Class III does not require immunosuppressive therapy.
    d. Race because African-Americans may respond better to mycophenolate mofetil.

3. You are approached by a physician colleague about a patient who is on mycophenolate maintenance therapy for her lupus nephritis. She has come in for a routine check up and mentioned that she's planning to get pregnant soon. All laboratory values and physical exam findings suggest that the patient is maintaining remission after 9 months of maintenance therapy. You recommend:

    a. Continuing mycophenolate as it has been successful in maintaining remission for the patient over the past 9 months.
    b. Having the patient come back when she does get pregnant so that her doses can be adjusted.
    c. Discontinuing mycophenolate as it is teratogenic and starting azathioprine.
    d. Stopping all immunosuppressants as the patient is in remission and no longer requires them.