Lupus Related Kidney Diseases

Jason Cobb MD
Assistant Professor
Renal Division
Emory University School of Medicine
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Renal Disease in SLE

• About 50% - 75% of systemic lupus erythematosus (SLE) patients have renal disease.
  – Abnormal urinalysis
    • Hematuria >5 rbc/hpf
    • Proteinuria >500 mg/day
  – Elevation of creatinine

Appel et al. JASN 2009; 20; 1103-12
Renal Disease in SLE

• Pathogenesis
  – Immune-complex mediated glomerulonephritis (GN) with formation of immune deposits.
    • Anti-double stranded DNA (dsDNA) antibodies against nucleosomes in the kidney.
    • Consumption of complement with low C3/C4 levels.
  – Elevated dsDNA
  – Low complements (low C3 and C4 levels)
GBM
When to Refer to Nephrology?

• Anyone with SLE and abnormal creatinine and urinalysis.

• Determine if need kidney biopsy
  – Lupus nephritis versus other causes of kidney disease (examples diabetes, hypertension)
When to Biopsy?

• No need to biopsy
  – Less than 500 mg/day proteinuria
  – Bland urine sediment <5 rbc/hpf
  – Normal creatinine

• Biopsy anyone else

• Guide clinical treatment
  – Labs can’t reflect pathology
  – Can be done as outpatient
  – Relapses
  – Protocol biopsy?
Diagnosis of Lupus Nephritis

• Better outcomes when diagnosed/treated promptly!

• SLE patients with renal disease 6 or more months prior to biopsy with increased rates of end-stage renal disease.
  – 47 vs. 14 per 1000 patients HR 9.3 (CI 1.8-47)
ISN/RPS Classification

• Class 1 - Minimal mesangial lupus nephritis
• Class 2 - Mesangial proliferative lupus nephritis
• Class 3 - Focal proliferative lupus nephritis
• Class 4 - Diffuse proliferative lupus nephritis
• Class 5 - Membranous lupus nephritis
• Class 6 - Advanced sclerosing lupus nephritis
Mesangial Lupus Nephritis

• Class I: Minimal mesangial lupus nephritis
  – Earliest and mildest
  – Usually normal urinalysis, minimal proteinuria, normal blood pressure, and normal creatinine.

• Class II: Mesangial proliferative lupus nephritis
  – Hematuria
  – Minimal proteinuria
  – Normal creatinine
  – Normal blood pressure
Proliferative Lupus Nephritis

• Class III: Focal proliferative lupus nephritis
  – Glomeruli affected <50%
  – Subendothelial deposits

• Class IV: Diffuse proliferative lupus nephritis
  – Glomeruli affected >50%
  – Subendothelial deposits

• Sub-divided
  – Active
  – Active/Chronic
  – Chronic
Proliferative LN cont.

• Clinical Characteristics
  – Hematuria
  – Proteinuria
  – Abnormal creatinine
  – Hypertension
  – Rapidly progressive glomerulonephritis (especially class IV)
  – Decreased complement levels (C3/C4)
  – Elevated dsDNA
Electron Microscopy
ISN/RPS Classification

• Class 1 - Minimal mesangial lupus nephritis
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Class V - Membranous

- Clinically
  - Nephrotic syndrome (lot of protein in urine)
  - Hematuria
  - Hypertension
  - Creatinine normal or slightly abnormal
Class VI - Advanced Sclerosing Lupus Nephritis

• >90% glomeruli with scarring/sclerosis
• Clinical characteristics
  – Bland urine sediment
  – Some proteinuria
Lupus Nephritis

TREATMENT
Mesangial Lupus Nephritis

- Class 1 - Minimal mesangial lupus nephritis
- Class 2 - Mesangial proliferative lupus nephritis
  - Treat other signs/symptoms of lupus
  - No renal specific treatment needed for lupus nephritis
Proliferative LN Treatment (Class III/IV)

• We get excited!!!!
• Needs renal specific treatment!!!!
• High rates of needing dialysis if failure to treatment
• Treatment
  – Induction (usually 6 months)
  – Maintenance 1.5 – 3 years - lifetime
Proliferative LN Treatment (Class III/IV)

• Cyclophosphamide
  – NIH Trial 1992 and 1996
    • Combo treatment – cyclophosphamide (Cytoxan) plus steroids is best at that time!
Toxicity

• Cyclophosphamide (Cytoxan)
  – Best treatment at that time
  – Toxicities
    • Infertility
    • Hemorrhagic cystitis
    • Anemia
    • Leukopenia
    • Thrombocytopenia
    • Infections
    • Alopecia

• We do use lower doses in kidney diseases on average in comparison to cancer treatment doses.
Proliferative LN Treatment (Class III/IV)

• Lower Doses of Cyclophosphamide
  – Euro-Lupus Nephritis Trial
    • 90 patients with proliferative GN
    • 6 doses of 500 mg IV cyclophosphamide qweeks for total 3 grams vs. 6 doses of higher dose IV cyclophosphamide. With steroids. With azathioprine as maintenance drug.
    • Similar results between groups
      – 16% vs. 20% renal failure
      – 71% vs. 54% remission
      – 27% vs. 29% renal flares
  • Careful with patient population

Houssiau FA et al. Arthritis and Rheumatism 2002;46(8):2121-2131

• 370 patients w/ Class III, IV, V Lupus nephritis
  – MMF (Cellcept) goal 3g/day (1500 mg bid) x 6 mos
  – Cyclophosphamide (Cytoxan) 0.5-1g/m2 in monthly doses x 6 mos
  – Both received prednisone, starting 60 mg/day
  – End points
    • Decrease in urine protein/creatinine ratio
    • Stabilization or improvement in serum Cr
  – Cellcept 56% (104 of 185 pts) responded
  – Cyclophosphamide 53% (98 of 185 pts) responded
  – Cellcept (mycophenolate) as good, but not superior to cyclophosphamide (Cytoxan) (p=0.58).
Class III and IV treatment (below + steroids)

- Induction therapy
  - 6 months
  - Cyclophosphamide IV vs. Cellcept (MMF) oral
    - Cyclophosphamide monthly or lower dose every 2 weeks for 6 doses
    - Side effect profile
      » Aggressive vs. less aggressive disease

- Maintenance therapy
  - 18-24 months or longer (possibly lifetime) if partial remission/relapse
  - MMF oral vs. azathioprine oral vs. cyclophosphamide IV (q 3-4 mos)
  - Mainly MMF or azathioprine now
Mycophenolate vs. Azathioprine as Maintenance Therapy for Lupus Nephritis. Mary Dooley et al. NEJM 2011: 365;1886-95

- **ALMs maintenance Trial** 36 month, RCT, 227 patients
  - MMF 2g/day
  - Azathioprine 2mg/kg/day
  - Up to 10 mg/day of prednisone allowed
  - Primary end point (time to tx failure: death, esrd, doubling of Cr, rescue therapy needed)
  - MMF 16.4% failure, Azathioprine 32.4%, p=.003
  - Adverse events same
  - Withdrawal due to adverse events (Azathioprine 39.6% and 25.2% MMF, p=.02)
  - MMF was superior to azathioprine in maintaining a renal response and preventing relapse in lupus nephritis.
Maintenance Treatment for Proliferative Lupus Nephritis

• Our patient population
  – Cellcept/Mycophenolate is preferred
    • ALMS Maintenance trial with more patients like our patient population.
    • Some use of azathioprine due to costs
Newer Therapies

• Possible benefit in combo or for resistant lupus nephritis. Recent trials!
  – Ocrelizumab
  – Abatacept
  – Rituximab (Rituxan)
  – Belimumab (Benlysta)
Rituximab

  – 144 patients
  – MMF and steroids
  – MMF, steroids, and rituximab (day 1, 15, 168, 182)
  – Rituximab group with better complement levels and greater reduction in dsDNA but no difference in clinical outcomes.

• Still might be role in resistant or relapsing patients
Abatacept

- 24 weeks of abatacept vs. placebo
- Both groups received Euro-lupus protocol induction plus maintenance with AZA.
- N=134
- No difference in complete remission at 24 to 52 weeks.
- Seems to be a safe drug.

Lupus Nephritis

• **Class V**
  – Membranous lupus nephritis
    • Need renal specific treatment but course usually not as severe at proliferative lupus nephritis.
  – Subepithelial immune deposits
  – Pure class V treatment
    • Cyclophosphamide vs. Cyclosporine vs. Cellcept (newer)
  – Can be mixed with Class III/V, IV/V
    • Treat disease like you would treat proliferative component (Class III or IV)
Lupus Nephritis

• Class V LN (membranous) Induction therapy
• ALMS
  – 370 patients w/ Class III, IV, V LN – 60 patients Class V
• US Study
  – 140 patients w/ Class III, IV, V LN – 24 pts Class V
• Between two studies 52 patients Class V LN with nephrotic syndrome and 40 patients completed study.
• Across all groups Cellcept (mycophenolate) as good as cyclophosphamide.

Lupus Nephritis

• Class VI
  – Advanced sclerosing lupus nephritis
    • >90% scarring on biopsy
  – Progressive Chronic Kidney Disease
    • Monitor closely
    • Prepare for hemodialysis when necessary
  – No special immunosuppressive therapy for renal disease
Lupus Nephritis in Pregnancy

- It happens too often!
- Lupus nephritis patient becomes pregnant or flare of lupus nephritis during pregnancy.
  - Talk about birth control and check for pregnancy at each visit during treatment.
  - Stop ACEI and ARB
  - Stop cyclophosphamide and MMF
  - When needed use azathioprine and prednisone for renal specific treatment.
Other Renal Disease in SLE

• Lupus podocytopathy
  – Glomerular podocytopathy with diffuse epithelial foot process effacement
  – SLE with
    • Minimal change disease
    • FSGS
  – Glomerular Podocytopathy in Patients with SLE Kraft SW et al. JASN 2005;16:175
    • 1 in 10,000 chance SLE and MCD
    • 7 of 470 patients with lupus nephritis
    • Most responded to steroids like MCD or FSGS patients without SLE

Steroids alone is main treatment for lupus podocytopathy
Review

• Indication for kidney biopsy?
  – A. 2 rbc per high-powered field (hpf) and normal shaped rbc
  – B. Bland urine sediment and 100 mg per day proteinuria
  – C. 2 gram proteinuria per day and 10 rbc/hpf with dysmorphic rbc
  – D. Bland urine sediment and 100 mg per day proteinuria
Review

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Review

• Clinical Characteristics of proliferative lupus nephritis (Class III and IV) includes all of the below except?
  – A. Hematuria
  – B. Proteinuria
  – C. Abnormal creatinine
  – D. Hypertension
  – E. Rapidly progressive glomerulonephritis
  – F. Elevated complement levels
  – G. Elevated dsDNA
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Review

• Which class of lupus nephritis does not need renal specific immunosuppressive therapy?
  – A. Class II lupus nephritis
  – B. Class III lupus nephritis
  – C. Class IV lupus nephritis
  – D. Class V lupus nephritis
  – E. Mixed class III/V lupus nephritis
  – F. Class VI lupus nephritis
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Review

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Another View

• Which classes of lupus nephritis need renal specific immunosuppressive therapy?
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  – E. Mixed class III/IV and V lupus nephritis
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Another View

- Which classes of lupus nephritis need renal specific immunosuppressive therapy?
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  - D. Class V lupus nephritis
  - E. Mixed class III/IV and V lupus nephritis
  - F. Class VI lupus nephritis
Treatment of Lupus Nephritis

• How long is induction therapy for lupus nephritis?
  – A. 1 month
  – B. 6 months
  – C. 9 months
  – D. 1 year
  – E. Lifetime
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Treatment of Lupus Nephritis

• Which is not a proven therapy for Class IV lupus nephritis induction therapy?
  – A. Cyclophosphamide (Cytoxan)
  – B. Cellcept (mycophenolate mofetil)
  – C. Azathioprine (Imuran)
  – D. Prednisone
Treatment of Lupus Nephritis

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  – B. Cellcept (mycophenolate mofetil)
  – C. Azathioprine (Imuran)
  – D. Prednisone
The End

• Thanks for your time and attention!