

Update on Lupus Nephritis – Review of KDIGO 2024 Guidelines



Jenny Ng BScPhm, ACPR
RPN Education Day
November 8, 2024
Toronto

Disclosures

No conflicts of interest to declare for this presentation

Objectives

- 1 Background on Lupus and Lupus Nephritis
- 2 Review KDIGO 2024 Guidelines on Treatment of Lupus Nephritis
- 3 Case review

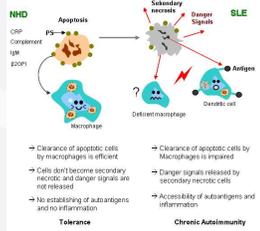
1 Background



Background on Lupus

Autoimmune disorder

Immune system activation characterized by exaggerated B-Cell and T-Cell responses and loss of immune tolerance against self antigens



Tolerance

- Clearance of apoptotic cells by macrophages is efficient
- Cells don't become secondary necrotic and danger signals are not released
- No establishing of autoantigens and no inflammation

Chronic Autoimmunity

- Clearance of apoptotic cells by macrophages is impaired
- Danger signals released by secondary necrotic cells
- Accessibility of autoantigens and inflammation

Fig. "Defects in the clearance of apoptotic cells is a possible pathway to autoimmune disease".
COP → Complement; IgE → Immunoglobulin E; PS → Phosphatidylserine; DC → Dendritic cell; DCAP → DC-Associated Apoptotic Phagocytosis; SLE → Systemic Lupus Erythematosus; NID → Normal Immune Defense.

Clinical Epidemiology

Sex
Occurs more occur in women (10 Females : 1 Males)

Age
Often diagnosed age 15-40 (women of child-bearing age)

Ethnicity
> African Americans, Hispanics and Asians vs Caucasians

Lupus Laboratory Tests

ANA- Antinuclear Antibody

- Positive in 98% of Lupus patients
- Titres > 1:80

Anti-dsDNA

- Anti-Double stranded DNA (75-90% positive in Lupus)
- Very specific for lupus
- Greater risk of lupus nephritis
- Can be used to measure disease activity

APLA

- antiphospholipid antibody (up to 60% positive in Lupus)
- Higher risk of blood clots, miscarriage or preterm birth

Complement levels

C3 and C4
Low levels reflect inflammation

Anti-SM

- Anti-Smith 30% positive
- Can help confirm a diagnosis

Clinical Presentation

- Fever
- Fatigue
- Joint Pain/Swelling (symmetrical)

Affecting other organs systems

- Kidney**
- Pulmonary
- Gastrointestinal
- Cardiac
- Hematologic
- Neurological

Dermatologic

- Malar Rash
- Discoid rash
- Photosensitivity




Epidemiology of Lupus Nephritis

Current landscape

Clinically evident renal disease occurs in about 35% with SLE at diagnosis and 50-60% develop nephritis over the first 10 years of disease

Ethnicity

LN is higher in the following ethnicities relative to the Caucasian population

- 40-69% in African Americans
- 36-61% in Hispanics
- 47-53% in Asians

Pathogenesis

B-lymphocyte produce antibodies against nuclear-related proteins

Antibody-Protein Immune complexes deposit in the glomeruli

Immune complexes then induce glomerular damage

Location of the deposited Immune complexes characterize the disease and dictates therapy

Presentation of Lupus Nephritis

- Abnormal Urinalysis**
 - Hematuria
 - casts
 - WBC in absence of infection
- Proteinuria**
- Elevated SCr**
- Edema**
- Dyslipidemia**
- Active Lupus**
 - Low C3 and C4 levels
 - Elevated anti-dsDNA titres

ACR Criteria for diagnosis of Lupus Nephritis

Persistent Proteinuria

- 24 hr urine protein > 0.5 g/day OR
- > 3+ protein by urine dipstick AND/OR
- Cellular Casts including RBC, Hgb, Granular, Tubular or mixed

Another option

- a spot urine creatinine/protein ratio >0.5 can be substituted for the 24 hour protein measurement, and "active urinary sediment" (>5 RBC/hpf, >5 WBC/hpf in the absence of infection, or cellular casts limited to RBC or WBC casts) can be substituted for cellular casts

Optimal

- Kidney Biopsy

Lupus Nephritis Classification

Class	Description	Treatment Notes
I	Minimal-Mesangial	Typically do not require Immunosuppressive treatment unless extrarenal manifestations (Class II if > 3 g)
II	Mesangial proliferative	
III	Focal	Requires Immunosuppressive treatment 20-50% ESRD at 10 yrs with treatment
IV	Diffuse	
V	Membranous	
VI	Advanced sclerosis	Preparation for dialysis

2 KDIGO 2024 Lupus Nephritis

Induction

Induction

Starting biopsy showing Class III-V lupus nephritis

- Concurrent systemic immunosuppression (Section 10.2.1)
- Active Class III-V lupus nephritis
 - Multitargeted
 - CH20 + MMF: Cyclophosphamide 27 mg/kg/d and MMF in patients with eGFR < 30 mL/min and > 1.5L creatinine clearance through level approximately 5 mg/dl to avoid GI discomfort from cyclophosphamide and sodium 1.2-1.8 g/kg/d. Practice Point 10.2.3.13
 - Mycophenolate acid analog (MPAA) for at least 6 months: MMF 1.5 g/kg/d for 6 months. Practice Point 10.2.3.13
 - Cyclophosphamide for up to 6 months: IV 500 mg every 2 weeks for 3 months. Practice Point 10.2.3.13
 - Oral 1.0-1.5 mg/kg/d for 2-6 months. Practice Point 10.2.3.13
 - Reduced-dose Class III-V lupus nephritis without activity
 - Supportive treatment for chronic kidney disease
 - If concomitant Class IV manage as Class V (Section 10.2.4)

Multitargeted

and one of the following options

Consider cyclosporine when cyclophosphamide and MMF are not available. Practice Point 10.2.3.14

MMF duration up to 18 months

<https://kdigo.org/guidelines/lupus-nephritis/>

Cyclophosphamide (Cytoxan®/Procytox®)

alkylating agent that prevents cell division and inhibits B and T cell proliferation

- NIH - 25% vs 48% in doubling of SCr compared with MP alone
- EURO-LUPUS - low dose may be as effective as high dose cyclophosphamide
- GI / Mucositis
- Bone Marrow Suppression
- Amenorrhea / Azospermia / Gonadal Suppression - pregnancy considerations
- Severe Infection
- Cancer risk (eg. Bladder cancer). Cumulative Toxicity > 22 g and longer duration of use

	High-dose intravenous cyclophosphamide (NIH regimen)	Low-dose intravenous cyclophosphamide (Euro-Lupus regimen)	Oral cyclophosphamide
Cyclophosphamide	iv. 0.5-1 g/m ² monthly for 6 months	iv. 500 mg every 2 weeks for 3 months	p.o. 1.0-1.5 mg/kg/d (max 150 mg/d) for 2-6 months
Comments	Efficacy data included patients of different races/ethnicities	Efficacy data mainly in Caucasian patients, with some data from patients of African or Caribbean descent, Hispanic descent, Indian patients, and other Asian countries	Efficacy data included patients of different races/ethnicities

<https://kdigo.org/guidelines/lupus-nephritis/>

Mycophenolate (Cellcept®/Myfortic®)

Prodrug that is metabolized to mycophenolic acid

- Inhibits inosine monophosphate dehydrogenase (IMPDH) which T & B lymphocytes are dependent on for proliferation
- ALMS and MAINTAIN study demonstrated that mycophenolate had similar efficacy to IV cyclophosphamide (NIH protocol) for induction
- Typical dose mycophenolate mofetil 1-1.5 g BID = mycophenolate sodium 720-1080mg BID
- GI (Nausea/Vomiting/Diarrhea)
- Headache
- Blood Dyscrasias (25-45%)
- Infection
- Cancer risk - skin
- Herpes zoster (20%)

ALMS

Multicenter, open-label, parallel-group, randomized, controlled trial

N=370 patients with biopsy-confirmed active lupus nephritis

- Mycophenolate mofetil (n=185)
- Cyclophosphamide (n=185)
- With steroid

Setting: 88 centers in 20 countries in North America, Latin America, Asia, Australia, and Europe

Race	Mycophenolate mofetil (%)	Intravenous cyclophosphamide (%)	P-value
Overall	58.2	53.0	0.58
Asian	62.9	52.2	0.24
Caucasian	54.2	56.0	0.83
Other	38.5	60.4	0.038

Figure 1. Rates of complete and partial remission in the Aspreva Lupus Management Study (ALMS) trial. After 6 months of therapy, induction therapy with either MMF or monthly intravenous cyclophosphamide pulses showed virtually identical rates of remission. In subgroup analyses by race, nonwhite and non-Asian subjects showed significantly higher rates of remission with MMF than cyclophosphamide. Reprinted from ref. 26.

Appel GB JASN 2009. 20(5): 1103-1112

Mycophenolate (Cellcept®/Myfortic®)

- Prodrug that is metabolized to mycophenolic acid
- Inhibits inosine monophosphate dehydrogenase (IMPDH) which T & B lymphocytes are dependent on for proliferation
- ALMS and MAINTAIN study demonstrated that mycophenolate had similar efficacy to IV cyclophosphamide (NIH protocol) for induction
- Typical dose mycophenolate mofetil 1-1.5 g BID = mycophenolate sodium 720-1080mg BID
- GI (Nausea/Vomiting/Diarrhea)
- Headache
- Blood Dyscrasias (25-45%)
- Infection
- Cancer risk – skin
- Herpes zoster (20%)

Calcineurin Inhibitor therapy (Tacrolimus/Cyclosporine)

- Immunosuppressive effects on T cells and ability to stabilize podocytes in kidney
- Level monitoring
- Addition of fixed dose tacrolimus to low dose mycophenolate and glucocorticoid therapy demonstrated higher response rate compared to cyclophosphamide
- Addition of CNI on long term kidney survival remains unclear
- Headache
- Increased BP
- GI upset
- Tremors
- Increased creatinine and potassium
- Increased LDL/TG, blood sugar (less with tacrolimus)
- Gingival Hyperplasia (more with cyclosporine)
- Infection

Voclosporin - (N/A in Canada)

- Calcineurin Inhibitor with better binding to calcineurin than cyclosporine
- its pharmacokinetic profile and oral bioavailability are more consistent, which eliminates the need for drug level monitoring
- AURORA 1, AURORA 2
- ~\$7800 per month
- Hypertension
- Headaches
- Diarrhea
- Nephrotoxicity (less than cyclosporine)
- UTI
- Diabetes (less than tacrolimus)

Aurora 1

- Randomized DB, placebo, multicentered trial
- Pts with a diagnosis of SLE with lupus nephritis and a kidney biopsy within 2 years that showed class III, IV, or V (alone or in combination with class III or IV)
- voclosporin (23-7 mg twice daily) or placebo, on a background of mycophenolate mofetil (1 g twice daily) and rapidly tapered low-dose oral steroids

Study week	Voclosporin group (n=175) (%)	Placebo group (n=178) (%)
Week 24	32%	20%
Week 52	41%	23%

Figure 2. Complete and partial response endpoints. (Rovin et al., Lancet 2021)

Rovin et al. Lancet. 2021; 397: 2070-80

Voclosporin - (N/A in Canada)

- Calcineurin Inhibitor with better binding to calcineurin
- its pharmacokinetic profile and oral bioavailability are more consistent, which eliminates the need for drug level monitoring
- AURORA 1, AURORA 2
- ~\$7800 per month
- Hypertension
- Headaches
- Diarrhea
- Nephrotoxicity (less than cyclosporine)
- UTI
- Diabetes (less than tacrolimus)

Cyclosporine and Mycophenolate Interaction

- Exposure to active metabolite of mycophenolate mofetil, mycophenolic acid (MPA) differs between cyclosporine and tacrolimus
- In liver MPA is glucuronidated to MPAG (inactive glucuronide metabolite of MPA) and excreted into bile
- Bile subsequently reaches the gut when it is deconjugated by bowel flora and is reabsorbed as MPA
- CsA may inhibit transport into bile and thus lead to increased level of MPAG in the liver and lower levels of MPA
- ~40% different in MPA AUC between cyclosporine and non-cyclosporine based regimens
- This interaction is not seen with tacrolimus or voclosporin

Implication:

- If using CsA regimen- could consider increase in Mycophenolate dose (level monitoring?)
- if stopping CsA – monitor for Mycophenolate toxicity

Gelder, T. Kidney International 2021; 1185-1189

Other Considerations:

CV complications

- Lifestyle Modifications – smoking cessation, dyslipidemia, body weight optimization, exercise
- Blood pressure control
- ASA during pregnancy

Cancer Risk

Minimizing UV light exposure/sunscreen
Routine age appropriate screening
Minimizing cyclophosphamide exposure

Pregnancy Considerations

Bone Injury

- BMD and fracture assessment
- Calcium (optimal intake 1000-1200 mg/day) and vitamin D supplementation
- Bisphosphonate where appropriate
- ACR 2022 Guidelines for prevention of glucocorticoid induced osteoporosis: <https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/art.42646>

Infection Risk

(avoiding live vaccines for those on intensive immunosuppressive therapy, efficacy of vaccination when on immunosuppressive therapy etc).

- PCP prophylaxis consideration



Pregnancy Considerations +

- Patients with active LN should be counseled to avoid pregnancy while the disease is active or when treatment with potentially teratogenic drugs is ongoing, and for 6 months after LN becomes inactive
- To reduce the risk of pregnancy complications, hydroxychloroquine should be continued during pregnancy, and low-dose aspirin should be started before 16 weeks of gestation.
- Glucocorticoids, hydroxychloroquine, azathioprine, tacrolimus, and cyclosporine are considered safe immunosuppressive treatments during pregnancy

Future biologic therapies

Anifrolumab (Saphnelo)

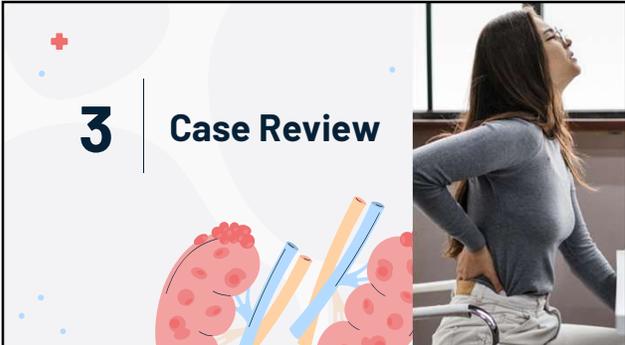
- Type 1 interferon (IFN) receptor antagonist
- Not indicated in Canada for lupus nephritis
- TULIP – LN – phase 2 study demonstrated improved renal outcome (5.5% vs. 31.1%)
- Phase 3 study has started

Obinutuzumab (Gazyva)

- humanized anti-CD20 monoclonal antibody
- Not indicated in Canada for lupus nephritis
- Phase 2 study demonstrated improved renal outcome (54% vs. 29%) at 104 weeks

3

Case Review



Case Review



Patient CC

32 year old female referred to our GN clinic from in 2018 October from another nephrologist for pregnancy counselling and lupus flare with 5.8 g of protein /day

PMHx

2005 - diagnosed with SLE flu like symptoms requiring ICU admission. No renal involvement at that time
 2016 – lupus flare when prednisone was tapered down and urine protein increased but continued on azathioprine
 July 2017 – Azathioprine was discontinued and Mycophenolate was initiated
 Dec 2017 – Kidney biopsy demonstrated Class IV/V lupus nephritis and tacrolimus was initiated

Labs

- SCr 49, K – 4.4 mmol/L.
- Urinalysis – no blood
- UPro 5.09 g
- Albumin 25 g/L
- ds-DNA – 115 (positive)
- C3 1.11 – N
- C4 0.14 – N
- Hgb 93 g/L
- LDL 4.07
- Weight 80 kg

Medications	
BP	Amlodipine 10 mg daily Ramipril 5 mg daily
BP swelling	Furosemide 80 mg daily
Lupus	Hydroxychloroquine 200 mg OD
	Mycophenolate 720 mg BID (missing doses)
	Tacrolimus 1 mg BID (dose reduced due to headaches)
	Prednisone 10 mg OD
GI protection	Pantoprazole 40 mg OD

References

KDIGO 2024 Lupus Nephritis Guidelines: https://kdigo.org/wp-content/uploads/2024/01/KDIGO_2024_Lupus_Nephritis_Guideline.pdf

ACR 2022 Prevention of Glucocorticoid Induced Osteoporosis: <https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/art.42646>



Thank you

Do you have any questions?

CREDITS: This presentation template was created by [Slidesgo](#), and includes icons by [Flaticon](#) and infographics & images by [Freepik](#)

