Treating Lupus Nephritis in 2021

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He has consultantships with: Alexion-Achillion, Apellis, Aurinia, Roche-Genentech, Mallinkrodt, Pfizer, Merck, Bristol-Myers Squibb, Up-to-Date, Genzyme-Sanofi, EMD Serono, Omeros.
24 yo AA F with SLE and DPLN

• What induction therapy is indicated for treatment?
• Does the fact that she is AA influence your therapy?
• What is the best maintenance therapy and for how long?
• What if she is resistant to the therapy?
• What other therapeutic options are available for her now and in the very near future?
KDIGO – Management and Treatment of GN - Lupus Nephritis

- Use anti-malarials in all patients.
- Although not always possible, attempt to minimize steroid Rx.
- For Immunosuppressive Therapy – Cyclophosphamide and MMF based regimens for remission induction remain the gold standard.
- Maintenance Rx after induction consists of MMF or Aza with or w/o low dose corticosteroids.
- ? how long for maintenance – most studies 3-5 yrs – Recommend a minimum of 3 years maintenance.

Roven BH, Caster DJ, Cattran DC et al Kidney Int. 95: 281-295, 2019
Proliferative LN EULAR/ERA – KDIGO 2019
Treatment guidelines

**INDUCTION**

- **MMF**
  - + glucocorticoids
    - (e.g. pulse methylprednisolone)

- **CYC**
  - + Glucocorticoids
    - (e.g. pulse methylprednisolone)

**6 months**

- **EURO LUPUS**
  - Low-dose CYC

- **NIH study**
  - Hi-dose CYC

**6 months**

CONFIDENTIAL
Randomized (n = 370) Open-label treatment

Allocated to MMF (n = 185)
Received MMF (n = 184)
Withdrawals (n = 35)
Due to adverse event (n = 24)
Consent withdrawn (n = 6)
Other reason (n = 5)

Allocated to IVC (n = 185)
Received IVC (n = 180)
Withdrawals (n = 29)
Due to adverse event (n = 13)
Consent withdrawn (n = 5)
Other reason (n = 11)

Primary endpoint: responders in randomized population (n = 370)

Responders

Maintenance phase
Double-blind re-randomization to corticosteroids plus MMF or azathioprine for up to 3 years
ALMS TRIAL Primary Endpoint: Responders at Month 6

Response judged by blinded Clinical Endpoint Committee:

Decrease in proteinuria to <3g if baseline nephrotic (≥3g/d), or by ≥50% in patients with subnephrotic (<3g/d) proteinuria and

Stabilization of serum creatinine level (24-week level ± 25% of baseline), or improvement

MMF was not superior to IVC (p = 0.575)

Appel, Contreras, Dooley et al JASN 2009
The Euro-Lupus Nephritis Trial

Multicenter, prospective trial of 90 LN pts with Proliferative LN
Initial Follow 41 months, subsequent long-term follow

Monthly High dose IV CYT (6 mo IVP 0.5-1 g/m²+2 quarterly pulses) vs
Low dose IV CYT (500 mg IVP every 2 wks x 3 months followed by oral AZA)

ELNT - 10 year FU - ESRD

Houssiau FA et al. Ann Rheum Dis 2009,
# ELNT - 10 year Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>High-dose</th>
<th>Low-dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IVCY</td>
<td>IVCY</td>
<td></td>
</tr>
<tr>
<td>Current serum creatinine (mg/dl)</td>
<td>1.0 ± 0.5</td>
<td>1.0 ± 0.4</td>
<td>1.0 ± 0.6</td>
</tr>
<tr>
<td>Current 24h-proteinuria (g)</td>
<td>0.6 ± 1.2</td>
<td>0.6 ± 1.3</td>
<td>0.5 ± 1.0</td>
</tr>
<tr>
<td>Ongoing GC therapy (% of patients)</td>
<td>73</td>
<td>71</td>
<td>75</td>
</tr>
<tr>
<td>Ongoing IS therapy (% of patients)</td>
<td>56</td>
<td>59</td>
<td>53</td>
</tr>
<tr>
<td>Ongoing BP lowering therapy (% of patients)</td>
<td>68</td>
<td>68</td>
<td>67</td>
</tr>
<tr>
<td>Additional IS drugs ever received** (n)</td>
<td>0.7 ± 0.9</td>
<td>0.7 ± 0.9</td>
<td>0.7 ± 0.9</td>
</tr>
<tr>
<td>Ever received MMF (% of patients)</td>
<td>30</td>
<td>30</td>
<td>29</td>
</tr>
<tr>
<td>Cumulative IVCY dose (g)</td>
<td>7.6 ± 2.5</td>
<td>9.5 ± 2.5</td>
<td>5.5 ± 4.8***</td>
</tr>
</tbody>
</table>

Houssiau FA et al. *Ann Rheum Dis* 2009
Effect of Race on Renal Survival

Renal Survival – LN IV
UNC    N = 90

Renal Survival LN III and IV
CUMC    N=129


Outcomes in African Americans and Hispanics with LN  U Miami N=213

Contreras et al  KI 69:1846, 2006
Treatment of LN with Abatacept and Low-Dose Pulse Cyclophosphosph- The ACCESS Trial

EuroLupus Low dose Cyclophosphamide and prednisone with Azathioprine maintenance w or w/o Abatacept

Complete Response Rates (%) at Week 52

<table>
<thead>
<tr>
<th>Treatment</th>
<th>All</th>
<th>All Others</th>
<th>Black</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abatacept</td>
<td>46%</td>
<td>46%</td>
<td>47%</td>
</tr>
<tr>
<td>Placebo</td>
<td>55%</td>
<td>58%</td>
<td>50%</td>
</tr>
</tbody>
</table>

While adding abatacept does not improve 6 or 12 month CRR rates, low-dose (Euro-Lupus) cyclophosphamide works well in a diverse N. American LN population

ACCESS Trial Group. Treatment of LN with abatacept: Arthritis Rheumatol 2014;66:3096
Proliferative Lupus Nephritis – Maintenance Treatment

ACR – KDIGO Treatment guidelines

MMF induction

IMPROVED

MMF1-2g/d or AZA 2 mg/kg/d ± lo dose daily GC

NOT IMPROVED

CYC (lo- or hi-dose) + pulse GC then daily GC

IMPROVED

MMF1-2g/d or AZA 2 mg/kg/d ± lo dose daily GC

NOT IMPROVED

MMF 2-3g/d x 6 months + pulse GC then daily GC
ALMS Maintenance Trial: MMF vs Azathioprine for Lupus Nephritis

24-wk induction phase

Response or Remission

No

I VC
0.5–1 g/m² Monthly

MMF
1.5 g BID

Yes

Re-randomization

No further treatment (exit study)

36-mo maintenance phase

MMF
1 g BID

AZA
2 mg/kg/d

Dooley MA, Jayne D, Ginzler E, Appel GB ...Solomons N
NEJM 365: 1926-1931, 2011
ALMS Maintenance Trial 2011
Kaplan-Meier Curve
Time to Treatment Failure ITT, N=227

Graph showing Kaplan-Meier curve for Time to Treatment Failure ITT with N=227. The graph compares MMF and AZA treatments with the probability of being event free on the y-axis and month on the x-axis. The graph indicates a statistically significant difference between the two treatments with p = 0.003.
The MAINTAIN Nephritis Trial
Primary endpoint: Time to renal flare
Analysis by intention-to-treat

RENAL FLARES

AZA: 25%
MMF: 19%

Maintenance Therapy – Type and Duration

• I favor MMF especially in minority groups in USA.
• However, I have no reluctance to use AZA as an alternative if side effects, cost, pregnancy, etc are factors.
• I favor 3-4 yrs treatment for proliferative LN III/IV unless special circumstance (e.g. pregnancy, side effects). At 3 yrs I taper the dose.
• For LN V– MLN – with the nephrotic syndrome, I use a shorter treatment if proteinuria remains decreased (1-2 years). I use either MMF or CNIs and steroids.
• Multitarget therapy is an option.
Complete Response Rates Are Low With Standard-of-Care First-line Therapies ALMS

Primary endpoint was response at 24 weeks. Response was defined as a decrease in UPCR to <3 mg/mg in patients with baseline nephrotic proteinuria (≥3 mg/mg) or by ≥50% in patients with subnephrotic baseline proteinuria (<3 mg/mg), and stabilization ±25% or improvement in SCr as adjudicated by a blinded Clinical Endpoints Committee. Complete response was a secondary endpoint defined as return to normal SCr, urine protein ≤0.5 g/d, and inactive urinary sediment (≤5 WBC and RBC/HPF, and a reading of lower than 2+ on dipstick and absence of red cell casts). CYC=cyclophosphamide; HPF=high-power field; IV=intravenous; MMF=mycophenolate mofetil; RBC=red blood cells; SCr=serum creatinine; UPCR=urine protein-to-creatinine ratio; WBC=white blood cells.

LUNAR RITUXIMAB Primary Endpoint: Percent Renal Response at Week 52

MMF plus placebo

- Complete Renal Response (CRR): 30.6%
- Partial Renal Response (PRR): 15.3%

Mean MMF dose: 2.4 g/d

N=72

MMF plus Rituximab

- Complete Renal Response (CRR): 26.4%
- Partial Renal Response (PRR): 30.6%

Mean MMF dose: 2.7 g/d

N=72

CRR: normal serum creatinine level if it was abnormal at baseline, or a serum creatinine level of ≤115% of baseline if it was normal at baseline; inactive urinary sediment (<5 RBCs/hpf and absence of RBC casts); and UPC ratio <0.5. PRR: serum creatinine level ≤115% of baseline; RBCs/hpf ≤50% above baseline and no RBC casts; and at least a 50% decrease in the UPC ratio to <1.0 (if the baseline UPC ratio was >3.0) or to ≤3.0 (if the baseline UPC ratio was 3.0).

A significant unmet need persists for FDA-approved LN treatment options that have demonstrated efficacy and safety.  

### Lack of FDA-approved Treatment Options

<table>
<thead>
<tr>
<th>Drug</th>
<th>Failed investigational agents for LN over the past 15 years</th>
<th>Clinical Trial Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abatacept-BMS</td>
<td>CTLA4-Ig, CTLA4-B7</td>
<td>Phase 3 - Failed</td>
</tr>
<tr>
<td>Abatacept-ACCESS</td>
<td>CTLA4-Ig, CTLA4-B7</td>
<td>Phase 2 - Failed</td>
</tr>
<tr>
<td>Anti-CD40 Ligand</td>
<td>Monoclonal Antibody, CD40 Ligand</td>
<td>Phase 2 - Terminated</td>
</tr>
<tr>
<td>Anti-TWEAK</td>
<td>Monoclonal Antibody, TWEAK</td>
<td>Phase 2 - Terminated</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Proteasome Inhibitor, Plasma Cells</td>
<td>Phase 4 - Terminated</td>
</tr>
<tr>
<td>Ocrelizumab</td>
<td>Monoclonal Antibody, CD20</td>
<td>Phase 3 - Failed</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Monoclonal Antibody, CD20</td>
<td>Phase 3 - Failed</td>
</tr>
<tr>
<td>Sirukumab</td>
<td>Monoclonal Antibody, IL-6</td>
<td>Phase 2 - Failed</td>
</tr>
<tr>
<td>Tabalumab</td>
<td>Monoclonal Antibody, BLyS</td>
<td>Phase 3 - Failed</td>
</tr>
</tbody>
</table>

3 recent clinical trials of LN drug candidates have positive results.

How to treat relapses and resistant pts in 2021?

Is it truly a relapse or resistance ???

Check for compliance ; Consider rebiopsy - scarring vs active treatable LN

Current Available Treatment Choices for 2021

• Rituximab
• Obinutuzumab
• Belimumab
• Voclosporin (new CNI )
• Multi-target therapy

LUNAR – RITUXIMAB Study Design

Screening

Treatment Period

Rituximab + MMF (n=72)

Placebo + MMF (n=72)

Follow-up Period

Weeks 1 and 2 (Days 1 and 15)

Week 16

Weeks 24 and 26 (Days 168 and 182)

Week 52

Week 78

= Study drug infusion.

= Corticosteroids:
  • 1000 mg IV methyprednisolone given at days 1 and then days 2, 3, or 4
  • Oral prednisone initiated at 0.75 mg/kg/day after IV steroids and then tapered to 10 mg/day by day 112
LUNAR RITUXIMAB Primary Endpoint: Percent Renal Response at Week 52

Mean MMF dose: Placebo: 2.4 g; Rituximab: 2.7 g

- **Complete Renal Response (CRR)**
  - Placebo (N=72): 30.6%
  - Rituximab (N=72): 26.4%

- **Partial Renal Response (PRR)**
  - Placebo (N=72): 15.3%
  - Rituximab (N=72): 30.6%

- **Complete + Partial Renal Response (C+PRR)**
  - Placebo (N=72): 46%
  - Rituximab (N=72): 57%
Efficacy of rituximab in **Refractory LN**
Response Rate in 300 Patients – pooled Data –
mean follow 60 weeks

A larger percentage of participants from the LUNAR trial who achieved complete peripheral depletion (n = 53) achieved complete response at week 52 and at week 78, compared to participants who did not achieve peripheral depletion (n = 15).
Obinutuzumab

- A humanized type II anti-CD20 monoclonal antibody approved for combination treatment of CLL and follicular lymphoma\(^1\).

- Compared to rituximab it has:
  - **Glycoengineering:** Up to 100x antibody-dependent cytotoxicity\(^2,3\)
  - **Type II binding conformation:** Greater direct cell death, reduced internalization, less reliance on complement-dependent cytotoxicity\(^2,3\)

- Obinutuzumab results in superior B cell depletion vs. rituximab in tissue\(^3\) and SLE patient samples\(^4\)

- Obinutuzumab was superior to rituximab in head-to-head trials in B-cell malignancies\(^5,6\)
A Phase 2 Randomized, Controlled Study of Obinutuzumab with Mycophenolate and Corticosteroids in Proliferative Lupus Nephritis - NOBILITY

Key inclusion criteria:
• ISN/RPS Class III or IV LN w/i six months, concomitant class V permitted
• UPCR ≥1 on 24-hour collection

Key exclusion criteria:
• Rapidly progressive GN
• eGFR <30 mL/min
• >50% of glomerulosclerosis

Primary endpoint
• Complete renal response (CRR) at week 52

Key secondary endpoints:
• Overall renal response (CRR or PRR)
• Change in dsDNA, C3, C4

Randomized, Controlled Study of Obinutuzumab with MMF and Corticosteroids in Proliferative LN - NOBILITY

Complete renal response (CRR)

- Week 52: 35% (Obinutuzumab + MMF) vs 23% (Placebo + MMF), Δ12%, P=0.11
- Week 76: 40% (Obinutuzumab + MMF) vs 18% (Placebo + MMF), Δ22%, P=0.007

Overall renal response (CRR or PRR)

- Week 52: 56% (Obinutuzumab + MMF) vs 36% (Placebo + MMF), Δ20%, P=0.02
- Week 76: 51% (Obinutuzumab + MMF) vs 29% (Placebo + MMF), Δ22%, P=0.02

CRR required all of:
- UPCR < 0.5
- Serum creatinine ≤ upper limit of laboratory normal
- Serum creatinine ≤115% of patient’s baseline
- <10 RBC/hpf without RBC casts

PRR required all of:
- UPCR ≥50% reduction to <1 (to <3 if baseline ≥3)
- Serum creatinine ≤115% of patient’s baseline
- RBC ≤50% above baseline or <10 RBC/hpf, without RBC casts

B Rovin, G Aroca, A Alvarez, et al.  ASN 2020
Randomized, Controlled Study of Obinutuzumab with MMF and Corticosteroids in Proliferative LN - NOBILITY

Last observation prior to treatment failure is applied for missing data. Comparisons were adjusted for stratification factors (region, race).

* P < 0.02;  ** P < 0.05;  *** P < 0.01 for comparison vs. placebo.

Obinutuzumab + MMF
Placebo + MMF

B Rovin, G Aroca, A Alvarez, et al. ASN 2020
Belimumab – FDA Approved for SLE

Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis

- 448 LN Pts - Phase 3 randomized, double blind trial of SOC vs IV Belimumumab + SOC
- Standard of Care = either Steroids + IV Cytoxan (EuroLupus regimen) followed by AZA maintenance or steroids + MMF followed by maintenance MMF.
- PBO or Belimumumab - Day 0,14,28 and then q 28 until 104 wks.
- Primary outcome at 104 weeks = Primary efficacy renal response (Up/Ucr < 0.7, GFR w/i 20% preflare, no rescue meds)
- Secondary Outcome = Complete renal response (PP/Ucr < 0.5, GFR > 60 or no 10% decrease in GFR from pre-flare, and no rescue therapy)
Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis

Study Design

104 week double-blind treatment

```
<table>
<thead>
<tr>
<th>Randomisation (1:1)</th>
<th>Induction</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stratified by standard therapy</td>
<td>Belimumab 10 mg/kg IV + Standard Therapy</td>
<td></td>
</tr>
<tr>
<td>HDCLS+MMF or HDCLS+CYC followed by MMF or AZA</td>
<td>Placebo IV + Standard Therapy</td>
<td></td>
</tr>
<tr>
<td>Week 24 Steroids must be ≤10 mg/day</td>
<td>Week 52 Key secondary endpoint: PERR</td>
<td></td>
</tr>
</tbody>
</table>
```

28-week open label
Belimumab 10 mg/kg IV + Standard Therapy

Key eligibility criteria:
- ≥18 years of age
- Clinically active LN (uPCR ≥1 at screening)
- Confirmed by recent* renal biopsy LN (Class III, IV, V or III+V or IV+V) and requiring standard therapy

Week 104
Primary endpoint: PERR
Key secondary endpoints:
- CRR
- Time to renal-related event or death
- ORR
Renal Responses over Time in BLISS Trial

PERR = Primary Efficacy Renal response Up/Ucr <0.7; GFR w/l 20%; no rescue therapy

Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis
## BLISS-LN Phase 3 results

### Primary and Key Secondary Efficacy Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Patients (%)</th>
<th>OR/HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo n=223</td>
<td>Belimumab 10 mg/kg IV n=223</td>
<td></td>
</tr>
<tr>
<td><strong>PERR</strong>* at Week 104</td>
<td>32.3</td>
<td>43.0</td>
<td>OR 1.55 (1.04, 2.32)</td>
</tr>
<tr>
<td><strong>CRR</strong>† at Week 104</td>
<td>19.7</td>
<td>30.0</td>
<td>OR 1.74 (1.11, 2.74)</td>
</tr>
<tr>
<td><strong>PERR</strong>* at Week 52</td>
<td>35.4</td>
<td>46.6</td>
<td>OR 1.59 (1.01, 2.38)</td>
</tr>
<tr>
<td><em>Time to first renal-related event or death up to Week 104</em></td>
<td>28.3</td>
<td>15.7</td>
<td>HR 0.51 (0.34, 0.77)</td>
</tr>
</tbody>
</table>

\*CR ≤0.7, eGFR no more than 20% of the pre-flare value or ≥60 ml/min/1.73m², no rescue therapy; †uPCR <0.5, eGFR no worse than 10% below pre-flare value or ≥50 ml/min/1.73m², no treatment failure. CI, confidence interval; CRR, Complete Renal Response; HR, hazard ratio; IV, intravenous; OR, odds ratio; PERR, Primary Efficacy Renal Response; uPCR, urine protein:creatinine ratio.
Time to a Renal-Related Event or Death in BLISS Trial


Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis

A

Hazard ratio, 0.51 (95% CI, 0.34–0.77)
P=0.001

B

<table>
<thead>
<tr>
<th>Event</th>
<th>Belimumab (N=223)</th>
<th>Placebo (N=223)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>35</td>
<td>63</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Progression to ESKD</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Doubling of creatinine level from baseline</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Increased proteinuria, impaired kidney function, or both</td>
<td>17</td>
<td>39</td>
</tr>
<tr>
<td>Treatment failure related to kidney event</td>
<td>16</td>
<td>20</td>
</tr>
</tbody>
</table>
Phase II Randomized Trial of Rituximab + Cyclophosphamide + Steroids w or w/o Belimumab


• 43 Pts with recurrent or refractory LN
• Complete or partial response 52% B vs 41% w/o B
  Not Significant
• No difference in adverse events.
• Better B cell depletion with Belimumab
Multitarget Therapy (MMF, Tacrolimus, Steroids) vs IV Cyclophosphamide + Steroids for Induction Treatment of LN: A Randomized, Controlled Trial

Voclosporin: A Novel CNI

- Novel CNI developed as a structural change from cyclosporine A, incorporating a single carbon extension with a double-bond
- Voclosporin has a consistent dose response potentially eliminating the need for therapeutic drug monitoring
- 4x potency over cyclosporine A

CNIs in Renal Disease: Two Separate Mechanisms of Action

1. Inhibition of calcineurin, reduced cytokine activation of t-cells

2. Potential disease-modifying podocyte stabilization, which protects against proteinuria
Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial


Summary
Background Voclosporin, a novel calcineurin inhibitor approved for the treatment of adults with lupus nephritis, improved complete renal response rates in patients with lupus nephritis in a phase 2 trial. This study aimed to evaluate the efficacy and safety of voclosporin for the treatment of lupus nephritis.

Methods This multicentre, double-blind, randomised phase 3 trial was done in 142 hospitals and clinics across 27 countries. Patients with a diagnosis of systemic lupus erythematosus with lupus nephritis according to the American College of Rheumatology criteria, and a kidney biopsy within 2 years that showed class III, IV, or V (alone or in combination with class III or IV) were eligible. Patients were randomly assigned (1:1) to oral 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, by use of an interactive web response system. The primary endpoint was complete renal response at 52 weeks defined as a composite of urine protein creatinine ratio of 0.5 mg/mg or less, stable renal function (defined as estimated glomerular filtration rate [eGFR] ≥60 mL/min/1.73 m² or no confirmed decrease from baseline in eGFR of >20%), no administration of rescue medication, and no more than 10 mg prednisone equivalent per day for 3 or more consecutive days or for 7 or more days during weeks 44 through 52, just before the primary endpoint assessment. Safety was also assessed. Efficacy analysis was by intention-to-treat and safety analysis by randomised patients receiving at least one dose of study treatment. The trial is registered with ClinicalTrials.gov NCT03021499.
Efficacy and safety of voclosporin vs PBO for lupus nephritis (AURORA 1)  

The Lancet  May 7, 2021

<table>
<thead>
<tr>
<th></th>
<th>Vocllosporin group</th>
<th>Placebo group</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>(n=179)</td>
<td>(n=178)</td>
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<tr>
<td>Median age, years</td>
<td>31 (18–62)</td>
<td>32 (18–72)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18 (10%)</td>
<td>26 (15%)</td>
</tr>
<tr>
<td>Female</td>
<td>161 (90%)</td>
<td>152 (85%)</td>
</tr>
<tr>
<td>Mean weight, kg</td>
<td>66.49 (17-07)</td>
<td>66.55 (16-11)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>68 (38%)</td>
<td>61 (34%)</td>
</tr>
<tr>
<td>Black</td>
<td>26 (15%)</td>
<td>19 (11%)</td>
</tr>
<tr>
<td>Asian</td>
<td>53 (30%)</td>
<td>56 (31%)</td>
</tr>
<tr>
<td>Other</td>
<td>32 (18%)</td>
<td>42 (24%)</td>
</tr>
<tr>
<td>Ethnicity*</td>
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</tr>
<tr>
<td>Hispanic or Latino</td>
<td>57 (32%)</td>
<td>59 (33%)</td>
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<tr>
<td>Non-Hispanic or non-Latino</td>
<td>122 (68%)</td>
<td>118 (66%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>North and Latin America</td>
<td>75 (42%)</td>
<td>74 (42%)</td>
</tr>
<tr>
<td>Europe and South Africa</td>
<td>52 (29%)</td>
<td>52 (29%)</td>
</tr>
<tr>
<td>Asia-Pacific</td>
<td>52 (29%)</td>
<td>52 (29%)</td>
</tr>
<tr>
<td>Mean time since initial lupus nephritis diagnosis, years</td>
<td>4.6 (5.1)</td>
<td>4.7 (4.9)</td>
</tr>
<tr>
<td>Mean time since systemic lupus erythematosus diagnosis, years</td>
<td>6.6 (6.4)</td>
<td>6.9 (6.1)</td>
</tr>
<tr>
<td>Biopsy class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pure class III</td>
<td>20 (11%)</td>
<td>29 (16%)</td>
</tr>
<tr>
<td>Pure class IV</td>
<td>91 (51%)</td>
<td>77 (43%)</td>
</tr>
<tr>
<td>Pure class V</td>
<td>25 (14%)</td>
<td>25 (14%)</td>
</tr>
<tr>
<td>Class II and V only</td>
<td>0 (0%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Class III and V only</td>
<td>24 (13%)</td>
<td>20 (11%)</td>
</tr>
<tr>
<td>Class IV and V only</td>
<td>19 (11%)</td>
<td>26 (15%)</td>
</tr>
</tbody>
</table>

(Data are median (range), n (%), or mean (SD), unless stated otherwise. Percentages might not add up to 100% because of rounding. eGFR=estimated glomerular filtration rate. UPCR=urine protein creatinine ratio. SELENA-SLEDAI=Safety of Estrogens in Systemic Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index. MMF=mycophenolate mofetil. *Analyses for race and ethnicity were post hoc. †Other races include American Indian, Alaska Native, Native Hawaiian, Pacific Islander, and other or mixed races except mixed Black race. ‡Data missing for one patient.)

Table 1: Demographic and baseline patient characteristics in the intention-to-treat population
Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1) The Lancet May 7, 2021

Figure 2: Complete and partial renal response endpoints (intention-to-treat population)
Efficacy and safety of voclosporin vs PBO for lupus nephritis (AURORA 1)  

**A**

- **Voclosporin group**
  - Probability of UG3 or UG3 mg/mg
  - Number at risk:
    - Voclosporin group: 179, 160, 147, 134, 119, 106, 90, 83, 80, 70, 68, 62, 61, 57, 51
    - Placebo group: 178, 170, 165, 149, 134, 126, 119, 114, 110, 102, 100, 95, 86, 83, 80
  - HR 2.02 (95% CI 1.51, 2.70); log-rank p<0.001

**B**

- **Voclosporin group**
  - Probability of 50% reduction in SLP3
  - Number at risk:
    - Voclosporin group: 179, 115, 74, 49, 36, 20, 15, 12, 11, 6, 6, 6, 5, 3
    - Placebo group: 178, 135, 113, 85, 66, 61, 55, 50, 46, 42, 41, 39, 38, 37, 35
  - HR 2.05 (95% CI 1.62, 2.60); log-rank p<0.001
Efficacy and safety of voclosporin vs PBO for lupus nephritis (AURORA 1)  The Lancet  May 7, 2021

Figure 4: Subgroup analysis of primary outcome of complete renal response at week 52 (intention-to-treat population)
Aurora Study My Conclusions

Results positive:
Effective – reaching all end points.
Good steroid tapering to very low levels.
Little toxicity in this study.
No level measurement necessary.

Limitations:
Only studied w MMF induction not Cyclophosphamide.
CNI – always concerned about long-term Nephrotoxicity – this is a one yr study. Drug interactions CYP enzymes.
Needs dose reduction at low GFR.
Algorithm for Refractory Disease in LN – KDIGO 2019

1. Verify adherence (check mycophenolic level if on MMF/check infusion records if on CYC)

2. Repeat biopsy if concern for chronicity or other diagnosis (e.g., TMA)

3. Switch from MMF to CYC or vice versa
   - Consider regimen with combined MMF/CNI “multi-target” therapy or
   - Addition of rituximab or
   - Consider prolonged course of i.v. pulse CYC

4. Before Belimumab and Voclosporin FDA approval, before Nobility trial
• MMF (2 to 3 g/day) or low-dose IV CYC (500 mg every 2 weeks for a total of 6 doses) plus GC are recommended

• Combination of MMF (1 to 2 g/day) with a CNI is an alternative, particularly in patients with nephrotic-range proteinuria

• In patients at high risk for kidney failure (reduced GFR, histological presence of crescents or fibrinoid necrosis or severe interstitial inflammation) high-dose IV CYC (0.5 to 0.75 g/m² monthly for 6 months) can also be considered

• To reduce cumulative GC dose, the use of IV methylprednisolone (total dose 500 mg to 2500 mg, depending on disease severity) is recommended, followed by oral prednisone (0.3 to 0.5 mg/kg/day) for up to 4 weeks, tapered to ≤7.5 mg/day by 3 to 6 months
## Induction and Maintenance Therapy of LN

### Evolving new drug options for continued combination therapy

- **Belimumab**
- **Corticosteroids**
- **i.v. low CYC**
  - or
  - **MMF 3.0 g/d**
- **Voclosporin**
- **Corticosteroids**
- **MMF 2.0 g/d**
- **Obinutuzumab**
- **Corticosteroids**
- **MMF 2–2.5 g/d**

**AZP 2 mg/kg**

**MMF 1.0–3.0 g/d**

**Left up to local PI**

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24 yo AA F with SLE and LN

- What induction therapy? MMF or IV clophosphamide.
- What if she were Caucasian and not AA? Same induction – MMF maintenance.
- What if she fails or relapses during these therapies. Other options – Rituximab, Obinutuzumab, Belimumab, Multi-Target Therapy - add CNI, voclosporin, etc.
- Many new choices and combinations will be available with good evidence they work and safety data but without comparative data.