Treatment of Severe Lupus Nephritis: Beyond Standard Regimens - A New Role for Biologics?

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A 23 year old woman with a 7 year history of Systemic Lupus Erythematosus develops nephrotic syndrome (urine protein excretion of 5.6gms/d, serum albumin of 2.4gms/dL). Her serum creatinine is 1.30mg/dL (115µM/L; eGFR- CKD-EPI-creatinine= 58ml/min/1.73m2). A C3 is 46mg/dL and a C4 is 9mg/dL/ The anti-dsDNA titer is 1:1280. A pregnancy test is negative. She indicates a desire to eventually have children.
A renal biopsy reveals Severe Lupus Nephritis Class IV- Segmental; a+c; 15 % of the glomeruli show crescents. Moderate interstitial nephritis is present. IF shows moderate (3+) segmental deposits of IgG, C3, C1q. EM shows mesangial and sub-endothelial electron dense deposits and scanty sub-epithelial deposits. Tubulo-reticular inclusions are present in endothelial cells.
In addition to 3 doses of IV methylprednisolone (500mg each), which one of the following treatments would you start now?

A. Oral MMF at 2.0gms/d + oral prednisone at 60mg/d
B. IV cyclophosphamide 500mg every two weeks for 3 months + oral prednisone at 60mg/d
C. IV cyclophosphamide 1000mg/m2 monthly for 6 months + oral prednisone at 60mg/d
D. Oral cyclophosphamide 2mg/kg/d or 3 months + oral prednisone at 60mg/d
E. Rituximab 375m/m2 every week times 4 weeks + oral prednisone at 60mg/d
F. Cyclosporine 4mg/kg/d + MMF 2 gms/d + oral prednisone at 60mg/d
The “correct” answer (my best choice) is A-MMF + Prednisone, but a regimen involving cyclophosphamide is also reasonable given the crescentic involvement.
Severe Lupus Nephritis*: Standard Treatment Regimens

*ISN/RPS Class III/IV (G or S; A or A/C)

Induction
- Oral CYC (1-1.5mg/kg/d) + steroids (2-4 months) - LNCSG Protocol
- IV CYC (0.5-1.0g/m2) monthly + steroids (6 months) - NIH Protocol
- IV CYC (low dose; 500 mg every 2 weeks) + steroids (3 months) - EUROLUPUS Protocol
- Oral MMF (2-3gms/d + steroids) (3-6 months) – ALMS Protocol

Maintenance
- Oral MMF (2-3gms/d) + low dose steroids x 24 months (+) (ALMS protocol)
- Oral AZA (2mg/kg/d) + low dose steroids x 24 months (+)-(EUROLUPUS Protocol)
  do not use if MMF used for Induction
- CNI (CsA or Tac) + low dose steroids if intolerant of MMF or AZA (Ponticelli/Moroni Protocol)
Severe Lupus Nephritis: Treatment Modifications-I

- Use IV CYC with great caution in renal failure; adjust dose of oral or IV CYC according to eGFR. Do not use CYC in liver failure.

- CYC based regimens effective in Caucasians and Blacks (except Euro-Lupus- not tested); perhaps less so in Hispanics and Asians

- MMF based induction and maintenance regimens may be preferred in Blacks, Hispanics and Asians
Severe Lupus Nephritis: Treatment Modifications

- ISN/RPS Class IV (G) + V may respond better to a MMF + Tac + steroid induction regimen ("Multi-Target Therapy")—not tested in Blacks or Caucasians.

- ISN/RPS Class V lesion may respond better to CYC- or CNI- based regimens—not tested in Blacks or Asians.

- ISN/RPS Class III >50% (called IV (Q) by Schwartz et al) may be a forme-fruste of SVV (ANCA ±) and respond better to CYC than MMF.
Unfortunately only about 60-70% of patients with severe LN will respond with a Complete or Partial remission to one or the other of the “Standard” regimens, often requiring over 6 months of treatment (greater unresponsiveness is seen in males and Blacks)
Renal relapses (nephritic and nephrotic) remain frequent with “Standard” treatment and maintenance regimens (About 8-10 relapses per 100 treated patient per year for the first 5 years after induction) and frequency/severity predict later onset of ESRD
Cumulative toxicity of “Standard” treatment regimens (particularly steroids) due to delayed remission and frequent relapses contribute significantly to morbidity and mortality.
Safe and effective regimens beyond "Standard" care are needed for management of "refractory" (treatment resistant) patients with severe LN and for those with frequent relapses and treatment related toxicity (especially steroids).
Is there a role for new **Biologic Agents** in the management of severe **Lupus Nephritis**?

A. For primary induction of remission  
B. For “rescue” of treatment refractory disease  
C. For maintenance of remission and avoidance of steroids (steroid-sparing)
New Biologic Agents in Treatment of Severe Lupus Nephritis

- Rituximab (chimeric anti-CD20 MoAb- B cells and ? Th-17 cells)
- Belimumab* (anti-Blys/BAFF MoAb- B-cells)
- Abatacept (CTLA-4/Ig fusion protein-inhibits CD80 and T-cell co-stimulation)
- Atacicept (Fusion protein that inhibits Blys + APRIL- B-Cells)
- Epratuzimab (anti-CD20 MoAb- B-cells)
- Ocreluzimab (fully humanized anti-CD20 MoAb-B-cells)
- Eculizimab** (anti-C5A MoAb)
- ACTH gel* (natural, porcine)

(*approved by FDA for treatment of SLE, but not specifically LN; **approved by FDA for use in atypical HUS)
RITUXIMAB
RITUXIMAB for INDUCTION of REMISSION IN SYSTEMIC LUPUS ERYTHEMATOSUS and SEVERE LUPUS NEPHRITIS:

The EXPLORER and LUNAR Trials
EXPLORER
(SLE without LN)
EXPLORER - A Randomized, Blinded Phase II/III Study Efficacy and Safety of Rituximab in Moderately to Severely Active SLE

Treatment Period

Rituximab + Prednisone Taper Arm (n = 169)

Placebo + Prednisone Taper Arm (n=88)

Screening

Week 1

Prednisone taper

Weeks 1 and 2 (Days 1 and 15)

Week 10

Weeks 24 and 26 (Days 168 and 182)

Week 52

Week 78

Follow-up Period

= Study drug infusion; 2 x 1000 mg Rituximab/Placebo

EXPLORER TRIAL -

Patient Disposition

Patients Randomized 2:1 (N = 257)

Placebo (n = 88)
- 24 Withdrawals Total
- 13 Adverse Events
- 5 Patients’ Decision
- 4 Physicians’ Decision
- 2 Lost to Follow-up
- 0 Death*

Completed Week 52 (n = 64)
- 73%

Rituximab (n = 169)
- 49 Withdrawals Total
- 19 Adverse Events
- 11 Patients’ Decision
- 13 Physicians’ Decision
- 3 Lost to Follow-up
- 3 Deaths

Completed Week 52 (n = 120)
- 71%

*One patient withdrew due to AE, and died one month later.
Primary Endpoint: **Patients Achieving Clinical Response** (ITT Population)

All early terminations treated as NCR.

*p value is based on Wilcoxon Rank sum test stratified by race and baseline assigned prednisone dose.
Pre-specified Exploratory Analysis: Clinical Response by Ethnicity

African-Americans/Hispanics

- Responders: 84.4% Placebo, 66.2% Rituximab (p=0.0408)

Other

- Responders: 64.3% Placebo, 73.1% Rituximab (p=0.0995)

African-American/Hispanic subgroup showed significant response in the rituximab-treated group compared with the placebo group.

The other (ethnic) group trended toward a worsening response with rituximab, but not statistically significant.

*
Pharmacodynamics: Mean CD19+ B-cell Counts Over 52 Weeks (Safety Population)

1000 mg rituximab infusions
At Days 1, 15, 168, and 182

3.4% of placebo patients were HACA +
26% of RTX patients were HACA +
Biomarkers: Increased Complement Levels in Rituximab-treated Patients

C3 Complement

C4 Complement

**p=0.0045
*p=0.0029

P values based on Wilcoxon rank sum test

1000 mg rituximab infusions At Days 1, 15, 168, and 182

*KDIGO**
EXPLORER: CONCLUSIONS

Primary and Secondary Endpoints

- EXPLORER evaluated patients with moderate to severe active extra-renal SLE on immunosuppression with steroid treatment and used a high bar for response
- Rituximab depleted CD19+ B cells.
- There were no statistically significant differences between rituximab and placebo in primary or secondary endpoints
- The subgroup of AA or Hispanic Patients may benefit
- Serology (anti-dsDNA and complement) appeared to respond better with Rituximab
- Adverse events balanced and not excessive
Safety and Efficacy of Rituximab in SLE: 136 Pts in the French Autoimmunity Registry - Observational Uncontrolled

- 136 SLE patients treated and evaluated by SELENA-SLEDAI
- 71% pts responded – no difference between RTX monotherapy and RTX + concurrent therapy.
- Improvements by Organ System –
  Articular (72%)
  Cutaneous (70%)
  Hematologic (88%)
  Renal (74%)
- 41% relapse with response again in 91% with retreatment
- Severe infections in 9% most within 3 months of RTX
- 5 Deaths - 3 due to infection, 2 refractory disease.

Arthritis and Rheumatism 62:2458-2466, 2010
LUNAR

SLE + Nephritis

LUNAR Study Design

Screening

Follow-up Period

Treatment Period

Rituximab + MMF (n=72)

Placebo + MMF (n=72)

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 methylprednisolone 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

Key Inclusion and Exclusion Criteria

• Inclusion Criteria
  – Age 16-75 years with SLE by ACR criteria,
  – ISN/RPS Class III or IV lupus nephritis (A or A/C) with a renal biopsy within 12 months
  – Proteinuria, with urine Protein/Creat ratio >1.0

• Exclusion Criteria
  – >50% of glomeruli with sclerosis and/or interstitial fibrosis on renal biopsy
  – Estimated glomerular filtration rate <25 mL/min per 1.73 m² or ESRD
  – CNS disease
  – Thrombocytopenia at high risk for significant bleeding
LUNAR: *Primary Endpoint* (Renal Response at 52 wks)

**Complete Renal Response (CRR)**
- Normalization of serum creatinine OR $\leq 15\%$ greater than baseline if day 1 serum creatinine within normal range of central lab
- Inactive urinary sediment
- Urinary protein to creatinine ratio $< 0.5$

**Partial Renal Response (PRR)**
- Serum creatinine $\leq 15\%$ above baseline value
- No worsening of urinary sediment
- 50% improvement in the urine protein to creatinine ratio,
  - If baseline ratio $\leq 3.0$, then urine P/Cr ratio $< 1.0$
  - If baseline ratio $> 3.0$, then urine P/Cr ratio $< 3.0$

**Non-Response (NR)**
- No response
- All early terminations and patients starting a new immunosuppressant were considered non-responders
LUNAR-
Patient Disposition

Patients Randomized 1:1 (N=144)

Placebo (n=72)
- 9 Withdrawals Total
  - 5 Lost to Follow-up
  - 3 Patients’ Decision
  - 1 Physician’s Decision
  - Completed Week 52 (n=63) 88%

Rituximab (n=72)
- 5 Withdrawals Total
  - 2 Lost to Follow-up
  - 2 Deaths
  - 2 Patients’ Decision
  - 1 Physician’s Decision
  - Completed Week 52 (n=67) 93%
### LUNAR:
**Patient Disease Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=72)</th>
<th>Rituximab (N=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urine protein:creatinine ratio, mean (SD)</strong></td>
<td>4.2 (3.0)</td>
<td>3.8 (2.8)</td>
</tr>
<tr>
<td><strong>Serum creatinine, mg/dL, mean (SD)</strong></td>
<td>1.0 (0.5)</td>
<td>1.0 (0.5)</td>
</tr>
<tr>
<td><strong>Estimated GFR (mL/min), mean (SD)</strong></td>
<td>96.0 (51.1)</td>
<td>87.7 (34.9)</td>
</tr>
<tr>
<td>60, n (%)</td>
<td>20 (27.8)</td>
<td>17 (23.6)</td>
</tr>
<tr>
<td>≥60, n (%)</td>
<td>52 (72.2)</td>
<td>55 (76.4)</td>
</tr>
<tr>
<td><strong>Serum albumin, g/L, mean (SD)</strong></td>
<td>2.6 (0.7)</td>
<td>2.7 (0.8)</td>
</tr>
<tr>
<td><strong>ISN/RPS classification, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class III</td>
<td>24 (33.3)</td>
<td>25 (34.7)</td>
</tr>
<tr>
<td>Class IV</td>
<td>48 (66.7)</td>
<td>47 (65.3)</td>
</tr>
<tr>
<td>Class V (coexistent)</td>
<td>23 (31.9)</td>
<td>26 (36.1)</td>
</tr>
<tr>
<td><strong>BILAG index global score, mean (SD)</strong></td>
<td>15.3 (6.2)</td>
<td>15.3 (6.4)</td>
</tr>
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</table>
LUNAR: Primary Endpoint:

Renal Response at Week 52

* Wilcoxon Rank-sum test to compare the proportions of (CRR, PRR, NR) between rituximab and placebo

Mean MMF dose: Placebo: 2.4±0.62 g; Rituximab: 2.7±0.41 g
LUNAR:
Renal Response Rates Over Time

Rituximab infusions (1000 mg)
PLC=placebo, RTX=rituximab, CRR=complete renal response, PRR=partial renal response
LUNAR0 Pre-Specified Analysis: Proportion of Subjects Achieving Response by Race

- **Black (n=40)**
  - Placebo: 45.0%
  - Rituximab: 70.0%

- **Hispanic (n=52)**
  - Placebo: 47.8%
  - Rituximab: 55.0%

- **Caucasian (n=45)**
  - Placebo: 50.0%
  - Rituximab: 52.6%
## LUNAR: Safety Summary

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (N=71)</th>
<th>Rituximab (N=73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event (AE)</td>
<td>68 (95.8)</td>
<td>71 (97.3)</td>
</tr>
<tr>
<td>Serious adverse event (SAE)</td>
<td>25 (35.2)</td>
<td>22 (30.1)</td>
</tr>
<tr>
<td>Infectious AE</td>
<td>61 (85.9)</td>
<td>61 (83.6)</td>
</tr>
<tr>
<td>Infectious SAE</td>
<td>12 (16.9)</td>
<td>12 (16.4)</td>
</tr>
<tr>
<td>Infusion-related AE</td>
<td>29 (40.8)</td>
<td>25 (34.2)</td>
</tr>
<tr>
<td>Infusion-related SAE</td>
<td>2 (2.8)*</td>
<td>1 (1.4)**</td>
</tr>
<tr>
<td>AE leading to withdrawal from study</td>
<td>3 (4.2)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Human anti-chimeric antibody (HACA)-positive</td>
<td>4 (5.6)***</td>
<td>8 (11.1)</td>
</tr>
<tr>
<td>Death</td>
<td>0 (0)</td>
<td>2 (2.7)</td>
</tr>
</tbody>
</table>

** Urticaria requiring interruption of infusion (HACA titer 35,000 ng/mL)

*** One subject received open-label RTX
LUNAR: Conclusions

- LUNAR is the largest randomized, placebo-controlled trial to evaluate Rituximab as a therapeutic intervention (induction of remission) in LN, when combined with “standard” immunosuppression (MMF + steroids).

- Although there were more renal responders with Rituximab (57% vs. 46%), the study did not show a statistically significant difference in primary or secondary endpoints at week 52.

- Rituximab had a statistically significant effect on levels of anti-dsDNA and C levels. AA may have a better renal response.

- Adverse events and serious adverse events were similar in frequency between groups, with no new or unexpected safety signals.
Rituximab is not currently indicated (or approved by the FDA) for induction of Remission in Lupus Nephritis; with or without concurrent therapy with MMF or CYC.
RITUXIMAB THERAPY for **REFRACTORY LUPUS NEPHRITIS**
(No Renal Response [CRR or PRR] after 3-6 months of CYC or MMF + steroids for Induction)
Rituximab in “Refractory” or Relapsing LN

- 31 patients with “refractory” or “relapsing” SLE (11 with LN) treated with Rituximab 375mg/m^2 x 4 or 1000mg x 2 and followed for a median of 30 months.

- 27/31 (87%) achieved a CR or PR. 10/11 with LN achieved a CRR or PRR

- 18/31 (53%) relapsed in 11 months on or after B-cell return in 10 but in the absence of B-cell return in 8

- Infusion reactions were common (58%) and infection developed in 26%
Rituximab in “Refractory” LN


- 146 patients with Class III, IV or V LN treated with Rituximab and CYC (n=124 or MMF (n=55)- uncontrolled
- 6 months- CRR= 27%; PRR= 40%
- 12 months- CRR= 30%; PRR= 37%
- Better response in Class III compared to Class IV or V
- Poorer response in NS or AKI
39 patients with SLE (44% with LN) refractory to treatment with CYC (44%) or MMF (49%) were treated with Rituximab and followed for 24 months.

- SLEDAI score - 11, 5.5 at 24 months
- 28/39 (72%) had a CRR or PRR
- Relapse at 25 months in 4/28 (14%) responders
- Infections in <10%

(Bang SY, et al Autoimmune Dis 2012)
20 Patients treated with RTX for LN and followed at least 12 months.

19F/1M Active IV (n=15) or V (n=5)

12 Patients refractory to standard therapy, 6 cases relapsing disease, 2 patients first line therapy

3 concurrent cyclophosphamide, 10 continued RTX as maintenance
Rituximab in Severe LN: Early B Cell Depletion Affects Long-Term Renal Outcome
(Melander et al CJASN 4: 579-587, 2009)

- At 22 months complete or partial renal remission in 12/20 (60%).
- LN relapsed in 1 patient who responded to another RTX course.
- Side effects: 5 infections and 4 moderate neutropenias (late onset).
- B cell depletion 1 month post-Rituximab was strongly associated with renal response (negatively associated with Black race and hypoalbuminemia).
- RPGN with crescentic disease did not respond.
Rituximab in “Refractory” LN


- 25 patients with LN “refractory” to standard therapy treated with Rituximab. Followed for a mean of 36 months.
- 22/25 (88%) had a PRR or CRR after median of 12 months; 16/25 (64%) had a CRR after a median of 24 months
- 6/22 (27%) responders had a relapse
- Longer B-cell depletion time associated with a better outcome
Rituximab in “Refractory” LN: Systematic Review

- Systematic Review of 26 published reports of use of Rituximab for “Refractory” LN (n=300; all observational; mean follow-up 60m)
  - Class III- CRR/PRR = 87%; CRR = 60%
  - Class IV—CRR/PRR = 76%; CRR = 45%
  - Class V-- CRR/PRR = 67%; CRR = 40%
  - Class III/IV + V = 76%; CRR = 24%
Observational studies of Rituximab therapy shows “beneficial” effects in “Refractory” or “Relapsing” LN (60-80% CRR + PRR) but relapses common (15-30%). Late onset neutropenia of concern. No benefit in RPGN with crescents.
RITUXIMAB for **STEROID-FREE MAINTENANCE** and for TREATMENT of **RELAPSES**
Treatment of Class IV LN with MMF and Rituximab with NO Oral Steroids

- 50 Patients; average age 35 years
- ISN/RPS Class IV Salb 2.2 g/dl Scr= 129 umol/L
- Treated with 2 doses Rituximab 1 g + IV methylprednisolone pulses 500mg 2 wks apart and then maintained on MMF. No oral steroids.
- Followed at 35 +/- 14 months

Treatment of Class IV LN with MMF and Rituximab with N0 Oral Steroids

- 45/50 (90%) CRR/PRR - Mean time - 37 weeks
- 36/50 (72%) CRR - Mean time - 32 weeks 6 months
- 11 patients (22%) relapsed by 65 weeks
- 9 Hospitalizations (18%) - 10% for a serious infection episode, 1 PVD died post surgery.

Condon MB, Griffith M, Cook HT, Levy J, Lightstone, L, Cairns T ASN 2010
Rituximab in SLE and LN:

**Conclusions**

- Rituximab appears to be beneficial as rescue therapy for some patients (Class III/IV LN) with relapsing or refractory (to standard therapy) disease.
- Rituximab is mostly used with other therapies – however, steroid-free maintenance with Rituximab is possible.
- The role of Rituximab as a first line agent in Induction for LN remains to be defined. May have a role in certain populations – Blacks and Hispanics.
- In general, Rituximab it has been well tolerated, expt for late onset leucopenia; Infusion reactions are uncommon but can be severe. Infection rate is low. PML rate is low but not zero.
- Rituximab is “an interesting therapeutic option” for difficult to treat LN.
Belimumab is approved by FDA for treatment of SLE (without nephritis) based on a positive Phase III RCT. Efficacy in African-Americans is uncertain.

A post-hoc pooled analysis of all Phase III trials in SLE patients with LN at baseline (n=267 of 1684 total) was conducted.*

Trends (not significant) for improved renal outcomes (proteinuria, BILAG, serology) seen in Belimumab vs placebo. Greater improvement was seen in subjects receiving MMF who were serologically active (*Dooley MA, et al. Lupus, 2013)
OCRELUZIMAB
Ocreluzimab for Lupus Nephritis (BELONG)

- **Ocreluzimab** (OCR) + MMF or CYC (Eurolupus protocol) vs Placebo + MMF or CYC underwent a Phase III pivotal trial in LN but the study was stopped prematurely due to excess infection rates in the active drug treated groups.

- At the time of discontinuation no difference in efficacy (ITT) between OCR + MMF or CYC and Placebo + MMF or CYC groups.
Efficacy of OCR in LN:
Exploratory (post-hoc) analysis of % Renal Response according to duration of disease prior to randomization

![Chart showing comparison of renal response between Placebo and OCR for different duration groups.](chart.png)
A Phase III trial of Abatacept (IM101075) for induction of remission in Lupus Nephritis on a background of MMF and steroids failed to meet the primary outcome (frequency of CRR at 12 months).

However a post-hoc analysis of the trial, using different end-point criteria (ALMS, LUNAR and ACCESS)- showed significant differences. Using LUNAR criteria a CRR was seen in 6% of controls vs 22-24% in the Abatacept arms (2 dosing levels).

The choice of how a CRR is defined can determine if a LN trial is a success or a failure!!!
Issues Concerning Selection of “Correct” Surrogate End-Points for Evaluation of Novel Drugs for LN

- The *Kidney Health Initiative* (a consortium of ASN, FDA, CDC, NIH, CMO, Pharma and Device Companies, CMS, Patients and Providers) to foster innovations in treatment of Kidney Disease

- One of 3 initial pilot projects (headed by Brad Rovin, MD- Ohio State and partnered with the Lupus Nephritis Trial Network) will examine the strengths and weaknesses of existing surrogate endpoints and make consensus recommendations for new outcome measures, biomarkers, remission and relapse definitions and surrogate end-points for trials of LN going forward

*(see www.kidneyhealthinitiative.org)*
Other Biologic Agents
Other Biologic Agents in Lupus Nephritis

- Ataticept
- Epratuzumab
- Abetimus
- CTLA4Ig
- Anti-TWEAK
- Anti-CD40L
- Eculizumab*
- ACTH**

(* approved by FDA for treatment of atypical HUS, not LN; ** approved by FDA for treatment of SLE)
Other Biologic Agents in SLE and LN

- **Atacicept**- NCT-01369628- Serono- Terminated for toxicity
- **Epratuzumab**- NCT- 01262365 (EMBODY-1)-Active Phase III- UCB- (Japan only)
- **Eculizumab**- No Trials in SLE or Nephritis
- **ACTH (Acthar Gel)**- NCT-01769937 (single site) and NCT-012753401 (multi-site- Phase IV- placebo-RCT- QuestCor
- **Abetimus (Riquent)**- NCT-00089804- Terminated –ineffective- La Jolla Pharm
- **Anti-TWEAK (ATLAS)**- NCT-0149935- Active- Phase II- Biogen
- **CTLA4Ig**- NCT-00094381- Active Phase II- (NIH)
- **Anti-CD40L (9588)**-- NCT00001789- Active – Phase II –(NIH)
SUMMARY - New Biologics in Treatment of Lupus Nephritis - I

- *Rituximab* (anti-CD20 chimeric MoAb) shows great promise for treatment of refractory and/or relapsing LN. Steroid-free remissions may be maintained by periodic Rituximab infusions (? 500-1000 mg every 4-6 months ). Long-term safety and efficacy (hard end-points of mortality or ESRD) still uncertain, but short term safety seems reasonable. Efficacy for induction unknown. No positive RCT (yet)- Evidence level B/C
SUMMARY -
New Biologics in Treatment of Lupus Nephritis-

- Other Biologic agents of uncertain value-(incompletely assessed)- need more RCT and observation studies
- Abatacept is promising, but a confirmed positive result in a RCT is needed
- Abetimus, Ocrelizumab, Atacicept not effective or unsafe
- Combinations of MoAb’s or fusion protein receptor antagonists (anti-CD20 + CTLA4Ig or anti-Blys/BAFF might be efficacious- not tested)
Long-term safety (especially for latent viral diseases like PML) is a nagging concern—risk seems low (<1:30,000 patient years)

Rituximab is contra-indicated if concomitant Hepatitis B viral infection is present (reactivation of viral replication)
A 23 year old woman with a 7 year history of Systemic Lupus Erythematosus develops nephrotic syndrome (urine protein excretion of 5.6gms/d, serum albumin of 2.4gms/dL). Her serum creatinine is 1.30mg/dL (115µM/L; eGFR- CKD-EPI-creatinine= 58ml/min/1.73m2). A C3 is 46mg/dL and a C4 is 9mg/dL/ The anti-dsDNA titer is 1:1280. A pregnancy test is negative. She indicates a desire to eventually have children.
A renal biopsy reveals Severe Lupus Nephritis Class IV- Segmental; a+c; 15 % of the glomeruli show crescents. Moderate interstitial nephritis is present. IF shows moderate segmental deposits of IgG, C3, C1q. EM shows mesangial and sub-endothelial electron dense deposits and scanty sub-epithelial deposits. Tubulo-reticular inclusions are present in endothelial cells.
QUESTION #2B

In addition to 3 doses of IV methylprednisolone (500mg each), which one of the following treatments would you start now?

A. Oral MMF at 2.0gms/d + oral prednisone at 60mg/d
B. IV cyclophosphamide 500mg every two weeks for 3 months + oral prednisone at 60mg/d
C. IV cyclophosphamide 1000mg/m2 monthly for 6 months + oral prednisone at 60mg/d
D. Oral cyclophosphamide 2mg/kg/d or 3 months + oral prednisone at 60mg/d
E. Rituximab 375m/m2 every week times 4 weeks + oral prednisone at 60mg/d
F. Cyclosporine 4mg/kg/d + MMF 2 gms/d + oral prednisone at 60mg/d