How I Treat Lupus Nephritis in 2018 and How I Will in the Future

Gerald B. Appel, M.D.
Professor of Medicine
Director - The Center for Glomerular Diseases
Division of Nephrology
Columbia University College of Physicians and Surgeons
Dr. Appel has research grants with Regulus, Achillion, BM Squibb, EMD Serono, and NIH.

He lectures for Genentech (ANCA + RPGN), Sanofi-Genzyme (renal side effects of Lemtrada used for M.Sclerosis).

He has consultancies with: Alexion, Achillion, Ionis, Genentech, Mallinkrodt, Pfizer, Merck, Roche, Bristol-Myers Squibb, Up-to-Date, Genzyme-Sanofi, EMD Serono, Omeros, Regulus.
30 yo F with SLE and New LN

A 30 yo Black F with a 6 mo hx of malar rash, arthralgias and arthritis in her hand joints, and recent pedal edema.
She is evaluated by her MD and found to have: high ds antiDNA ab, low complement, U/A with 3 + proteinuria and 2 + hematuria and a creatinine of 1.3 mg/dl.
Diagnosis: SLE and LN active clinically.
Her Bx shows DPLN with extensive mesangial and subendothelial immune deposits
30 yo Black F with SLE and LN

- What induction therapy would you use?
- Does the fact that she is Black influence your therapy?
- What if she had a Creatinine of 3.5 mg/dl? What if her biopsy had extensive crescents or tubulo-interstitial fibrosis?
- What maintenance therapy? For how long?
- What if she has Membranous LN?
- What if she relapses or is resistant to these treatments
Proliferative LN
ACR- KDIGO 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**
Multicenter Trial MMF vs IVCytoxn for Induction Therapy of Severe LN (N=140)

- Complete Remission: MMF 22.5%, IVC 4%
  - MMF vs IVC: P=0.005
- Partial Remission: MMF 29.6%, IVC 24.5%
  - MMF vs IVC: P=NS
- Complete + Partial Remission: MMF 52.1%, IVC 30.4%
  - MMF vs IVC: P=0.009

Ginzler E. ... Appel G  N Eng J Med  Nov. 2005
ALMS TRIAL – RCT  MMF vs IVC in Severe LN
Appel, Contreras, Dooley et al JASN 2009

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Consent withdrawn (n = 6)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Consent withdrawn (n = 5)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, prospecitive trial of 90 LN pts with Proliferative LN
Initial Follow 41 months, subsequent long-term follow

Monthly High dose IVCYT ( 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 )

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></td>
<td>IVCY</td>
<td>IVCY</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><strong>Cumulative IVCY dose (g)</strong></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,
## ELNT - 10 year FU

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>High-dose</th>
<th>Low-dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>IVCY</td>
<td>IVCY</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>

Effect of Race on Renal Survival

Renal Survival – LN IV
U N Carolina   N = 90

Renal Survival LN III and IV
Columbia U Med Ctr   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 Cyclophosph- 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
Crescentic glomerulonephritis in most glomeruli

Diffuse glomerulosclerosis, tubular atrophy & interstitial fibrosis
What I Look for on the Biopsy in LN

1) Is the biopsy adequate – the more glomeruli the better; < 7 making guesses.

2) ISN Class. ONLY III and IV and only A or A/C not C. III+V or IV + V gt vigorous treatment !

3) The more chronicity especially interstitial fibrosis the lower the benefits. BUT glomerulosclerosis must be very extensive to make me avoid therapy. TIF!!!

4) Are the deposits extensive extensive espec by EM.

5) Fibrinoid necrosis of glomerular caps and especially lots of Crescents are bad but treatable.
Controversy: Is MMF superior or equal to IV Cyt in LN with severe renal dysfunction.

Post Hoc analysis of 29 pts (18 MMF 11 Cyt) with GFR < 30 ml/min, Baseline: similar in age, proteinuria (5.1 and 4.6 g/day), chronicity on bx, and GFR (21 vs 24 ml/min).

No difference in composite outcome of proteinuria and Scr. GFR increased 20 ml/min more with MMF. Proteinuria decreased (0.8g/d) more with MMF. 25% of both groups had treatment limiting adverse events.

Conclusion: No evidence that IVC is more effective than MMF in pts with severe LN. (Did not calculate crescents)
Proliferative Lupus Nephritis – Maintenance Treatment
ACR – KDIGO Treatment guidelines

**MMF induction**
- IMPROVED
  - MMF 1-2g/d or AZA 2 mg/kg/d ± lo dose daily GC
  - CYClophos (lo- or hi-dose) + pulse GC then daily GC
- NOT IMPROVED

**CYCclophos induction**
- IMPROVED
  - MMF 1-2g/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

6 months
ALMS Maintenance Trial: MMF vs Azathioprine for Lupus Nephritis

24-wk induction phase

MMF 1.5 g BID

IVC 0.5–1 g/m² Monthly

Response or Remission

Yes

MMF 1 g BID

No

No further treatment (exit study)

Re-randomization

No

AZA 2 mg/kg/d

36-mo maintenance phase

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

- MMF
- AZA

Probability of being event free

Month

p = 0.003
Subjects Achieving Primary and Key Secondary Endpoints

Dooley MA, Jayne D, Ginzler E, Appel GB …Solomons N
NEJM 365: 1926-1931, 2011
Summary of Failure Rate - Race and Region

Overall       White       Black       Asian       Other
  116/111  48/51       12/11       39/37       17/12

Overall USA/CAN Latin Asia Europe/RoW
  116/111  22/25  25/35  37/35  32/16

MMF   AZA
Summary of Treatment Failure Rate by Induction Treatment

Patients with Tx failure (%)

Overall Induction MMF Induction IVC

MMF AZA
The MAINTAIN Nephritis Trial
Primary endpoint: Time to renal flare
Analysis by intention-to-treat

RENAL FLARES

AZA: 25%
MMF: 19%

RENAL FLARE SURVIVAL CURVES

Groups of Treatment

<table>
<thead>
<tr>
<th>Groups of Treatment</th>
<th>Months at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMF-MMF</td>
<td>47 44 34 22 14 12 9</td>
</tr>
<tr>
<td>IVC-MMF</td>
<td>17 15 12 9 9 5 4</td>
</tr>
<tr>
<td>IVC-AZA</td>
<td>34 30 28 20 15 10 6</td>
</tr>
<tr>
<td>AZA-AZA</td>
<td>18 16 15 10 7 3 3</td>
</tr>
</tbody>
</table>
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.
Membranous Lupus Nephropathy  
( vs Idiopathic MN )

- Mesangial proliferation
- IF – full house staining IgG, IgA, IgM, C1q, C3
- EM deposits in mesangium or subendothelial as well as expected subepithelial deposits
- EM tubuloreticular inclusions in endothelial cells
Treatment of Membranous LN

- Corticosteroids
- IV Cyclophosphamide
- Cyclosporine or Tacrolimus
- Mycophenolate
- Rituximab
- Etc – ACTHAR, Belimumumab,
No difference in remission of proteinuria between MMF and IVC in Membranous LN

Radhakrishnan J, Moutzouris D, Ginzler E, and Appel G
Unmet Needs in Lupus Nephritis

• Induction
  – Improved remission rates ("Proteinuria, GFR")
  – Resistant Lupus

• Maintenance
  – Reduction of flares

• General
  – Consistent Endpoints in clinical trials
  – Lack of non-invasive biomarkers for diagnosis and therapy monitoring
  – Reduction of side effects
  – Costs !!!

Four drugs FDA-approved:
  1948 Aspirin
  1955 Corticosteroids
  1955 Hydroxychloroquine
  2011 Belimumab

Table 1 – Medications used off label for SLE

- Abatacept
- Azathioprine
- Cyclophosphamide
- Cyclosporine
- Leflunomide
- Methotrexate
- Mycophenolate mofetil
- Rituximab
- Tacrolimus
- Thalidomide

SLE, systemic lupus erythematosus.
How do you treat relapses and resistant patients?

- Rituximab
- Belimumab
- Abatacept
- ACTH
- Voclosporin (new CNI)
- Anifrolumab anti IFNa
- Multi-target therapy
LUNAR – RITUXIMAB Study Design

Screening

Rituximab + MMF (n=72)

Prednisone taper

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 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 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 30.6%, Rituximab 26.4%
- Partial Renal Response (PRR): Placebo 15.3%, Rituximab 30.6%
- Complete + Partial Renal Response (C+PRR): Placebo 46%, Rituximab 57%
Time to remission and relapse

CR + PR (90% overall)
CR (72% overall)

Relapse

In CR:
- 12 wks 9 (18%)
- 26 wks 16 (32%)
- 52 wks 26 (52%)

Condron et al 2013 Ann Rheum Dis. 72:1280-6
Time to remission similar for class III/IV/V

Proportion achieving remission vs. Time since treatment (weeks)

P=0.96

Condron et al 2013 Ann Rheum Dis. 72:1280-6
Efficacy of rituximab in **Refractory LN**
Response Rate in 300 Patients – pooled Data – mean follow 60 weeks

B-Lymphocyte Survival factors
(baFF: TNFSF13b; BLYSS)

1. Monocytes are activated by foreign antigens such as viruses and bacteria

2. The activated monocyte releases BLYS, which assists in B-cell activation

3. B-cells are activated by a combination of foreign antigen and BLYS

4. A primary consequence of this wave of cellular activation is the enhanced production of plasma cells (i.e. Activated B-cells), which will expand and produce more antibodies

www.hgsi.com/
Belimumab – FDA Approved for SLE


SRI, SLE Responder Index
Renal Remission with > 1 Gm Proteinuria
Efficacy and Safety of Belimumab in Pts with Active LN (BLISS-LN)

- 464 LN Pts - Phase 3 randomized, double blind trial of PBO + standard care vs Belimumab 10 mg/kg + standard care (Fully enrolled 2017)
- Standard of Care = either Steroids + IV Cyclophosphamide followed by AZA maintenance or steroids + MMF followed by maintenance MMF.
- Primary outcome = Complete renal response at week 52 and 104 weeks
- PBO or B - Day 0,14,28 and then q 28 until 104 wks.

CALIBRATE Trial - ITN– Ritux + IVC vs Ritux +IVC followed by Belimumab
Abatacept - a fusion protein of the Fc region of IgG1 fused to the extracellular domain of CTLA-4. Binds to CD80 (B7-1) and CD86 (B7-2) and prevents second signal of T cell activation.
Treatment of LN with Abatacept and Low-Dose Pulse Cyclophosphamide- 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>

- Adding abatacept + low-dose cyclophosphamide/steroids Induction does not improve 6 or 12 month CRR rates
- Low-dose (Euro-Lupus) cyclophosphamide works well in a diverse N. American LN population
Voclosporin: AURA Study Phase IIB

Study aims to demonstrate that voclosporin added to SoC can increase speed of remission & overall remission rates in the presence of extremely low steroids

Primary endpoint 24 weeks

Secondary endpoint 48 weeks

1:1 Randomization
N=265

VOCLOSPORIN 23.7 mg bid
MMF 2 g + oral corticosteroids

VOCLOSPORIN 39.5 mg bid
MMF 2 g + oral corticosteroids

PLACEBO
MMF 2 g + oral corticosteroids

AURA - forced steroid taper

500mg-1g MP to start
5mg by 8 weeks
2.5mg by 16 weeks
Complete Remission (CR) Rates at 24 & 48 weeks

23.7mg BID VCS demonstrates statistically significant CR rates at 24 & 48 weeks

- **23.7mg BID**
  - 24 week CR: *32.6%;* OR: *2.03; p=.045*
  - 48 week CR: *49.4%;* OR: *3.21; p=.001*
- **39.5mg BID**
  - 24 week CR: *27.3%;* OR: *1.59; p=.204*
  - 48 week CR: *39.8%;* OR: *2.10; p=.026*
- **Control**
  - 24 week CR: *19.3%*
  - 48 week CR: *23.9%*

Interferon signature metric (ISM)

PNAS 2003;100:2610-2615

Ann Rheum Dis 2016;75:196-202
Treatment Approach: Intermediate Events

Autoantigen presentation and activation of autoreactive leukocytes
Anifrolumab, anti-IFN alpha receptor monoclonal Ab for Severe SLE

Activation of IFN system is a major inflammatory mediator in SLE.
All cell signaling by IFN is mediated by type I alpha IFN receptors.
Recent studies with anti IFN antibodies have given mixed results. Rontalizumab failed, sifalimumab showed only modest benefit.

Anifrolumab binds to IFNR - studied in 305 Pts with moderate to severe lupus.
When added to SOC more responders by SLRI, BILAG, and SLEDAI etc… very positive results!
Anifrolumab, an Anti-Interferon-α Receptor Monoclonal Antibody, in Moderate-to-Severe Systemic Lupus Erythematosus
Multitarget Therapy (MMF, Tacrolimus, Steroids) vs IV Cyclophosphamide + Steroids for Induction Treatment of LN: A Randomized, Controlled Trial

Multitargeted Therapy: Probability of no relapse during Maintenance Phase
Haitao Zhang et al. JASN 2017;28:3671-3678

(Tac 2-3mg/d+MMF0.5-0.75g/d+Pred10mg/d vs. Aza+Pred)

No. at risk
Multitarget group 116 116 113 112 109 104 101
AZA group 90 87 83 76 72 66 64

No. of relapse
Multitarget group 0 0 0 1 3 2 0
AZA group 0 2 1 0 2 0 1

unadjusted HR 0.68 (95% CI: 0.22-2.10)
adjusted HR 0.82 (95% CI: 0.25-2.67)
The changes in SCr levels and eGFR during the maintenance treatment.

Haitao Zhang et al. JASN 2017;28:3671-3678
30 yo AA F with SLE and LN

- What induction therapy? MMF or IV cyclophosphamide.
- What if she were Caucasian and not AA? Same induction – MMF maintenance.
- What if extensive crescents or tubulo-interstitial fibrosis? Aggressive for cellular crescents – more TIF less likely to succeed.
- What maintenance therapy? MMF, alt AZA, alt multitarget Rx with pred, MMF, Tacro.
- What if she fails or relapses during these therapies. Other options – Rituximab, belimumab, ACTH, add CNI. ? Anifrolumab etc.