Update on Systemic Lupus Erythematosus (SLE)

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Adult and Pediatric Rheumatology
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Objectives

- Present a case of a patient with SLE
- Review long-term complications of SLE with focus on atherosclerosis
- Discuss recent clinical trials in non-renal SLE
- Discuss good news about an old SLE drug (hydroxychloroquine)
### Case: Nicole

- **31 yr old**
  - 8 week history of fatigue, facial rash, hair loss, joint pain
- **Past Medical History**
  - 2 first trimester miscarriages
- **Medications**
  - multivitamin, oral contraceptive
- **Soc HX:**
  - single, works full time, smokes ½ pack cigarettes daily
- **FHX:**
  - Hypertension, DM-2, no autoimmune disease

### Exam:
- HR 105, BP 147/90
- malar rash
- polyarticular arthritis

### Labs:
- WBC 2,200 (absolute lymphocytes 800)
- H/H 10.5/32
- ESR 45 mm/hr
- Urinalysis with 100 mg/dl protein, 15 RBCs
- +ANA, +double stranded DNA,
  +anticardiolipin IgG
- Low C3 and C4
<table>
<thead>
<tr>
<th>ACR 1997 Classification Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Malar rash</td>
</tr>
<tr>
<td>• Discoid rash</td>
</tr>
<tr>
<td>• Photosensitivity</td>
</tr>
<tr>
<td>• Oral/nasal ulcers</td>
</tr>
<tr>
<td>• Non-erosive arthritis</td>
</tr>
<tr>
<td>• Pleuritis/pericarditis</td>
</tr>
<tr>
<td>• Nephritis</td>
</tr>
<tr>
<td>• Cytopenia</td>
</tr>
<tr>
<td>• Encephalopathy</td>
</tr>
<tr>
<td>– seizure or psychosis</td>
</tr>
<tr>
<td>• ANA</td>
</tr>
<tr>
<td>• Serology</td>
</tr>
<tr>
<td>– anti-double stranded DNA</td>
</tr>
<tr>
<td>– anti-Smith</td>
</tr>
<tr>
<td>– anti-phospholipid antibody</td>
</tr>
</tbody>
</table>

4 OF 11 CRITERIA GIVES 96% SENSITIVITY/SPECIFICITY
Pathophysiology of SLE

Exposure(s)
- Immune dysregulation

Susceptible host

Tissue damage

Genes
Gender/Sex Hormones
Pathophysiology of SLE

Exposure(s)
- UV light
- Drugs
- Infectious agents

Immune dysregulation

Susceptible host
- Genes
- Gender/Sex Hormones

Tissue damage

Pathophysiology of SLE

Exposure(s)
- UV light
- Drugs
- Infectious agents

Immune dysregulation
- Complement activation
- Immune complex deposits
- B and T cell hyper-reactivity
- Loss of self tolerance
- Autoantibodies
- Cytokines

Susceptible host
- Genes
- Gender/Sex Hormones

Tissue damage
Immune Dysregulation in SLE

- Lymphocyte proliferation
- MHC class II expression (HLA DR)
- Immune cell maturation (e.g., CD40, B7)
- Inflammatory cytokines
- Adhesion molecules
- Endothelial NO synthase

Macrophage, B and T lymphocyte activation

Vessel inflammation

Autoantibody formation and autoreactivity

Vasculitis and organ damage

Survival in SLE

<table>
<thead>
<tr>
<th></th>
<th>5 year</th>
<th>10 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult</td>
<td>95%</td>
<td>90%</td>
</tr>
<tr>
<td>Pediatric</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1975</td>
<td>83%</td>
<td>76%</td>
</tr>
<tr>
<td>2003</td>
<td>99%</td>
<td>86%</td>
</tr>
</tbody>
</table>

Predictors of poor outcome

- Childhood onset
- Low SES
- Health care access
- Education
- Race/ethnicity

- Male gender
- Disease activity
- CNS
- Renal
The Bimodal Mortality Pattern of SLE

Causes of Death in SLE

- **Early:** Within first 5 years of diagnosis
  - Active SLE
  - Infection

- **Late:** > 5 years since diagnosis
  - Infection
  - Atherosclerosis
  - Malignancy

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Urowitz M Am J Med 1976; 60: 221

Malignancy

- Increased incidence in SLE
  - Cervical HPV infection and cancer
  - Hodgkins lymphoma
  - Lung cancer
  - Breast cancer

- Hydroxychloroquine protective?

- Malignancy screening and prevention key


Atherosclerosis

- Increased incidence and earlier presentation in SLE

- Bland vasculopathy (not vasculitis)

- Independent of Framingham risk factors, glucocorticoid use

- “Lupus factor” elusive
  - Inflammation, dyslipidemia, autoantibodies
Incidence of MI per 1000 person years in women with SLE (Pittsburgh) and from the Framingham Offspring Study: 1980-1993

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>SLE (N=498)</th>
<th>Framingham (N=2208)</th>
<th>Rate Ratio</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-24</td>
<td>6.33</td>
<td>0.00</td>
<td>∞</td>
<td>–</td>
</tr>
<tr>
<td>25-34</td>
<td>3.66</td>
<td>0.00</td>
<td>∞</td>
<td>–</td>
</tr>
<tr>
<td>35-44</td>
<td>8.39</td>
<td>0.16</td>
<td>52.43</td>
<td>[21.6, 98.5]</td>
</tr>
<tr>
<td>45-54</td>
<td>4.82</td>
<td>1.95</td>
<td>2.47</td>
<td>[0.8, 6.0]</td>
</tr>
<tr>
<td>55-64</td>
<td>8.38</td>
<td>1.99</td>
<td>4.21</td>
<td>[1.7, 7.9]</td>
</tr>
</tbody>
</table>


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Role of Traditional Risk Factors

- High frequency of CV risk factors in SLE.
- After adjusting for CHD risk using the Framingham risk factor estimate, patients with SLE still had a 7- to 10-fold increased risk of CHD and stroke.


89.7% have > 3 CV risk factors
Timeline for SLE Drug Development

- Aspirin
- Hydroxychloroquine
- Methotrexate*
- Leflunomide*
- Cyclophosphamide*
- Glucocorticoids
- Azathioprine*
- Mycophenolate mofetil*
- Rituximab*
- Belimumab

* Not an FDA approved indication

Treatment of SLE

- Tailored to organ involvement
- Few controlled trials

Mild disease
- Hydroxychloroquine
- NSAIDs
- Low dose corticosteroids
- Methotrexate
- Leflunomide
- Azathioprine
- Belimumab

Severe disease
- High dose corticosteroids
- Mycophenolate mofetil
- Cyclophosphamide
EXPLORER TRIAL
Rituximab to Treat Non-Renal SLE
Study Design

Mean age 40.4y
Nonwhite 42%

Active non-renal SLE (n=257)
Background
immunosuppression

52 wk follow up

Rituximab (days 1, 15, 168, 182)
Prednisone taper
(n=88)

Placebo (days 1, 15, 158, 162)
Prednisone taper
(n= 189)

Primary Endpoint: major or partial clinical response (BILAG)

Secondary Endpoints:
Time to disease flare
Quality of life


EXPLORER Trial: Proportion of patients with major, partial or no clinical response at 52 weeks

Belimumab to Treat Active Non-Renal SLE: Study Design

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active non-renal SLE (n=867)</td>
<td>52 wk follow up</td>
<td></td>
</tr>
<tr>
<td>Background immunosuppression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo (n=288)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belimumab 1 mg/kg (n=289)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belimumab 10 mg/kg (n=290)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Primary Endpoint:** Improvement in SLE Responder Index (SRI)

**Secondary Endpoints:**
- Physician Global Assessment

Navarra S et al. Lancet 2011; 377: 721-731

**Efficacy of Belimumab to Treat Active Non-Renal SLE at 52 Weeks**

![Graph showing proportion of patients with improved SLE Responder Index (SRI)]

- Placebo
- Belimumab 1 mg/kg
- Belimumab 10 mg/kg

Odds ratio for response to belimumab 10 mg/kg vs placebo 1.83 (1.30 to 2.59), p = 0.0006

Navarra S et al. Lancet 2011; 377: 721-731
Lupus Atherosclerosis Prevention (LAPS) Study Design

Mean age: 44 yrs
Mean SLEDAI: 2
Nonwhite: 39%

Adult SLE (n = 200) 2 year follow up

Standard therapy

Atorvastatin 40 mg/day
Placebo

Primary Endpoint: CT coronary calcium score

Secondary Endpoints:
- CIMT
- Disease activity (SLEDAI)
- Inflammatory Mediators (hs-CRP)

LAPS Study: Change in Coronary Calcium Score and CIMT

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean baseline</th>
<th>Mean 2 years</th>
<th>Mean change</th>
<th>P Value</th>
<th>Difference in change, statin minus placebo (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loge (coronary artery calcium score + 1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>1.16</td>
<td>1.24</td>
<td>0.08</td>
<td>0.52</td>
<td>-0.08 (-0.39 to 0.23)</td>
<td>0.62</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.19</td>
<td>1.35</td>
<td>0.15</td>
<td>0.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carotid intima media thickness (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>0.59</td>
<td>0.66</td>
<td>0.07</td>
<td>&lt;0.0001</td>
<td>-0.02 (-0.05 to 0.01)</td>
<td>0.24</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.57</td>
<td>0.66</td>
<td>0.09</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Petri et al Ann Rheum Dis 2011
**Atherosclerosis Prevention in Pediatric Lupus Erythematosus**

**Study Design**

- **Pediatric SLE (>10 and <21)**
  - (n = 221)
  - 3 year follow up

**Standard therapy**
- hydroxychloroquine, ASA, folate, AHA TLC diet + placebo

**Primary Endpoint: IMT progression**

**Secondary Endpoints:**
- Disease Severity (SLEDAI, SLICC)
- Quality of Life (PedsQL)
- Inflammatory Mediators (hs-CRP)

**APPLE Results: CIMT Endpoints**

- atorvastatin slower
- placebo slower

Schanberg et al, Arthritis Rheum 2010 Difference of CIMT Progression (mm/year) with 95% CI
Hydroxychloroquine

- Antimalarial; limited toxicity
- Beneficial in SLE
  - Prevents flares
  - Improves lipid profiles
  - Improves pregnancy outcomes
  - Reduces clotting risk
  - Associated with decreases in mortality, renal morbidity, malignancy
- Mechanism
  - Mediates Toll-like receptor 7, 9 signaling?


Back to our Case: Nicole

- Additional evaluation:
  - 24 hour urine protein with 2 grams protein
  - LDL 144, HDL 38

- Plan:
  - Prednisone
  - Hydroxychloroquine
  - Address CV risk: dyslipidemia, BP, tobacco use
  - Referral to nephrology to evaluate for lupus nephritis
New Developments in the Treatment of Lupus Nephritis

Brad H. Rovin, MD, FACP, FASN
Professor of Medicine and Pathology
Vice Chairman of Research for Internal Medicine
Director, Division of Nephrology
The Ohio State University College of Medicine

MAJOR NEW FINDINGS IN THE THERAPY OF PROLIFERATIVE LN

- LOW-DOSE CYCLOPHOSPHAMIDE IS EFFECTIVE INDUCTION THERAPY IN SOME POPULATIONS
- MMF AND IV CYCLOPSHOSPHAMIDE ARE EQUALLY EFFECTIVE AS INDUCTION THERAPY
- RITUXIMAB DOES NOT IMPROVE INDUCTION THERAPY
- MMF MAY BE THE IMMUNOSUPPRESSIVE OF CHOICE FOR MAINTENANCE THERAPY
Low-Dose (Euro-Lupus) Cyclophosphamide

- Low Dose CYC: 500 mg every 2 weeks for 6 doses/Cumulative Dose 3g
- High Dose CYC: 0.5-1g/m² monthly for 6 months, followed by 2 quarterly pulses/Cumulative Dose >8g
- Done mainly in Caucasians with mild-moderate disease
- The current Immune Tolerance Network CTLA4 Trial is using Euro-Lupus in African American, Asian, Hispanic, and Caucasian

Houssiau, et al., Arth Rheum, 2002

Prevention of Kidney Failure in the Long-Term

- These seminal studies, despite criticism of low numbers at follow-up showed that the addition of CYC to steroids improved the long-term outcome of kidneys in LN
- The benefit of CYC was not seen for about 3-5 years
- All new therapies/regimens should provide similar evidence to be generally accepted as equivalent to CYC for long-term kidney survival

Austin, et al, NEJM, 1986
Low-Dose Cyclophosphamide-Long-Term Results

Failure:
- Absence of primary response at 6 months
- Occurrence of steroid-resistant flare
- Doubling of SCr

<table>
<thead>
<tr>
<th></th>
<th>High Dose</th>
<th>Low Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>46</td>
<td>44</td>
</tr>
<tr>
<td>Lost to Follow-Up</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Mean Follow-Up</td>
<td>119</td>
<td>111</td>
</tr>
<tr>
<td>Mean Age</td>
<td>40</td>
<td>42</td>
</tr>
<tr>
<td>Deaths</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Doubling SCr</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>ESRD</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

10 Year Follow-Up

Houssiau, et al., Arth Rheum, 2002; Ann Rheum Dis, 2010

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**MMF vs Cyclophosphamide**

- Despite ALMS results, and fact that ALMS was *NOT* designed as a non-inferiority trial, it has increasingly become standard of care
- Although MMF is perceived as safer than CYC, ALMS showed a similar incidence of adverse events for MMF and CYC, including serious infections and death; while not statistically significant, there were almost twice as many withdrawals for side-effects from the MMF arm

### Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>MMF</th>
<th>IVC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>9 (4.9%)</td>
<td>5 (2.8%)</td>
</tr>
<tr>
<td>W/drawals</td>
<td>24 (13%)</td>
<td>13 (7.2%)</td>
</tr>
</tbody>
</table>

*Long-term outcomes are key for a true comparison with CYC*
Long-Term Outcome After MMF Treatment

Data from the ALMS Maintenance Trial-Ninth International Congress on SLE, Vancouver, 2010

Long-Term Outcome: MMF vs Oral CTX

Comparing induction with MMF to CYC, after median of 64 months there were no differences in renal function; however MMF group trended to have more relapses, prolonged proteinuria >1gm/d, and more subjects with SCr > 2 mg/dl, all risk factors for CKD.
Choosing Initial Therapy

• Consider a full-dose CYC protocol for patients with severe, proliferative LN; severity is defined as rapidly progressive loss of kidney function, usually accompanied by widespread crescents and glomerular capillary necrosis
  • WHY: IV CYC protocols have been used in prospective trials in patients with severe LN whereas MMF and Euro-lupus have mainly been used to treat mild-moderate LN
• Consider Euro-lupus, low-dose CYC protocol for Caucasian patients with mild-moderate LN
  • WHY: Euro-lupus has not been tested in a Black population, a group that traditionally has more severe LN than Caucasians
• Consider MMF in those patients who have received CYC in the past and are near or above a life-time cumulative dose of 36 grams

Biomarkers of Renal Response
A Post-Hoc Analysis of ALMS

ODDS OF A RENAL RESPONSE AT 24 WEEKS BASED ON PARAMETER IMPROVEMENT AT 8 WEEKS-MULTIVARIATE MODEL

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>ODDS RATIO</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ proteinuria by ≥25%</td>
<td>2.9</td>
<td>1.6-5.1</td>
</tr>
<tr>
<td>Normalization of C3/C4*</td>
<td>2.7</td>
<td>1.4-5.0</td>
</tr>
</tbody>
</table>

*only applicable if patients had baseline low C3 and C4

Do we need to think about changing therapy sooner during induction?

Dall’Era et al., Arth Care Res, 2011
Therapeutic Drug Monitoring for MMF
Improving Outcomes

- Responders have a higher mycophenolic acid area under the curve (12 hour) than non-responders
- Response rate increases with increasing mycophenolic acid area under the curve
- This is not practical for most patients with LN undergoing MMF therapy

Lertdumrongluk et al., Kidney Int, 2010

Therapeutic Drug Monitoring for MMF
Improving Outcomes

- Need to have a practical way to determine therapeutic MMF dosing
- The trough and one hour peak MPA were significantly correlated with the MPA-AUC and also response
  - For trough MPA \( r=0.90 \)
  - For 1 hour Peak MPA \( r=0.92 \)
- One may be able to use trough and peak to optimize MMF dosing
- Our recommendation:

Dose MMF so that:
- Trough level is 3 mg/l
- 1 hour peak level is > 22 mg/l

Lertdumrongluk et al., Kidney Int, 2010
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What About Rituximab?

As suggested by the outcomes with CYC or MMF as initial therapy for proliferative LN, there is plenty of room for improvement in CR and PR rates!

Treatment Period

<table>
<thead>
<tr>
<th>Rituximab + MMF (n=72)</th>
<th>Placebo + MMF (n=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>Prednisone taper</td>
</tr>
<tr>
<td>Weeks 1 and 2</td>
<td></td>
</tr>
<tr>
<td>(Days 1 and 15)</td>
<td></td>
</tr>
<tr>
<td>Week 16</td>
<td></td>
</tr>
<tr>
<td>Weeks 24 and 26</td>
<td></td>
</tr>
<tr>
<td>(Days 168 and 182)</td>
<td></td>
</tr>
<tr>
<td>Week 52</td>
<td></td>
</tr>
<tr>
<td>Week 78</td>
<td></td>
</tr>
</tbody>
</table>

= Study drug infusion.

ANTE = Corticosteroids: 2 doses of 1000 mg IV methylprednisolone given on day 1 and day 2, 3, or 4. This was followed by oral prednisone initiated at 0.75 mg/kg/day and then tapered to 10 mg/day by day 112.
Primary Endpoint: Renal Response at Week 52

- Placebo
- Rituximab

![Bar chart showing renal response proportions](chart1.png)

- Complete Renal Response (CRR)
- Partial Renal Response (PRR)
- No Response (NR)

P = 0.55*

Mean MMF dose: Placebo: 2.4 ± 0.62 g; Rituximab: 2.7 ± 0.41 g

* Wilcoxon Rank-sum test

Pre-Specified Analysis: Proportion of Subjects Achieving Response by Race

- Placebo
- Rituximab

![Bar chart showing response proportions by race](chart2.png)

- Black (n=40)
- Hispanic (n=52)
- Caucasian (n=45)
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ALMS Maintenance Trial
Time to Treatment Failure, n=227

MAINTAIN Nephritis Trial
Time to Flare

Appel, ASN Denver 2010

- Open versus blinded (ALMS)
- Different ethnic background
- ALMS larger study
- Composite endpoint in ALMS (ESRD, Flare, Double SCr, Rescue Meds)
- Only patients with a response (including to MMF...) were entered in ALMS
- In MAINTAIN patients were randomized for maintenance at baseline and given maintenance after Euro-Lupus no matter the response

Houssiau et al., Ann Rheum Dis, 2010
Apoptosis

1. Deficient clearance

2. Nucleosome-IC deposition in glomerular capillaries

3. Complement activation
   - FcγR activation
   - TLR activation

4. Increased production of pro-inflammatory cytokines
   - e.g. C3a/C5a, MCP-1, IL-17, IL-18

Auto-reactive B Cell

Anti-dsDNA

Anti-IL-6 (Tocilizumab)

Endothelial Cell

Podocyte

Anti-CD20 (Rituximab, Ocrelizumab)

Anti-CD22 (Epratuzumab)

Production of pro-inflammatory cytokines

Cell infiltration and activation
   - Monocytes, Lymphocytes, pDCs

Increased production of cytokines
   - IFN-α

Increased IC accumulation and complement and FcγR activation

Renal tissue damage

Auto-reactive Plasma Cell

26