Update on Systemic Lupus Erythematosus (SLE)

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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

Case: Nicole

• 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

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ACR 1997 Classification Criteria

- Malar rash
- Discoid rash
- Photosensitivity
- Oral/nasal ulcers
- Non-erosive arthritis
- Pleuritis/pericarditis
- Nephritis
- Cytopenia
- Encephalopathy
  - seizure or psychosis
- ANA
- Serology
  - anti-double stranded DNA
  - anti-Smith
  - anti-phospholipid antibody

4 OF 11 CRITERIA GIVES 96% SENSITIVITY/SPECIFICITY

Pathophysiology of SLE

Exposure(s)

Immune dysregulation

Susceptible host

Tissue damage
Pathophysiology of SLE

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

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>
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<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>
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</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

Death

CV Disease

SLE Infection

Time

Malignancy

- Increased incidence in SLE
  - Cervical HPV infection and cancer
  - Hodgkin lymphoma
  - Lung cancer
  - Breast cancer
- Hydroxychloroquine protective?
- Malignancy screening and prevention key


Causes of Death in SLE

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

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


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>


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.

Esdaile JM, Arthritis Rheum 2001

Timeline for SLE Drug Development

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

Severe disease
- High dose corticosteroids
- Mycophenolate mofetil
- Cyclophosphamide

Treatment of SLE

- Tailored to organ involvement
- Few controlled trials
EXPLORER TRIAL
Rituximab to Treat Non-Renal SLE
Study Design

Active non-renal SLE (n=257)
Placebo (days 1, 15, 158, 162)
Rituximab (days 1, 15, 168, 182)

Background immunosuppression
Prednisone taper
(n=189)
(n=189)

Primary Endpoint: major or partial clinical response (BILAG)

Secondary Endpoints:
- Time to disease flare
- Quality of life

Mean age 40.4y Nonwhite 42%
52 wk follow up


Belimumab to Treat Active Non-Renal SLE: Study Design

Active non-renal SLE (n=867)
Placebo
Belimumab 1 mg/kg
Belimumab 10 mg/kg
Mean age 35 y Nonwhite 75%
52 wk follow up

Background immunosuppression
Prednisone taper
(n=288)
(n=289)
(n=290)

Primary Endpoint: Improvement in SLE Responder Index (SRI)

Secondary Endpoints:
- Physician Global Assessment

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

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

Proportion of Patients (%)

No Clinical Response
Partial Clinical Response
Major Clinical Response
Major + Partial

P = 0.9750


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

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)
- Standard therapy
- 2 year follow up
- Atorvastatin 40 mg/day
- Placebo
- Primary Endpoint: CT coronary calcium score
- Secondary Endpoints: CIMT, Disease activity (SLEDAI), Inflammatory Mediators (hs-CRP)

**APPLE Study Design**

- Mean age 15.7 y
- Nonwhite 65%
- Pediatric SLE (>10 and <21) (n = 221)
- Standard therapy
- 3 year follow up
- hydroxychloroquine, ASA, folate, AHA TLC diet + placebo
- hydroxychloroquine, ASA, folate, AHA TLC diet + atorvastatin
- Primary Endpoint: IMT progression
- Secondary Endpoints: Disease Severity (SLEDAI, SLICC), Quality of Life (PedsQL), 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>Log(e) (coronary artery calcium score + 1) 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) 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>
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**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?


**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

**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

**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

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>
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<tbody>
<tr>
<td>Randomized</td>
<td>48</td>
<td>44</td>
</tr>
<tr>
<td>Lost to Follow-Up</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Mean Follow-Up</td>
<td>119</td>
<td>111</td>
</tr>
<tr>
<td>Mean Age</td>
<td>42</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>
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Houssiau, et al., Arth Rheum, 2002; Ann Rheum Dis, 2010

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, 1988

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MMF vs Cyclophosphamide

- Randomized to iv CYC pulses for 6 months or MMF 3 gm/d target dose for 6 months
- ALMS Trial
  - Non-inferiority trial
  - ALMS was NOT designed as a non-inferiority trial, it has increasingly become standard of care

Long-Term Outcome After MMF Treatment

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

MMF Concerns and Caveats

- 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

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>MMF</th>
<th>IVC</th>
</tr>
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<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: 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

Therapeutic Drug Monitoring for MMF

Improving Outcomes

Biomarkers of Renal Response

A Post-Hoc Analysis of ALMS

<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?

Methylprednisolone (mg/d)

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

Dall'Era et al., Arch Care Res, 2011
MAJOR NEW FINDINGS IN THE THERAPY OF PROLIFERATIVE LN

- Low-dose cyclophosphamide is effective induction therapy in some populations
- MMF and IV cyclophosphamide are equally effective as induction therapy
- Rituximab does not improve induction therapy
- MMF may be the immunosuppressive of choice for maintenance therapy

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!

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

Primary Endpoint: Renal Response at Week 52

*Wilcoxon rank-sum test
Mean MMF dose: Placebo: 2.4g±0.42 g
Rituximab: 2.7±0.41 g
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ALMS Maintenance Trial
Time to Treatment Failure, n=227

MAINTAIN Nephritis Trial
Time to Flare

Appl, ASN Denver 2010

Follow-up (months)
Houssiau et al., Ann Rheum Dis, 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