Lupus – The Clinical Perspective

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Systemic Lupus Erythematosus

- SLE is a prototypical autoimmune disease with a wide range of manifestations and variable course, which makes diagnosis/treatment/evaluation/study a challenge.
- Autoantibodies and immune complexes are hallmarks of SLE.
- The immune dysfunction in SLE leads to inflammation and tissue injury.
- Organ damage is associated with active disease and treatment side effects. Even with low disease activity, patients can still accrue organ damage.
- SLE patients are at risk for premature mortality.
SLE can affect any part of the body

The disease manifests differently in every person

The disease impacts people differently
Lupus Syndromes

• Incomplete lupus
  – patients who have lupus, but do not meet criteria for SLE.

• Cutaneous lupus
  – Includes several clinically heterogeneous subtypes;
  – some cause permanent damage (scarring) while others do not,
  – significant severity despite involvement of relatively small areas, such as situations in which excruciatingly painful, permanently disfiguring discoid lesions affect the face.
SLE Updated Incidence/Prevalence

(CDC Project)

• Incidence = new cases
  5.5 per 100,000
• Prevalence = all cases
  ~75 per 100,000
• Female: Male Ratio
  9 : 1, 90% of people with lupus are women
• Peak Age: 15 – 44 yr

Number of patients eligible for clinical trails in U.S. > 250,000

Racial differences in SLE
Incidence/Prevalence vary by race

Comparing Blacks/Hispanics to Whites:

- Earlier age at diagnosis

- More than 2 fold increase in SLE prevalence and incidence

- Increased proportion with severe disease, long-term complications (i.e. renal disease)

Racial differences in SLE
Clinical Manifestations Vary by Race

Cumulative ACR Criteria Manifestations (%) in PROFILE Cohort per Ethnic Group

- Hispanic (n=78)
- African American (n=216)
- Caucasian (n=260)

Pooled cohort analysis (University of Birmingham, AL; Johns Hopkins University, MD; University of Texas Houston Health Sciences Center, TX) of 568 adults with SLE with a disease duration of <10 years from diagnosis to enrollment. Mean ages were 38-42 years, with 86%, 92%, and 96% female in the Caucasian, African American, and Hispanic patient groups, respectively.
Racial differences in SLE
Response to Medications Vary by Race –
Patients of African Descent respond better to certain medications

Influence of race/ethnicity on response to lupus nephritis treatment: the ALMS study. Isenberg D et al, Rheumatology 2010
Development of Autoimmunity in Pts With SLE

- Assessment of autoantibodies in US military personnel with SLE and available serum samples prior to and following diagnosis (N = 130)
- Key findings:
  - Autoantibodies present up to 5 years prior to clinical manifestations/diagnosis
  - Anti-Ro/anti-La antibodies develop early prior to diagnosis; anti-Sm and anti-dsDNA antibodies develop closer to appearance of symptoms

• The most common lupus symptoms
  – joint pains
  – fatigue
  – photosensitive rash
SLE Diagnosis/Classification: ACR Criteria ≥ 4/11

• Malar rash
• Discoid lupus rash
• Photosensitivity
• Oral or nasal ulcers
• Arthritis
• Serositis
  • Pleuritis
  • Pericarditis
• Renal disorder
  • Proteinuria >500 mg
  • Urinary cellular casts
• Neurologic disorder
  • Seizures
  • Organic brain syndrome

• Hematologic disorder
  • WBC <4000
  • Lymphocytes <1500
  • Platelets <100,000
  • Hemolytic anemia

• Immunologic disorder
  • Anti-dsDNA
  • Anti-Sm
  • False positive VDRL
  • Antiphospholipid ab
  • Positive LE cell test

• Antinuclear antibody
**SLICC† Classification Criteria for Systemic Lupus Erythematosus**

Requirements: ≥ 4 criteria (at least 1 clinical and 1 laboratory criteria) OR biopsy-proven lupus nephritis with positive ANA or Anti-DNA

### Clinical Criteria

1. Acute Cutaneous Lupus *
2. Chronic Cutaneous Lupus *
3. Oral or nasal ulcers *
4. Non-scarring alopecia
5. Arthritis *
6. Serositis *
7. Renal *
8. Neurologic *
9. Hemolytic anemia
10. Leukopenia *
11. Thrombocytopenia (<100,000/mm³)

### Immunologic Criteria

1. ANA
2. Anti-DNA
3. Anti-Sm
4. Antiphospholipid Ab *
5. Low complement (C3, C4, CH50)
6. Direct Coombs’ test (do not count in the presence of hemolytic anemia)

†SLICC: Systemic Lupus International Collaborating Clinics
* See notes for criteria details

Goal of Treatment - I
Decrease Activity to Low Disease Activity or Inactive Disease

Therapeutic Decisions:
How sick is this patient?

Mild Activity: malar rash, fatigue, arthralgia
Mild/Moderate Activity: more severe skin rash, alopecia, arthritis
Moderate Activity: arthritis with moderate loss of function
Severe Activity: life or organ threatening disease, e.g. renal, brain, lung, heart disease
Pharmacologic Treatment Approaches for SLE According to Disease Severity
Induce remission or low disease activity

<table>
<thead>
<tr>
<th>Disease Severity</th>
<th>Agents to Consider</th>
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<tbody>
<tr>
<td>Mild</td>
<td>Hydroxychloroquine / NSAIDS / low dose prednisone</td>
</tr>
<tr>
<td>Moderate</td>
<td>Hydroxychloroquine / NSAIDS / moderate dose prednisone</td>
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<tr>
<td></td>
<td>Immunosuppressants: methotrexate, azathioprine,</td>
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<tr>
<td></td>
<td>mycophenolate mofetil</td>
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<tr>
<td></td>
<td>Biologics: belimumab</td>
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<tr>
<td>Severe</td>
<td>Hydroxychloroquine / high dose prednisone</td>
</tr>
<tr>
<td></td>
<td>Immunosuppressants: azathioprine, mycophenolate mofetil,</td>
</tr>
<tr>
<td></td>
<td>cyclophosphamide, calcineurin inhibitors (eg, cyclosporin)</td>
</tr>
<tr>
<td></td>
<td>Biologics: rituximab, abatacept, belimumab</td>
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Goal of Treatment - II
Maintain Low Disease Activity/Remission

Therapeutic Decisions:
How did we get here?

• Regimens for maintenance therapy
  • HCQ
  • Prednisone – try to minimize
  • Cytoxan, MMF, azathioprine, MTX, Benlysta
• prevention of flares
• prevention of chronic irreversible damage
Major Advances in Lupus

- Use of cortisone 1948-1949
  - Nobel prize for cortisone 1950
- IF – ANA 1950-1960
- Antimalarials 1951
  - HCQ, CQ, atabrine
- Animal models of SLE 1960
- Classification/DX criteria 1982
- Cyclophosphamide 1986
- Mycophenolate Mofetil 1998
- Rituxan 2000
- Belimumab – FDA approval 2011
<table>
<thead>
<tr>
<th>FDA-Approved Therapies for Lupus = 4</th>
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<tbody>
<tr>
<td>1. Aspirin</td>
</tr>
<tr>
<td>2. Corticosteroids</td>
</tr>
<tr>
<td>Prednisone, ACTH</td>
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<tr>
<td>3. Hydroxychloroquine (Plaquenil®)</td>
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<tr>
<td>Failed phase 3 clinical trials</td>
</tr>
<tr>
<td>Mycophenolate mofetil (CellCept®)</td>
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<tr>
<td>TV-4710 (Edratide)</td>
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<tr>
<td>Abatacept (Orencia®)*</td>
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<tr>
<td>Prasterone (Prestara™)</td>
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<td>Abetimus sodium (Riquent™)</td>
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<tr>
<td>Rituximab (Rituxan®)</td>
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<tr>
<td>Atacicept</td>
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<tr>
<td>Tabalumab</td>
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<tr>
<td>Anti-CD40 ligand</td>
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<tr>
<td>Epratuzumab – CD22</td>
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<tr>
<td>4. Benlysta</td>
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The Consequence of Disease Activity and Inflammation
Organ damage

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<thead>
<tr>
<th>Organ System</th>
<th>Risks</th>
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| Renal                         | • 50 - 60% of adult patients with SLE develop renal manifestations at some point during their disease¹  
  • Approximately 17% of lupus nephritis patients progress to ESRD²  
  • More common in men, African Americans, and Hispanics³,⁴  
  • More common and more severe in childhood-onset vs adult-onset SLE⁵ |
| Cardiovascular and Cerebrovascular | • Compared with expected rates based on Framingham models  
  • 7.5 times greater risk of CHD⁶  
  • **17.0 times greater risk of death due to CHD⁶**  
  • 7.9 times greater risk of stroke than expected⁶  
  • 2.1 times greater risk of hospitalization for cerebrovascular event compared with women without SLE⁷ |

CAD = coronary artery disease; CHD = coronary heart disease; ESRD = end-stage renal disease

Disease Activity Is Related to Future Organ Damage and Death

- Increased disease activity is associated with significantly increased risk of organ damage and death
- A 1-point increase in adjusted BILAG score was associated with:
  - 8% increase in the risk of any new organ damage
  - 11% increase in risk of CV, pulmonary, or musculoskeletal damage
  - 15% increase in mortality

Retrospective analysis of multiethnic patient cohort from University College of London SLE Clinic followed since 1991. At baseline, median age: 36 years; median SLE duration: 6 years; 92% female; 63% white, 17% Afro-Caribbean, 11% South Asian, 6% Asian (other), 3% “other.” Disease activity level was based on mean observational year mean adjusted BILAG score. Scoring began 1 year after the patient’s first clinic visit.

Patients Still Accrue Organ Damage Even with Low Disease Activity

Prospective analysis of patients in the SLICC cohort recruited within 15 months of diagnosis and followed annually for ≥5 years. Mean age at enrolment: 35.3 years; 87% female; 55% white, 12% black, 14% Asian, 16% Hispanic, 2% “other.” At enrollment, mean disease duration=5.5 months; mean SLEDAI-2K score=5.9.
Progression to ESRD Has Not Decreased Over Time, and Varies by Race and Socioeconomic Status

Patients aged ≥15 years with incidence of ESRD due to lupus nephritis were identified using the US Renal Data System, a national population-based registry of all patients needing chronic renal replacement therapy for ESRD. Incidence rates were age-, sex-, and race-adjusted to the composition of the US population. Mean age was 40.9 years, 82% of patients were female, 43% were white, 48% were black, 14.7% were Hispanic, 4.6% were Asian/Pacific Islander, 1.1% were Native American, and 2.7% were “other.”

Work Loss Is a Common Consequence of SLE

- At baseline, 26% were aged 18-34 years and 60% were 35-55 years
  - Individuals who reached age 65 without work loss were censored
- Overall, 33% (160/484) of patients stopped working during the 4-year follow-up period
- Work loss associated with incident SLE manifestations by Year 4:
  - Musculoskeletal: 34% (58/170)
  - Neuropsychiatric: 38% (68/179)
  - Thrombotic: 58% (34/59)

SLE patients (N=484) who were working at baseline participated in the University of California at San Francisco Lupus Outcomes Study, a longitudinal cohort of 1204 persons with SLE sampled between 2002 and 2009. Annual telephone interviews were conducted to assess manifestations and time to work loss, the trajectories of which were analyzed by the Kaplan-Meier method. Mean disease duration at baseline was 10.8±7.7 years, 91% of patients were women, 65% were white, 8% were black, 10% were Hispanic, 12% were Asian/Pacific Islander, and 6% were “other.”
Despite Improvements in Dx and Treatment, SLE Remains a Disease with Higher than Expected Mortality Rate

- However, survival is significantly worse than in the general population

Retrospective review of 430 medical records identified SLE cases (n=48) according to the 1982 ACR criteria, which were documented between January 1, 1980, and December 31, 1992. Drug-induced cases were excluded. Cases were followed up until death, migration from the county, or October 1, 1997. Trends over time were compared to similar data from a 1950-1979 cohort (n=21) in the same community, which was reabstracted using the 1982 ACR criteria.
Collaboration of the Systemic Lupus International Collaborating Clinics (SLICC) and the Canadian Network for Improved Outcomes in Systemic Lupus (CaNIOS) investigator groups (US, Canada, England, Scotland, Iceland, Sweden, South Korea). Death data were prospectively collected or acquired through probabilistic linkage to vital statistics registries. Expected deaths in the general population were determined by multiplying person-years at risk in the cohort by the geographically appropriate age-, sex-, and calendar-year period-matched mortality rates. Risk of death was assessed as a standardized mortality ratio, calculated as the observed number of deaths divided by the number expected in the general population. Duration of disease at time of enrollment was <2 years for most patients, and 90% of patients were female.
Racial differences in SLE
Mortality Varies by Race

Mean age at death ~ 48 for Blacks and Asians
  – infectious diseases.
Mean age at death ~ 65 for Rural Whites
  – cardiovascular diseases, neoplasms.

  – Blacks sharing the same social/geographic context as whites are disproportionately more likely to die at a younger age.

  – Blacks inhabiting 3 vastly different geographic and social contexts have similar mortality patterns.

  – Race may transcend social and geographic parameters as a key determinant in mortality in SLE.
We need to do better.

A patient in whom lupus is diagnosed at age 20 has a 1 in 6 chance of dying by 35 years of age, most often from lupus or infection.

How do we do better?

More effective, targeted therapies for patients with SLE.

– Clinical trials
– Observational data

Rahman and Isenberg, NEJM, March, 2008
Clinical Trial Challenges

• Two major obstacles to drug development for lupus:
  – The nature of the disease itself
  – Not enough patients for all the studies
The Nature of Lupus

• Lupus is not a common disease.
• Lupus is difficult to diagnose.
• Lupus is difficult to evaluate – cannot tell that the person is sick
• Lupus symptoms can come and go—even when a person takes medicine—making it hard to tell whether new drugs are effective and safe.
• Lupus can affect and impact people differently.
Nature of Lupus—Clinical Trials are Complicated

• Complex disease
• Disease activity instruments are cumbersome
• Biomarkers are complex
• Clinical trials have been unsuccessful in the past – lessons learned:
  – Well trained investigators – several networks of investigators are being formed
  – Better designed clinical trials (smaller, shorter trials)
  – Better outcomes and biomarkers, consider organ-specific outcomes
  – Better designed medications
Not Enough Patients for All the Studies

• Encourage participation in clinical trials

• Create a culture of excitement and appreciation for the research and development in SLE, just like in cancer research

• Discuss the advantages of participating in clinical trials (even in the placebo arm)

• Drugs in development
  – Need to make sure enough patients of different races and ethnicities are represented in the trials

• Patients can respond to the same drug differently
  – CellCept: works better in AA than whites
  – Benlysta
    • Conflicting results from Phase II and Phase III clinical trials for Benlysta
    • Large Phase IV clinical trial for patients of black race
There is Hope for the Future

On Clinicaltrials.gov
SLE: 531 studies
Cutaneous Lupus Erythematosus: 65 studies
Lupus Nephritis: 119 studies
Summary

• Lupus is “underserved.”

• Only 4 drugs have been approved by the FDA over the last half-century.

• There is a great unmet need for more therapeutic options due to high morbidity and mortality.

• Better understanding of the role of race and SES factors in SLE is likely to improve outcomes.
Disclosures

- Grants from ITN, LFA, LuCIN

Consultant and/or investigator for:

- GSK
- Genentech
- Questcor
- ASPREVA
- MedImmune
- BMS
- TEVA
- HGS
- Takeda
- Celgene
- Eli Lilly
- Pfizer
- EMD Serono
- Merck
THANK YOU...