Systemic Lupus Erythematosus: Diagnosis – Laboratory and Clinical Presentation
Treatment – Current Methods and Emerging Biological Treatment

C. Michael Neuwelt, M.D.
Clinical Professor of Medicine
University of California, San Francisco,
Chief of Rheumatology
Alameda County Medical Center, Oakland, CA
Director of Rheumatology, Core Curriculum
St. Mary’s Medical Center, San Francisco, CA
UPDATE 2015 AND BEYOND
Numerous Factors Contribute to Underlying SLE Pathogenesis and Subsequent Organ Damage\textsuperscript{1,2}

Multiple Elements of the Immune Response Play a Role in Autoimmunity in SLE$^{1-6}$ (cont)

- Abnormally activated T and B cells are a feature of SLE pathogenesis$^{1,2}$
  - Overexpression of B- and T-cell costimulatory ligands/receptors$^1$
  - Higher concentrations of B- and T-cell cytokines$^{1,2}$
- Increased numbers of antibody-producing B cells, hypergammaglobulinemia, autoantibody production, and immune-complex formation$^2$

Immune Reactivity

Adaptive Immunity

- B Cells
- T Cells
- Autoantibodies
- Cytokines

Inflammation

Tissue Damage

mDC=myeloid dendritic cells; pDC=plasmacytoid dendritic cells; MØ=macrophages

Autoantibodies Are a Key Feature of SLE

- Characteristic immunologic disturbance in SLE present in almost all patients at some time\(^1\)-\(^3\)
- Form immune complexes with nuclear, cytoplasmic, and cell-surface self antigens\(^2,4\)
- Amplify immune-system activation through stimulation of innate and adaptive immune pathways and recruitment of inflammatory cells to immune complexes\(^1,5\)

<table>
<thead>
<tr>
<th>Autoantibody Detected(^6)</th>
<th>At Onset</th>
<th>At Any Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA</td>
<td>76%</td>
<td>94%</td>
</tr>
<tr>
<td>Anti-dsDNA</td>
<td>34%</td>
<td>71%</td>
</tr>
</tbody>
</table>

ANA=antinuclear antibodies; anti-dsDNA=anti-double-stranded deoxyribonucleic acid

### Autoantibody Associations in SLE

<table>
<thead>
<tr>
<th>Antigen Specificity</th>
<th>Prevalence (%)</th>
<th>Main Clinical Effects</th>
</tr>
</thead>
</table>
| Anti-dsDNA          | 70-80          | • Kidney disease  
                      |                                | • Skin disease               |
| Nucleosomes         | 60-90          | • Kidney disease  
                      |                                | • Skin disease               |
| Ro                  | 30-40          | • Kidney disease  
                      |                                | • Skin disease               
                      |                                | • Fetal heart problems        |
| La                  | 15-20          | • Fetal heart problems                       |
| Sm                  | 10-30          | • Kidney disease                             |
| Phospholipids       | 20-30          | • Thrombosis                                 
                      |                                | • Pregnancy loss              |
| α-Actinin           | 20             | • Kidney disease                             |
| C1q                 | 40-50          | • Kidney disease                             |
SLE Is an Autoimmune Disease That Primarily Affects Women of Childbearing Age

• SLE is a chronic, multisystem autoimmune disease¹-³
  – Diverse clinical manifestations are the result of inflammation in affected organ systems¹
  – Potentially life threatening when major organs are affected²,³
  – Waxing and waning disease activity⁴

• SLE patient profile:
  – Nine out of 10 cases occur in women²; tends to be more severe in men⁵
  – Most prevalent in women 14 to 50 years of age⁶
  – More common and severe among nonwhite populations⁵

A Range of Organ Systems May Be Involved

Commonly Involved Organ Systems

- Central Nervous System
- Kidneys
- Eyes and Mucous Membranes
- Gastrointestinal
- Heart and Lungs
- Skin
- Hematologic
- Musculoskeletal

Variability in Clinical Presentation Can Result in Difficulty in Diagnosis

- SLE diagnosis is challenging due to its multisystem involvement and protean manifestations\(^1\)
- A positive anti-nuclear antibody (ANA) test alone is insufficient to establish diagnosis\(^1\)
- 47% of patients with presumptive SLE referred to an autoimmune disease center from the community ultimately had other diagnoses\(^2\)

### SLE Manifestations May Be Mistaken for Other Common Conditions\(^1\)

<table>
<thead>
<tr>
<th><strong>SLE</strong></th>
<th><strong>Other Condition</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lupus arthritis(^1)</td>
<td>Fibromyalgia with positive ANA; early rheumatoid arthritis</td>
</tr>
<tr>
<td>Lupus-associated rash(^3)</td>
<td>Rosacea; polymorphous light eruptions</td>
</tr>
</tbody>
</table>

Clinical Manifestations Vary by Race

- Hispanic and black patients tend to have more renal, hematological, and serosal manifestations following diagnosis

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

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.

Rate of SLE Mortality Remains High Relative to the General Population

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.

<table>
<thead>
<tr>
<th>SLE Patient Age (years)</th>
<th>General Population</th>
<th>19.2 X Greater Rate</th>
<th>8.0 X Greater Rate</th>
<th>3.7 X Greater Rate</th>
<th>1.4 X Greater Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>16-24</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-39</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-59</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥60</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Risk of Myocardial Infarction (MI) Is More Than 50 Times Greater for Women With SLE Aged 35-44

- Cardiovascular disease is an ongoing issue for patients with SLE
- Compared to the general population, incidence rate of MI was higher in women with SLE overall
- Incidence of MI in younger and premenopausal women was notably higher vs the age-matched general population

Prospective analysis of the incidence of MI in 498 women with SLE. Cardiovascular incidence rates were compared to 2208 women of similar age participating in the Framingham Offspring Study, a prospective investigation of cardiovascular disease in the children of the 5209 men and women who participated in the original Framingham Heart Study. A comparison of MI rates was made over the same time period (1980-1993).

What Is Systemic Lupus Erythematosus?

- Systemic lupus erythematosus (SLE) is a progressive autoimmune disease that results in inflammation and tissue damage.
- Characterized by flares, spontaneous remission, and relapses, SLE is a chronic disease.
- SLE can affect any part of the body but often results in damage to the skin, joints, heart, kidneys, lungs, and nervous system.
The following are the ACR diagnostic criteria presented in the "SOAP BRAIN MD" mnemonic

- Serositis
- Oral ulcers
- Arthritis
- Photosensitivity
- Blood disorders
- Renal involvement
The following are the ACR diagnostic criteria presented in the "SOAP BRAIN MD" mnemonic

- Antinuclear antibodies
- Immunologic phenomena (eg, dsDNA; anti-Smith [Sm] antibodies)
- Neurologic disorder
- Malar rash
- Discoid rash
Non-Specific Manifestations of SLE

- Fever
- Weight loss
- Fatigue
- Myalgias, fibromyalgia
- Lymphadenopathy
- Raynaud’s phenomenon
Mucocutaneous Features of SLE

- Malar (butterfly) rash
- Discoid lupus (DLE)
- Mucosal ulcers
- Alopecia
- Subacute cutaneous lupus (SCLE)
- Cutaneous vasculitis
- Bullous lupus
- Panniculitis

Malar (Butterfly) Rash
Discoid Lupus Rash
Mucosal Ulcers
Alopecia
Arthritis
Neuropsychiatric Manifestations of SLE

- Central nervous system
  - Diffuse cerebral manifestations
  - Psychiatric manifestations (depression)
  - Cognitive impairment
  - Seizures
  - Headache
  - Focal manifestations
- Peripheral nervous system

Cardiac Manifestations of SLE

- Pericarditis
- Myocarditis, congestive heart failure
- Hypertension
- Coronary vasculitis
- Libman-Sacks endocarditis
- Valvular insufficiency

- SLE patients have a 7-10x increased risk of Coronary Heart disease and stroke

Other Mechanisms of cardiovascular events in SLE

ASSOCIATIONS OF CIRCULATING CELL-FREE MICRO RNA WITH VASCULOPTHY AND VASCULAR EVENTS IN SLE PATIENTS FURTHER INCREASE IF:

- (+) Lupus Anticoagulant
- Decreased C3
- High disease activity

American College of Rheumatology scientific session November 10, 2015.
Susan Due Kay.
Michele Petri, et.al.
John Hopkins cohort
Proinflammatory HDLs in SLE – Role in Atherosclerosis

- In the inflammatory state, HDLs may lose their protective capacity and become proinflammatory (AP-HDL)
- Presence of AP HDL:
  - **SLE**: 7.9–10.1-fold increased risk of atherosclerosis
  - **RA**: Approx. 5-fold increased risk
- In SLE patients with evidence of atherosclerosis (CAD, stroke etc), 90% have proinflammatory HDLs
- Presence of proinflammatory HDLs likely in future to be a good measure of propensity to develop atherosclerosis independent of absolute lipid values

![Diagram of HDL and AP-HDL](image)

Pulmonary Manifestations of SLE

- Pleuritis (also pericarditis)
- Lupus pneumonitis/alveolitis
- Pulmonary hemorrhage
- Pulmonary fibrosis
- Shrinking lung syndrome
- Pulmonary embolism/in situ thrombosis
- Pulmonary hypertension
Pleural and Pericardial Effusions

- Pleural disease occurs in >30% of SLE patients during their course:
  - Often asymptomatic
  - May present with chest pain, SOB
  - Effusions are usually small and bilateral
  - Exudative, usually with WBC <10,000
  - Predominance of polys and lymphs
Clinical Features of Active Lupus Nephritis

- Urinary protein excretion → edema
- Active urine sediment – WBCs, RBCs, protein casts, cellular casts
- Decreased glomerular filtration rate
- Hypertension
Progressive Decline in Renal Function

- Amount of renal damage can predict renal failure and mortality
  - 5%–10% of LN patients progress to end-stage renal disease
  - In one study, 25% of patients with early renal damage versus 7.3% without early damage died within 10 years of initial assessment


Red cell cast from urinary sediment of a patient with chronic glomerulonephritis
RACIAL AND ETHNIC DIFFERENCES
LUPUS NEPHRITIS – END STAGE MORTALITY

I. Highest – African American
II. Moderate – White
III. Lowest – Asian and Hispanic (“Hispanic Paradox”)
    * ? Perhaps hispanics migrate home at end of life
      “Salmon Hypothesis”
    * Asians – more lost to follow up at end of life

• Gomez – Puerta, et.al; Arthritis Care & Research October 2015; 67: 1453-1461
Gastrointestinal Manifestations of SLE

- Peritonitis
- Mesenteric vasculitis
- Vasculitis of the bowel
- Inflammatory bowel disease
- Autoimmune hepatitis
- Pancreatitis
## Incidence of Clinical and Laboratory Manifestations of SLE (%)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive ANA</td>
<td>97%</td>
</tr>
<tr>
<td>Arthritis and Arthralgia</td>
<td>80%</td>
</tr>
<tr>
<td>Skin Changes</td>
<td>71%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>60%</td>
</tr>
<tr>
<td>Low Complement</td>
<td>51%</td>
</tr>
<tr>
<td>Fever</td>
<td>48%</td>
</tr>
<tr>
<td>High Anti DNA</td>
<td>46%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>46%</td>
</tr>
<tr>
<td>Pleuritis</td>
<td>44%</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>42%</td>
</tr>
<tr>
<td>Anemia</td>
<td>42%</td>
</tr>
<tr>
<td>Anticardiolipin Antibody</td>
<td>35%</td>
</tr>
<tr>
<td>CNS</td>
<td>32%</td>
</tr>
<tr>
<td>High gamma globulin</td>
<td>32%</td>
</tr>
<tr>
<td>Effusion*</td>
<td>12%</td>
</tr>
<tr>
<td>** adenopathy</td>
<td>10%</td>
</tr>
</tbody>
</table>

*Pleural or pericardial; **adenopathy.

Cumulative % incidence of clinical and laboratory manifestations of SLE (1084 cases).
Heredity and SLE

A children’s risk of developing SLE if their mother has the disease is:

- 1 in 40 if she has a daughter
- 1 in 250 if she has a son
Proactive and Preventive Strategies in SLE

- **Proactive**
  - Patient education programs
  - Eliminate patient nonadherence
  - Specialist access
  - Exercise, PT, OT, ergonomic work stations
  - Cognitive therapy (lupus fog), biofeedback (Raynaud’s)

- **Preventive**
  - Aggressive vigilance for hypertension, hyperglycemia, hyperlipidemia, obesity, smoking cessation
  - Yearly bone densitometry and use of bisphosphonates
  - Annual EKG, chest X-ray, duplex scanning, stress tests, 2-D echo for pulmonary pressures in high-risk patients
  - Prompt evaluation of all fevers
  - Antiphospholipid antibody screening and prophylaxis
Management of Non-Organ Threatening Lupus

• Physical measures
  – Sun avoidance, use of sunscreens
  – Temperature
  – Physical therapy (use of heat)
  – Occupational therapy

• Medication
• Counseling
• Surgery

  – Vocational rehabilitation
  – Exercise
  – Diet and vitamins
  – Management of fatigue
Anti-Malarials in the Treatment of Lupus

First use of quinine for cutaneous disease (Payne, 1894)

Plasmochn helps 22/28 with cutaneous lupus (Mastenstein, 1928)

Chloroquine patent (1934)

Hydroxychloroquin synthesized (mid-1940s)

“Excellent” results in 1920 with quinine bisulfate (Davidson, 1938)

3 million US and allied soldiers had used atabrine between 1943-1946; efficacy is documented in lupus from these observations (Page et al, Lancet. 1951;21:755-758)
1948: A Turning Point in Lupus Treatment

- Before 1948 lupus treatments also included Aspirin, bismuth, arsenic, vitamins E and B12, and liver extract
- In 1948, LE cells were discovered by Hargraves (Mayo Clinic)
- Steroids were first used in rheumatic diseases
- Nitrogen mustard was first used for glomerulonephritis
- Marian Ropes reported that half with lupus die in 2 years, and the others survive, dividing the disease into organ vs non-organ threatening manifestations
Advances in Lupus Management (1948–2000)

**Immune suppressives**
- 1947: Nitrogen mustard, methotrexate
- 1965: cyclophosphamide, azathioprine

**Corticosteroids**
- 1948: Cortisone
- Early 1950s: Prednisolone, prednisone

**Nonsteroidals**
- 1951: phenylbutazone
- 1965: Indomethacin
- 1974: Ibuprofen

**Antimalarials**
- 1940: Quinacrine
- 1951: Chloroquine
- 1955: Hydroxychloroquine

1998, 1999: Biologics approved for use in RA
### Current Standard Therapy: Mild-to-Moderate Disease

<table>
<thead>
<tr>
<th>Mild-to-Moderate Disease</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Arthritis</td>
<td>– Photoprotection</td>
</tr>
<tr>
<td>– Fever</td>
<td>– NSAIDs</td>
</tr>
<tr>
<td>– Pleurisy</td>
<td>– Corticosteroids</td>
</tr>
<tr>
<td>– Pericarditis</td>
<td>– Methotrexate</td>
</tr>
<tr>
<td>– Cutaneous</td>
<td>– Leflunomide</td>
</tr>
<tr>
<td></td>
<td>– Thalidomide</td>
</tr>
<tr>
<td></td>
<td>– Antimalarials</td>
</tr>
<tr>
<td></td>
<td>– Topicals</td>
</tr>
<tr>
<td></td>
<td>– Physical therapy</td>
</tr>
</tbody>
</table>
## Current Standard Therapy

<table>
<thead>
<tr>
<th>Moderate-to-Severe Disease</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Nephritis</td>
<td>– Corticosteroids</td>
</tr>
<tr>
<td>– Vasculitis</td>
<td>– Cyclophosphamide</td>
</tr>
<tr>
<td>– Pneumonitis</td>
<td>– Azathioprine</td>
</tr>
<tr>
<td>– CNS</td>
<td>– Mycophenolate Mofetil</td>
</tr>
<tr>
<td>– Hematologic</td>
<td>– Cyclosporine</td>
</tr>
<tr>
<td></td>
<td>– IV Ig</td>
</tr>
<tr>
<td></td>
<td>– Plasmapheresis?</td>
</tr>
</tbody>
</table>
Reasons for Improved Prognosis Other than Lupus Medicines

• Availability of dialysis and transplantation
• Development of joint replacement surgeries
• Available of platelet and red cell transfusions and growth factors
• Introduction of improved antihypertensives, antihyperlipidemic, and antibiotic therapies
• Utilization of bone mineralization treatments
Loneliness – Insomnia - **Culture Shock** = SLE (51 Years of Waiting)!!!

Modern Asian City – (Translation Antibodies)
“Bench to Bedside”
Systemic Lupus Erythematosus: After 50 Years No Longer “Lost in Translation”
### B-Cell Therapies Under Investigation for SLE

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Design</th>
<th>Phase</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abetimus (putative toleragen)</td>
<td>AutoAb</td>
<td></td>
<td>III</td>
<td>Active</td>
</tr>
<tr>
<td>Lymphostat B (anti-BLyS)</td>
<td>B cells</td>
<td></td>
<td>III</td>
<td>Active</td>
</tr>
<tr>
<td>Rituximab (anti-CD20)</td>
<td>B cells</td>
<td></td>
<td>II</td>
<td>Active</td>
</tr>
<tr>
<td>Anti-CD40 Ligand Abs</td>
<td>T cells</td>
<td></td>
<td>II</td>
<td>Inactive</td>
</tr>
<tr>
<td>Abatacept (CTLA4Ig)</td>
<td>T-B cells</td>
<td></td>
<td>II</td>
<td>Active</td>
</tr>
<tr>
<td>MMF</td>
<td>Lymph</td>
<td></td>
<td>III</td>
<td>Active</td>
</tr>
<tr>
<td>Ablation; transplantation</td>
<td>WBC</td>
<td></td>
<td>I</td>
<td>Active</td>
</tr>
<tr>
<td>Epratuzumab (anti-CD22)</td>
<td>Lymph</td>
<td></td>
<td>II</td>
<td>Active</td>
</tr>
<tr>
<td>Anti-IL6 R</td>
<td>Cy R</td>
<td></td>
<td>I</td>
<td>Active</td>
</tr>
</tbody>
</table>
## Evaluation of Rituximab in 7 Small-Scale, Open-Label, Uncontrolled Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albert et al. <em>A&amp;R</em>. 2004;50:S446.</td>
<td>N = 11 8 completed</td>
<td>375 mg/m² x 4 100 mg methylprednisolone prior</td>
</tr>
<tr>
<td>Leandro et al. <em>A&amp;R</em>. 2002;46:2673.</td>
<td>N = 6</td>
<td>500 mg/m² x 2 750 mg x 2 CTX + oral steroids</td>
</tr>
<tr>
<td>Looney et al. <em>A&amp;R</em>. 2004;50:S2580.</td>
<td>N = 19 8 completed</td>
<td>100 mg/m² x 1 (n = 6), 375 mg/m² x 1 (n = 6), 375 mg/m² x 4 (n = 4) 40 mg x 2 prednisone prior</td>
</tr>
<tr>
<td>Neuwelt et al. EULAR05. Vienna.</td>
<td>N = 22 CNS lupus</td>
<td>375 mg/m² x 4, 54% monotherapy, 32% combined with CTX, 14% concomitant CTX/PP</td>
</tr>
<tr>
<td>Sfikakis PP, et al. <em>A&amp;R</em>. 2005;52:501-13.</td>
<td>N = 10 Active proliferative nephritis</td>
<td>375 mg/m² x 4 0.5 mg/kg/day prednisone for 10 weeks, then tapered</td>
</tr>
<tr>
<td>Smith and Jayne. <em>J Am Soc Nephrol</em>. 2003;14:380A.</td>
<td>N = 6</td>
<td>375 mg/m² x 4 500 mg CTX prior infusion</td>
</tr>
<tr>
<td>Van Vollenhoven. <em>A&amp;R</em>. 2004;50:S414.</td>
<td>CTX refractory, nephritis</td>
<td>375 mg/m² x 4 500 mg x 2 CTX 250 mg methylprednisolone prior</td>
</tr>
</tbody>
</table>
Efficacy and Safety of Rituximab in Patients with Moderately to Severely Active Systemic Lupus Erythematosus (SLE): Results from the Randomized, Double-blind Phase II/III Study EXPLORER

- Joan T Merrill¹, C Michael Neuwelt², Daniel J Wallace³, Joseph C Shanahan⁴, Kevin M Latinis⁵, James C Oates⁶, Tammy O Utset⁷, Caroline Gordon⁸, David A Isenberg⁹, Hsin-Ju Hsieh¹⁰, David Zhang¹⁰, Paul G Brunetta¹⁰

¹Oklahoma Medical Research, Oklahoma City, OK; ²Alameda Medical Center, Oakland, CA; ³Cedars-Sinai/UCLA, LA, CA; ⁴Duke University, Durham, NC; ⁵University Kansas Medical Center Kansas City, KS; ⁶Medical University South Carolina, Charleston, SC; ⁷University of Chicago, Chicago, IL; ⁸University Birmingham, Birmingham, United Kingdom; ⁹University College, London, United Kingdom; ¹⁰Genentech Inc, South San Francisco, CA
Pre-specified Exploratory Analysis: Clinical Response by Ethnicity

African-Americans/Hispanics

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

*p value refers to the test on 3-category endpoints (MCR/PCR/NCR).
Systemic Lupus Erythematosus Pathogenesis

Targets for Translational Antibodies

- B Cells (B)
- T Cells (T)
- Interferon α (IFN)
- Inducible Costimulator (ICOS)
- Unique Toleragens
Belimumumab (Benlysta®)
March 3, 2011!

U.S. Food and Drug Approval – Why:

• Innovative outcome measures
• 50 year need
• Steroid sparing effect
• Toxic medications we currently use
• Belimumumab – acceptable safety profile
What Does BLyS (BAFF) Do to B Cells?

Normal person: B cell receives signals from Macrophage.

Lupus patient: B cell releases BLyS, which is then taken up by Macrophage.
Subset of patients for use:

- Arthritis
- Serositis
- Hematologic
- Steroid dependent
- Fever
- Fatigue
- Skin Rash
### Comparison of Lupus Trials

<table>
<thead>
<tr>
<th></th>
<th>EXPLORER Rituximab</th>
<th>BLISS-52/76 Belimumab</th>
<th>EMBLEM Epratuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>257 (2 groups)</td>
<td>865 or 816 (3 groups)</td>
<td>227 (6 groups)</td>
</tr>
<tr>
<td><strong>Baseline steroids</strong></td>
<td>Required 100% ≥ 0.5 mg/kg</td>
<td>Allowed 46%-69% &gt; 7.5 mg/day</td>
<td>No increases at baseline</td>
</tr>
<tr>
<td><strong>% on Immunosuppressants</strong></td>
<td>100</td>
<td>56-42</td>
<td>60</td>
</tr>
<tr>
<td><strong>Type of analysis</strong></td>
<td>Cumulative</td>
<td>Landmark</td>
<td>Landmark</td>
</tr>
<tr>
<td><strong>Bar for response</strong></td>
<td>Hard to improve Easy to flare</td>
<td>Hard to improve Hard to flare</td>
<td>Easy to improve Hard to flare</td>
</tr>
<tr>
<td><strong>Effect size</strong></td>
<td>None prespecified 18.1% BL/Hisp 15% “A” flares</td>
<td>14% and 9%</td>
<td>24.8%</td>
</tr>
<tr>
<td><strong>% Meeting improvement definition</strong></td>
<td>29.6 33.8 50</td>
<td>57.6 and 43</td>
<td>43.2 and 45.9</td>
</tr>
</tbody>
</table>

---

*BL = Black, Hisp = Hispanic*

Efficacy and Safety of Epratuzumab in Patients with Moderate to Severe Systemic Lupus Erythematosus: Results from Two Phase 3, Randomized, Placebo-Controlled Trials

• M.E.B. Clowse, ¹ D.J. Wallace, ² R. Furie, ³ M. Petri, ⁴ M. Pike, ⁵ P. Leszczyński, ⁶ C. M. Neuwelt, ⁷ Et. al

¹Duke University Medical Center, Durham, USA; ²Division of Rheumatology, Cedars-Sinai Medical Center, Los Angeles, USA; ³Division of Rheumatology, North Shore-Long Island Jewish Health System, New York, USA; ⁴Division of Rheumatology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, USA; ⁵MedPharm Consulting, Inc., Cambridge, USA; ⁶Department of Rheumatology and Rehabilitation, Poznan University of Medical Sciences, Poznan, Poland; ⁷Division of Rheumatology, Alameda County Health System, Oakland, USA
Epratuzumab

- Epratuzumab is a humanized monoclonal antibody that targets CD22 on B cells
- This modulates B cell signalling, without substantial reductions in the number of peripheral B cells
- In Phase 2b trials, epratuzumab treatment led to improvements in disease activity in patients with moderate to severe systemic lupus erythematosus (SLE)\(^1\)

Epratuzumab Structure
New Biologicals in pipeline with different mechanisms of action

I. Anifrolumab – blocks receptor to interferon.

II. XMAB5871-04 – Fc Fraction of immunoglobulins.

III. Lupuzor – blocks T cell CD4 T cells

IV. Many others ...
Epigenetics

Epigenetics – caused by external or environmental factors that switch genes on and off.

Epigenetics in SLE – DNA in African Americans make their T cells more pro-inflammatory and more active compared to other populations.
Conclusions

- Neither EMBODY™ 1 nor EMBODY™ 2 met the primary endpoint of BICLA response rate at Week 48.

- Patients treated with epratuzumab + standard of care therapies did not show improvements in disease activity, corticosteroid use or health-related quality of life compared to those receiving placebo + standard of care therapies.

- The safety profile of epratuzumab was consistent with previous studies, with no new safety signals identified.
EPRATUZUMAB: SUSTAINED SAFETY PROFILE AND EFFECT ON CORTICOSTEROID USE ON LONG-TERM TREATMENT IN PATIENTS WITH MODERATE-TO-SEVERE SYSTEMIC LUPUS ERYTHEMATOSUS: RESULTS FROM AN OPEN-LABEL LONG-TERM EXTENSION STUDY (SL0008)

D. J. Wallace 1, *, J. Ordi-Ros 2, M. Neuwelt 3, K. Kalunian 4, B. Kilgallen 5, S. Bongardt 6, M. Petri 7, M. Pike 8, S. Jeka 9, C. Gordon 10, V. Strand 11

1 Cedars-Sinai Medical Center, David Geffen School of Medicine at UCLA, Los Angeles, United States, 2 Hospital Vall d’Hebron, Barcelona, Spain, 3 East Bay Rheumatology Medical Group, San Leandro, 4 UCSD School of Medicine, La Jolla, 5 UCB Pharma, Raleigh, United States, 6 UCB Pharma, Brussels, Belgium, 7 School of Medicine, Johns Hopkins University, Baltimore, 8 Harvard Medical School, Harvard, United States, 9 University Hospital No. 2, Bydgoszcz, Poland, 10 University of Birmingham, Birmingham, United Kingdom, 11 Stanford University School of Medicine, Palo Alto, United States
Individualized Cocktails of the Present and Near Future for Systemic Lupus Erythematosus

I. Experience suggests that in order to deplete B cells in all patients, one must use the **SYNERGISM** of Cyclophosphamide, Rituximab, and Corticosteroids\(^1\)

II. Increased production of BLyS after B cell depletion may counteract the clinical benefit. **Rituximab plus Belimumab** may be a rational combination to test\(^2\)

---

TREAT-TO-TARGET: THE NEW GOAL IN LUPUS (T2T)
International task force 2014. Published online 2015
The Principles (T2T)

- Recognize the patient’s autonomy, with decision – making shared between the patient and clinicians.

- Treatment should encompass survival, preservation of organ function, and encouraging the optimal quality of life.

- Recognition of the protean nature of SLE with its effects on multiple organ systems, requiring an interdisciplinary approach.

- Regular monitoring & treatment adjustments are needed to balance disease control and potential treatment toxicities.
The Recommendations (T2T)

- Prevention of disease flares, and particularly severe flares of nephritis, neuropsychiatric symptoms, and SLE overall.

- There are interventions that can prevent at least some flares with a reasonable balance to risks/side effects.

- Prevention of damage also was addressed and accorded considerable importance because of the associations between organ damage and poor prognosis.

- Patients who are clinically asymptomatic should be monitored closely but are at risk for overtreatment if serology alone guides treatment.
The Recommendations (T2T)

- Promptly evaluate renal function for all patients because of evidence in the literature suggesting that each 1-month delay in diagnosis and initiating immunosuppression increases the risk of relapse (RR1.03).

- Lupus nephritis consists of both induction and maintenance, and, in general, the maintenance phase should include at least 3 yrs of treatment.

- Using the lowest dose of steroids that can control the disease and recommending that most patients be on an anti-malaria if not contraindicated.

- Treatment of comorbidities, such as antihypertensives and lipid-lowering agents.
Bill Murray and Scarlett Johannson & SLE are no longer Lost In Translation!!