SLE: CLINICAL TRIALS – CHALLENGES, PITFALLS, AND STEPS TOWARDS SUCCESS

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Cedars-Sinai Medical Center
David Geffen School of Medicine at UCLA
• Introduction to SLE Clinical Development

• SLE Clinical Trials Landscape
  – Clinical Domains and Tools – Pros / Cons / Considerations
  – Clinical Trials – Landscape

• How to Design a Successful SLE Trial
  – Lessons Learned
  – Recommendations
Lupus Drug Development 1950-2005

- Single center reports not using statistics (e.g., antimalarials, methotrexate, azathioprine, cyclophosphamide, corticosteroids)
- Handful of controlled studies using statistics (e.g., hydroxychloroquine withdrawal, NIH studies with cyclophosphamide, apheresis, pulse steroids)

1980-2000

- Non-targeted therapy after 1990 of highly variable quality: mycophenolate, leflunomide, DHEA
- Disastrous early biologic trials (e.g., anti CD40L) led advocacy groups, pharma, academia, rheumatology community to lobby the FDA for greater clarity and a roadmap
New drugs are needed for lupus

• Only 1 new drug has been approved by the FDA for lupus in over 50 years
• Lupus has an unacceptably high morbidity and mortality rate with its current management
• In 1965, corticosteroids, methotrexate, azathioprine and cyclophosphamide were available. We have made little progress since that time
• Mycophenolate mofetil (MMF) and Leflunomide are the only DMARD agents that were introduced between 1980 and 2000.
• Status of biologics: Belimumab (approved 2011 for lupus). Available: Tociluzumab, rituximab, abatacept, anti TNFs are reported to be helpful in lupus but are not approved.
OMERACT for Lupus: Outcome Measures in Rheumatology

First effort to define lupus outcomes for clinical trials (1999).

A lupus study should demonstrate improvement in:

- Disease Activity
- Damage
- Health Related Quality of Life (PRO)
- Toxicity/Adverse Events (MD/PRO)
- Superseded by FDA Guidance for SLE - March 2005

Most Phase 2/3 studies use outcomes that have not been formally validated in clinical trials

Two adequate and well controlled trials; Superiority trials with open label extension preferred

RCTs of 1-year duration; patients to fulfill ACR criteria for SLE

Patients should be stratified by severity

BILAG-2004 is preferred DAI; SLEDAI, ECLAM, and SLAM acceptable

Definitions for major; partial clinical responses, remission, reduction in flare, increase in time to flare

Steroid use variability best if minimized and sparing effects defined

Patient reported outcome measures should be evaluated

Subpart H and E relating to biomarkers are potentially applicable
Since 2005, 20 SLE drugs in Phase II/III trials have failed to meet their primary endpoint using FDA guidance document. Many of these agents are clearly effective. 

**Positive Results:** belimumab and possibly anifrolumab
Why did 20 Phase II/III trials fail?

• DRUG does not work or was not safe
• TRIAL DESIGN was flawed.
• Poor choice of a PRIMARY OUTCOME MEASURE
• TRIAL WAS BADLY IMPLEMENTED: Complex logistics, hassle factors to centers discourage enrollment, poor site selection (geographical bias)
• POOR CHOICE OF CONCOMITANT MEDICATIONS allowed or disallowed
• ARTIFICIAL MANDATED USE OF STEROIDS AND TAPERING that are not used in clinical practices. Corticosteroids always work; its hard to show differences
• DOMAINS OF SLE ASSESSMENT (SLEDAI, BILAG) not adequately assessed. Composite indices (SRI, BICLA) may amplify flaws of SLEDAI and BILAG
Agenda

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Domains of SLE Activity Assessment/Tools

- **Disease Activity Tools**: SLEDAI, BILAG, PGA, LLDAS
- **Composite Indices**: SRI, BICLA
- **Disease Damage**: SLICC DAMAGE INDEX, LDIQ
- **Quality of Life**: SF-36, LupusPRO, Lupus Impact Tracker (LIT), Lupus QoL
- **Flare Indices**: SLEDAI flare index, BILAG flare
- **Organ Specific Endpoints**: CLASI, Nephritis
SELENA SLEDAI
(Safety of Estrogens in Lupus Erythematosus: National Assessment Version of the Systemic Lupus Erythematosus Disease Activity Index)
Shortcomings of the SELENA-SLEDAI*

- Devised in 1992 and never intended for use in clinical trials
- 24 items with a maximum score of 105
- Not sensitive to change in joints, blood counts
- No subjectivity
- Weighted against laboratory tests (6 points)
- Heavily weighted towards CNS and Renal organs (56 CNS, 24 renal). Lupus headache does not exist.
- Ignores pulmonary hypertension, TTP, hemolytic anemia, interstitial lung disease
- Validated for clinical activity, but a poor measure of change in activity

British Isles Lupus Assessment Group (BILAG)

- Includes 86 items in one of 9 organ domains (musculoskeletal, mucocutaneous, cardiorespiratory, renal, neuropsychiatric, hematologic, constitutional, gastrointestinal, ophthalmic) listed as A,B,C,D,E based on clinical manifestations over the last 30 days.

- Intended and validated to demonstrate clinical activity.

- Used 95% of the time.
BILAG: No Significant Worsening in Any Specific Organ System¹,²

- Included in the SRI to ensure no significant worsening in any specific organ system over the previous month by tracking flares and flare severity¹,²
- 86 items reflecting disease activity within 8 organ systems; each organ receives a letter score³

<table>
<thead>
<tr>
<th>BILAG SCORE⁴</th>
<th>DESCRIPTION⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>BILAG-A</td>
<td>Requires disease-modifying treatment (prednisone &gt;20 mg/day or immunosuppressant)</td>
</tr>
<tr>
<td>BILAG-B</td>
<td>Mild, reversible problems requiring symptomatic therapy (antimalarials, NSAIDs, prednisone &lt;20 mg/day)</td>
</tr>
<tr>
<td>BILAG-C</td>
<td>Stable, mild disease</td>
</tr>
<tr>
<td>BILAG-D</td>
<td>No activity in previously affected system</td>
</tr>
<tr>
<td>BILAG-E</td>
<td>System never involved</td>
</tr>
</tbody>
</table>

Only patients with no new BILAG-A organ domain score or 2 new BILAG-B organ domain scores at Week 52 could be considered SRI responders⁴

Shortcomings of the BILAG

- Designed in 1988 and never intended for use in clinical trials
- Not amenable to statistics. Scoring system came out 20 years later.
- Soft BILAG B’s
- Central scoring/site scoring correlations are poor
- English language proficiency requirements
- Even though 86 factors are included, Raynaud’s is not and its weighted towards GI and Eye findings seen in <1%
- Time consuming to understand definitions
“Severe” means the worst in the universe of lupus, not the worst for that particular patient!
### Table 1  LLDAS definition

<table>
<thead>
<tr>
<th>Domain and items</th>
<th>Mean agreement score* in Delphi Round 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease activity</strong></td>
<td></td>
</tr>
<tr>
<td>1. SLEDAI-2K ≤4, with no activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, fever) and no haemolytic anaemia or gastrointestinal activity</td>
<td>5.0</td>
</tr>
<tr>
<td>2. No new features of lupus disease activity compared with the previous assessment</td>
<td>4.7</td>
</tr>
<tr>
<td>3. SELENA-SLEDAI physician global assessment (PGA, scale 0–3) ≤1</td>
<td>4.8</td>
</tr>
<tr>
<td><strong>Immunosuppressive medications</strong></td>
<td></td>
</tr>
<tr>
<td>4. Current prednisolone (or equivalent) dose ≤7.5 mg daily</td>
<td>4.5</td>
</tr>
<tr>
<td>5. Well tolerated standard maintenance doses of immunosuppressive drugs and approved biological agents, excluding investigational drugs</td>
<td>4.5</td>
</tr>
</tbody>
</table>

*Scale 1 to 5, where 1=strongly disagree, 2=disagree, 3=unsure, 4=agree, 5=strongly agree.

CNS, central nervous system; LLDAS, Lupus Low Disease Activity State; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

Domains of SLE Activity Assessment/Tools

- Disease Activity Tools: SLEDAI, BILAG, PGA, LLDAS
- Composite Indices: SRI, BICLA
- Disease Damage: SLICC DAMAGE INDEX, LDIQ
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- Organ Specific Endpoints: CLASI, Nephritis
Primary Endpoint: SLE Responder Index (SRI) Response Rate at Week 52


SRI responders had to meet all 3 criteria

SELENA-SLEDAI

≥4-point reduction in SELENA-SLEDAI score

BILAG

No new BILAG A or 2 new BILAG B organ domain scores

PGA

No worsening in PGA (<0.3-point increase)

References:
**BICLA: Primary end point: combined responder index of clinical disease activity at Week 12**

**BILAG improvement**
- All BILAG A scores at study entry improved to B/C/D, and
- All BILAG B scores at study entry improved to C/D, and
- No BILAG worsening in other body systems = no new BILAG A or ≥2 new BILAG B scores

**SLE Disease Activity Index (SLEDAI)**
- No worsening in SLEDAI total score compared with study entry

**Physician’s global disease activity assessment**
- No worsening (defined as <10% worsening) compared to study entry on 100 mm visual analog scale (VAS)

**Treatment failure**
- Patients who are treatment failures cannot be responders
  - Defined as added or increased immunosuppressants or anti-malarials, or corticosteroid increase above baseline or tapering level at any point following randomization

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*BILAG 2004 version, scored by independent central efficacy reader*
Concerns relating to composite indices

- SLEDAI entry criteria:
  - ≥2 for DHEA
  - ≥4 for belimumab Phase 2
  - ≥6 for most ongoing trials
  - ≥10 for blisibimod. Higher number powers the study but enrollment is harder. Change in SLEDAI sets a high bar (e.g., arthritis, rash, cytopenias)

- SRI: PGA and new BILAGs are of little value and represent <20% of the changes

- BICLA: 90% of change related to BILAG changes and less than 10% to the 4 other components

- High response rates to community standard of care with international biases
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SLICC/ACR* Damage Index

Calculated on a scale of 12

Measures nonreversible change (not related to active inflammation) occurring since onset of lupus, ascertained by clinical assessment and present for > 6 months unless otherwise stated. Repeat episodes must occur > 6 months apart to score “2”. The same lesion cannot be scored twice.

*SLICC/ACR = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index
Shortcomings of Damage Indices in Clinical Trials

- It takes several years to show any changes in the SLICC/ACR damage index (derived from SLICC 1800 member cohort studied for 20 years)

- Worthless as a secondary outcome for trials two years in duration or less, but used in most trials nevertheless

- LDIQ is entirely subjective and not well validated
Systemic Lupus International Collaborating Clinics/ACR Damage Index (SLICC)

<table>
<thead>
<tr>
<th>Item</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peripheral vascular</strong></td>
<td></td>
</tr>
<tr>
<td>Claudication for 6 months</td>
<td>1</td>
</tr>
<tr>
<td>Minor tissue loss (pulp space)</td>
<td>1</td>
</tr>
<tr>
<td>Significant tissue loss ever (e.g., loss of digit or limb) (score 2 if &gt; 1 site)</td>
<td>1</td>
</tr>
<tr>
<td>Venous thrombosis with swelling, ulceration, or venous stasis</td>
<td>1</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
</tr>
<tr>
<td>Infarction or resection of bowel below duodenum, spleen, liver, or gall bladder ever, for cause any (score 2 if &gt; 1 site)</td>
<td>1</td>
</tr>
<tr>
<td>Mesenteric insufficiency</td>
<td>1</td>
</tr>
<tr>
<td>Chronic peritonitis</td>
<td>1</td>
</tr>
<tr>
<td>Stricture or upper gastrointestinal tract surgery ever</td>
<td>1</td>
</tr>
<tr>
<td><strong>Musculoskeletal</strong></td>
<td></td>
</tr>
<tr>
<td>Muscle atrophy or weakness</td>
<td>1</td>
</tr>
<tr>
<td>Deforming or erosive arthritis (including reducible deformities, excluding avascular necrosis)</td>
<td>1</td>
</tr>
<tr>
<td>Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis)</td>
<td>1</td>
</tr>
<tr>
<td>Avascular necrosis (score 2 if &gt; 1)</td>
<td>1</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>1</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td></td>
</tr>
<tr>
<td>Scarring chronic alopecia</td>
<td>1</td>
</tr>
<tr>
<td>Extensive scarring or panniculitis other than scalp and pulp space</td>
<td>1</td>
</tr>
<tr>
<td>Skin ulceration (excluding thrombosis) for &gt; 6 months</td>
<td>1</td>
</tr>
<tr>
<td>Premature gonadal failure</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes (regardless of treatment)</td>
<td>1</td>
</tr>
<tr>
<td>Malignancy (exclude dysplasia) (score 2 if &gt; 1 site)</td>
<td>1</td>
</tr>
</tbody>
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Non-disease specific QOL Measure: SF-36

Does not take into account fibromyalgia, medications such as steroids, and other co-morbidities

<table>
<thead>
<tr>
<th>Measure</th>
<th>Number of Items</th>
<th>Domains Assessed</th>
<th>Administration Time to Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOS SF-36</td>
<td>36</td>
<td>Physical functioning</td>
<td>Self-or interview administered &lt; 10 minutes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Role limitations due to</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>▪ physical problems</td>
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<td></td>
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<td>▪ bodily pain</td>
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<td></td>
<td></td>
<td>▪ general health,</td>
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<td></td>
<td></td>
<td>▪ social functioning, mental health;</td>
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<tr>
<td></td>
<td></td>
<td>• Role limitation due to</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ emotional problems</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ vitality</td>
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</table>
## SLE-Specific PRO Tools

<table>
<thead>
<tr>
<th>Tool</th>
<th>Description</th>
<th>Characteristics</th>
</tr>
</thead>
</table>
| SLE Symptom Checklist (SSC)¹                        | • Developed in Netherlands  
• Includes physical aspects of SLE symptoms                                      | • Validated in small samples with stable disease  
• Only 1 QOL component  
• Cross-cultural validation of English version |
| SLEQOL²                                            | • Developed in Singapore  
• Includes physical and psychological aspects of QOL in SLE                        | • Cross-cultural validity unclear  
• Poor construct validity  
• More sensitive but less specific to change |
| Lupus QOL Index³                                   | • Developed in UK  
• Includes fatigue, sleep, body image, and emotional intimacy  
• Item generation included patient interviews                                      | • Males  
• Ethnic heterogeneity lacking  
• Some domains missing  
• Application to varied healthcare settings |
| L-QoL¹                                             | • Developed in UK  
• 55-item questionnaire derived from interview transcripts                         | • Small study size  
• Criterion validity against physician-assessed outcomes not available |
| LupusPRO²                                          | • Developed in US  
• Includes 43 items, including HRQoL-related and non-HRQoL related               | • More sensitive, specific than SF-36  
• Time-intensive to complete |
| Lupus Impact Tracker³                              | • Developed in US  
• Consists of 10 items derived from the LupusPro  
• Selected based on quantitative, qualitative measures; input from patients and rheumatologists  
• Intended for clinical practice to monitor effects of SLE on QOL                  | • Demonstrated reliability, validity for assessing impact of SLE on patients  
• Most patients and physicians found LIT acceptable and feasible to administer in a clinic setting  
• Not yet validated in large-scale studies  
• Experience in clinical trial population may not represent SLE population |

The PROMIS initiative

• Patient Response Outcomes Measurement Information System (PROMIS) was established in 2015 by the National Institutes of Health for patients with rheumatic disease

• Dynamic, precise methodology to derive a validated patient outcome measure and has been published for RA and scleroderma.


• Remarkable preliminary findings will render all other PROs obsolete
What is PROMIS?

• Combines Item Response Theory (IRT) and Computer Adaptive Testing (CAT)
  – **Precision**: in measurement of individual symptoms and health-related quality of life
  – **Efficiency**: less respondent burden
  – **Larger range**: Minimizes floor-ceiling effects
  – **Adaptability**: with short forms, scales, profiles and item banks-improve with iteration
  – **Standardization**: same metric-same meaning

• IRT models ‘latent traits’
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SELENA SLEDAI Flare Index

Mild or Moderate Flare □
- Change in SELENA-SLEDAI instrument score of 3 points or more (but not to more than 12)
- New/worse:
  - Discoid, photosensitive, profundus, cutaneous vasculitis, bullous lupus
  - Nasopharyngeal ulcers
  - Pleuritis
  - Pericarditis
  - Arthritis
  - Fever (SLE)
- Increase in prednisone, but not to >0.5 mg/kg/day
- Added NSAID or hydroxychloroquine for SLE activity
- ≥1.0 increase in PGA score, but not to more than 2.5

Severe Flare □
- Change in SELENA-SLEDAI instrument score to greater than 12
- New/worse:
  - CNS-SLE
  - Vasculitis
  - Nephritis
  - Myositis
  - Plt <60,000
  - Hemolytic anemia: Hb <70 g/L or decrease in Hb >30 g/L
  - Requiring: double prednisone, or prednisone increase to >0.5 mg/kg/day, or hospitalization
- Increase in prednisone to >0.5 mg/kg/day
- New cyclophosphamide, azathioprine, methotrexate for SLE activity
- Hospitalization for SLE activity
- Increase in Physician’s Global Assessment score to ≥2.5
BILAG Flare and Flare Issues

• Most studies consider a new BILAG A or two new BILAG Bs to be a flare
• Soft BILAG Bs
• BILAG flares and Selena SLEDAI flares do not correlate with each other
• There is no international standard for a flare and renal flares have their own definitions. If the annual flare rate at Johns Hopkins is 30% but in Des Moines its 10%, how can a study be powered to reduce flare rates?
• Examples: Atacicept, Riquent used artificially derived flare rates as their primary outcome measure and did not meet their primary end point
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Organ-Specific Endpoints / Instruments

- CLASI can be used for skin disease
- Renal: ACR and EULAR nephritis guidelines are published; evolving agreement for developing outcome measures
- Studies can be powered for many fewer participants
- Danger: Narrower FDA approval even if drug may be effective for other aspects of lupus
Cutaneous LE Disease and Severity Index (CLASI)

<table>
<thead>
<tr>
<th>Extent</th>
<th>Activity</th>
<th>Damage</th>
<th>Scarring/Atrophy/Atrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoulders</td>
<td>Head</td>
<td>Face</td>
<td>Neck</td>
</tr>
<tr>
<td>Back, buttocks</td>
<td>Lower back</td>
<td>Lower back</td>
<td>Lower back</td>
</tr>
<tr>
<td>Feet</td>
<td>Feet</td>
<td>Feet</td>
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</tbody>
</table>

**Mucous membrane**

<table>
<thead>
<tr>
<th>Dyspigmentation</th>
<th>Extent</th>
<th>Area of dyspigmentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoulders</td>
<td>Head</td>
<td>Face</td>
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<tr>
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<tr>
<td>Feet</td>
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</tbody>
</table>

**Alopecia**

<table>
<thead>
<tr>
<th>Extent</th>
<th>Area of alopecia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoulders</td>
<td>Head</td>
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<td>Back, buttocks</td>
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</table>

**Total Activity Score**

<table>
<thead>
<tr>
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<th>Activity</th>
<th>Damage</th>
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**Total Damage Score**

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</tbody>
</table>
The nephrology vs rheumatology conundrum (should nephrologists do SLEDAI, BILAG, and vice versa and how does extra renal lupus with nephritis fit in). Should all patients in a trial see a nephrologist and a rheumatologist?

• Agreed upon primary endpoints for studies

• Poor/slow enrollment in nephritis trials
Nephritis

Complete Response Criteria

<table>
<thead>
<tr>
<th>Trial</th>
<th>UPCR</th>
<th>Creat (eGFR)</th>
<th>U/A</th>
<th>GC Taper Required</th>
<th>Two Visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>* IM101075</td>
<td>&lt;0.27</td>
<td>10%</td>
<td>wnl</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>ACR</td>
<td>&lt;0.2</td>
<td>25%</td>
<td>wnl</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>LUNAR</td>
<td>&lt;0.5</td>
<td>15%</td>
<td>wnl</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>ALMS</td>
<td>&lt;0.5</td>
<td>25%</td>
<td>wnl</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>ACCESS</td>
<td>&lt;0.5</td>
<td>nl or 25%</td>
<td>-</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

* Entry criteria: UPCR >0.45 g/g (other trials UPCR >1.0)
• Introduction to SLE Clinical Development

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  – Clinical Domains and Tools – Pros / Cons / Considerations
  – Clinical Trials – Landscape

• How to Design a Successful SLE Trial
  – Lessons Learned
  – Recommendations
New developments: Calcineurin Inhibitors and other oral agents

• Tacrolimus: Nephritis controlled trials: favorable results at 6 months but not two years compared with cyclophosphamide or MMF (ARD 75:30, 2016, Ann Int Med 2015 162:18-26, AJ Kid Dis 2011; 56: 235). Suggest as add on to azathioprine or MMF in patients with refractory disease

• Voclosporin (Aurinia) 265 nephritis patients as controlled add on to MMF: 32.6 vs 27.3 vs 19.3% met primary endpoint. 12 deaths in treatment group; none in control group. All outside USA. (ACR Late Breaking, 2016)

• N-acetyl cysteine (NAC)—NIH grant (Lai ZW, Arth Rheum 2012; 64: 2937-46) blocks mTOR
AURA: Primary Endpoint Results

First therapeutic agent to meet primary endpoint in global clinical trial for active LN

**PRIMARY OUTCOME MEASURES**

32.6% of patients in low dose Voclosporin arm achieved CR ($p=0.045$); compared to 27.3% ($p=0.204$) in high-dose arm and 19.3% in control arm - Odds Ratio (95% CI) vs. Control = 2.03

CR in AURA is a composite end-point which includes efficacy, safety and low-dose steroids:

- UPCR ≤ 0.5mg/mg (confirmed)
- eGFR >60ml/min or within 20% of baseline
- Steroids ≤ 10mg/day

Study was powered to show a difference in either arm vs. control arm, not between doses.
NAC and RAPA control T cell lineage specification in SLE via mTOR
New developments: Immune-Suppressives/ Modulators, Antibiotics and Anti-inflammatories

- Leflunomide approved in China in 2010 for lupus nephritis in a dose of 40 mg a day
- CC220 (Celgene) in Phase II trial. Thalidomide analogue that targets Ikaros and Aiolos (degradation of those proteins after ubiquitination) <Iberdomide.
- Ajulemic acid (Resunab/Arbus/AB-111) is a cannabinoid in Phase II trials
- Nelfinavir---HIV-1 protease inhibitor in Phase II trials (B Diamond, Autoimmune Centers for Excellence)
- Corticosteroids—Rayos (timed release prednisone blocks IL-6 release); selective glucorticosteroid antagonists; ACTHar
## Targeted Therapies in SLE

<table>
<thead>
<tr>
<th>MOA</th>
<th>Examples of Targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>T Cells</td>
<td>CTLA4-lg; modified CD40L mAb; ICOS, expand CD4+CD25+ and T reg cells, CD8+CD28- cells</td>
</tr>
<tr>
<td>B Cells</td>
<td>mAbs to CD20, CD22, proteosome/plasma cells antiBLyS, TACI-lg, BAFF-RFc</td>
</tr>
<tr>
<td>Complement</td>
<td>Anti-C5a</td>
</tr>
<tr>
<td>Cytokines</td>
<td>mAbs to sIL-6R, IL-6, IL-10, IL-17, IL-18, anti-TNFs</td>
</tr>
<tr>
<td>Innate immune system</td>
<td>Anti-IFNα and IFNγ; blockade of TLR7 and/or 9</td>
</tr>
<tr>
<td>Toleragens</td>
<td>Peptides derived from nucleosomes, Sm Ag, Igs, 16/6 idiootype, splicosomes</td>
</tr>
<tr>
<td>Cell surface receptor activation inhibition</td>
<td>Syk-kinase inhibition; sirolimus; BTK inhibition</td>
</tr>
</tbody>
</table>

MOA = mechanism of action; Ig = immunoglobulin; mAb = monoclonal antibody; Sm Ag = Smith antigen; ICOS = inducible costimulator; TACI = transmembrane activator and calcium reproducing initiator; BAFF-RFc = B cell activation factor-rosette-forming cells.

T Cell Modulators

- **CTLA-4 inhibition:** Abatacept: 2 nephritis trials (Neither Immune Tolerance Network <ACCESS> nor BMS funded trial met primary endpoint, controversy regarding response measures) (A+R 2013; 65: 1586). Signals that it is useful for non nephritis but did not meet primary endpoint in poorly designed trial. New study on going. T cell co-stimulation modulator.

- **Blockade of CD40L** (BG9588; IDEC 1)—being reconfigured Biogen, dapirolizumab (UCB). (BI655064)

- **ICOS-B7 RP1** (Amgen 557)—arthritis and SCLE trials; also MEDI-570 (AZ) in Phase 1

- **Edratide** (XTL—Israel) Phase II trial promising and being repeated (Urowitz, 2012). Ppeptide based on CDR region 1 of a human monoclonal Mab

- **Lupuzor** (Immunopharma—France) in large Phase II trial

- **Autologous T reg cell therapy** (Autoimmune Centers for Excellence—UCSF) TAB08—CD28 superagonist

**T Cell: Recent treatment strategies for lupus**

Lupuzor™: A promising small peptide which acts as an immune modulator to treat Lupus via a T-cell approach.

Positive Phase II trials in Argentina, Bulgaria, Phase IIb in progress (Ann Rheum Dis 2013; 72: 1830-1835)
T-Cell Subsets: Th17 and T\textsubscript{REG} Cells

- Th17 cells are abundant in the gut; maintain mucosal homeostasis
- Th17 upregulated in inflammatory diseases: MS, RA, SLE, IBD
- IL-23 important for the maintenance of the Th17 phenotype

**T\textsubscript{REG} cell (CD4+CD25+)**

<table>
<thead>
<tr>
<th>Naïve T cell</th>
<th>FoxP3</th>
<th>IL-10</th>
<th>T\textsubscript{REG} cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self Ag + TGF\beta</td>
<td>TGF\beta</td>
<td>IL-17</td>
<td>PROTECTION</td>
</tr>
<tr>
<td>IL-23 (survival)</td>
<td>ROR\gamma</td>
<td>IL-22</td>
<td>INFLAMMATION</td>
</tr>
</tbody>
</table>

Th17 = T helper cell 17; T\textsubscript{REG} = regulatory T cells; MS = multiple sclerosis; RA = rheumatoid arthritis; IBD = irritable bowel disease; Ag = antigen; TGF\beta = tumor growth factor beta; TNFR = tumor necrosis factor receptor; CTLA-4 = cytotoxic T-lymphocyte antigen 4; AITR = activation-inducible tumor necrosis factor receptor; GITR = glucocorticoid-induced tumor necrosis factor receptor; ROR\gamma = RAR-related orphan receptor gamma (t).

T Cell: Targeting the CD40L/CD40 Pathway

- Members of TNF superfamily (CD40L→TNF; CD40→TNFR)
- CD40L expressed on activated T cells, platelets, and activated leukocytes
- CD40 constitutively expressed on antigen presenting cells (APCs) and stromal cells
- CD40 ligation delivers intracellular signals while CD40L does not

CD40L-CD40 pathway acts as an amplifier of T-APC signaling:
**B Cell Dysregulation: A Contributing Factor in SLE**

BLISS-52 and BLISS-76: SRI Response Rates at Week 52

Patients Meeting Primary Endpoint at Week 52 in 2 Phase III Trials

BLISS-52

- **58%** (n=290)
- **44%** (n=287)
- *P* < 0.001

BLISS-76

- **43%** (n=273)
- **34%** (n=275)
- *P* < 0.05

Belimumab 10 mg/kg + standard therapy

Placebo + standard therapy

---

**B Cell Inhibition:**

**Many fewer agents being studied**

- IMMU-115 (milatuzumab) - humanized antibody targeting the CD74 antigen present on antigen-presenting cells (APC), including B-cells and dendritic cells.

- Trials cancelled: tabalumab, ritixumab, ofatumumab, ocrellizumab, blisbimod and 5 others in Phase I

- B cell depletion anti CD 20 (rituximab; obinutuzumab-Roche, approved for leukemia being studied for lupus nephritis)

- CD19 blockade (Xencor) (XmAb5871) Also blocks Fc gamma lib receptor) In Phase 2 Trials

- BLyS/BAFF/APRIL/TRAIL blockade (atacicept—TACI-Fc fusion that binds to APRIL and TRAIL), RC18 (Ronghang) TACI-antibody fusion protein

- Proteosome blockade (bortezomib, carfilzumib) blocks plasma cell activation---case reports of efficacy but toxic. Ixazomib-MM drug proteosome inhibitor in clinical trial. KZR-616, a selective immunoproteosome inhibitor is starting clinical trials.

B Cell Summary: Rituximab, Ocrelizumab, Obinutuzumab and Ofatumumab

- Rituximab did not meet primary outcome measures in poorly designed trials (nephritis and non-nephritis) where both arms received effective (high dose steroid and immune suppressive) therapy. (A+R 2010; 62:222 and 2012; 64: 1215)
- Rituximab appears to be effective for thrombocytopenia, TTP, inflammatory arthritis, hemolytic anemia and central nervous system vasculitis in large case series and may be useful in combination with cyclophosphamide in selected cases
- Rituxilup (Lightstone, UK) not Pharma funded, outlook tenuous
- Ocrelizumab did not meet primary outcome measures in similarly designed nephritis and non-nephritis trials but had increased rate of infections and development has been suspended. (A+R 2013; 65: 2368)
- Ofatumumab is approved for leukemia; SLE studies on hold. Positive Phase III RA trial. Fully human as opposed to humanized.
- Obinutuzumab is in clinical trials for lupus nephritis
B Cell: Lunar Primary Endpoint: Renal Response at week 52 Rituximab or Placebo Added to MMF

CRR AND PRR: 46% (PLA) vs. 57% (RTX)

* Wilcoxon Rank-sum test to compare the proportions of (CRR, PRR, NR) between rituximab and placebo

50 consecutive patients at Imperial College, London

<table>
<thead>
<tr>
<th>Number</th>
<th>Complete Remission</th>
<th>Partial Response</th>
<th>Any Response</th>
<th># Patients Relapsing</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>26 (52%)</td>
<td>17 (34%)</td>
<td>43 (86%)</td>
<td>11</td>
</tr>
</tbody>
</table>

**Complete response (CR)** — urine PCR of <50 mg/mmol and a rise of no greater than 15% in serum creatinine.

**Partial response (PR)** — urine PCR <300 mg/mmol if nephrotic at baseline, or a >50% reduction if baseline non nephrotic, and a rise of no greater than 15% in serum creatinine.
Atacicept blocking BLyS and APRIL binding their Receptors
The primary endpoint (75 mg vs. Placebo flare prevention) was not met; however, ad hoc analysis suggested that 150 mg significantly prevented flare. Other study designs being tested. 150 mg dose terminated for questionable reasons, role is being revisited. Phase III trial in progress.

<table>
<thead>
<tr>
<th>Statistics</th>
<th>Placebo (n=157)</th>
<th>Atacicept 75mg (n=159)</th>
<th>Atacicept 150mg (n=145)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flare (%)</td>
<td>54.14%</td>
<td>57.86%</td>
<td>36.55%</td>
</tr>
<tr>
<td>CI</td>
<td>[46.01%; 62.11%]</td>
<td>[49.79%; 65.64%]</td>
<td>[28.72%; 44.95%]</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>1.149</td>
<td>0.5430</td>
<td>0.483</td>
</tr>
<tr>
<td>p-value</td>
<td>0.5430</td>
<td>0.0021</td>
<td>0.0021</td>
</tr>
</tbody>
</table>
Blockade of Complement

- Eculizumab (Soliris-Alexion), an anti C5a on the market for paroxysmal hemoglobinuria and atypical hemolytic uremic syndrome (some with SLE) had a Phase I trial conducted in SLE in 2002 (R Furie) which suggested safety.
- Evidence (J Salmon) that blocking C5a may reduce pregnancy loss in patients with antiphospholipid syndrome (J Immunol 2015; 1129-1135).
- Omeros 721 (blocks mannan binding lectin associated serine protease inhibition <MASP>) in lupus nephritis trial.
- C5a receptor inhibitor positive trial in ANCA positive vasculitis (ChemoCentryx).
Cytokines

- IL-6 inhibition (tocilizumab, PF-04236921, Ablynx IL-6 ALX-0061 receptor nanoantibody)
- IL-2 (Aldesleukin; ILT-101) agonist in low doses improves SLE in trials in Germany and China
- IL-10 monoclonal antibody (BTO63)
- Ustekinumab (Stelara) trial blocks IL-12/23 in progress using doses much larger than in psoriasis Successful Phase 11a trial. Phase III to start in 2018. IL-23 Phase 1b trial (Boston)
Cytokines: Efficacy of Tocilizumab in SLE

• Prompt decrease in acute phase reactants
• Decrease in anti-dsDNA antibodies
• Improvement in overall disease activity
• Normalization of circulating B cell subsets

These results indicate:
• IL-6 plays an important role in lupus pathogenesis
• IL-6 may be a good target for therapeutic intervention.

*p= 0.076; DJ Wallace et al, Ann Rheum Dis 2016
Targeting the Innate Immune System: Anti-Interferons and Anti-TLR 7,9

- NNC 0152 (Novo Nordisk) now Argos—study halted due to leukopenia
- Neovasc IFN-alpha kinoid vaccine in Phase IIb
- AMG 811 (Amgen) to IFN-gamma—not effective
- MEDI 545 (Sifalumumab) blocked IFN signature but had possible moderate clinical effects
- Rontalizumab did not meet its primary endpoint but is safe; those without interferon signature did better
- Anti TLRs: First 5 efforts failed
- BIIB059 (Biogen) anti TLR9 in Phase
- Anifrolumab IgG1 kappa binds to IFN-alpha receptor. Met primary endpoint in 305 patient study

Interferons and Systemic Lupus Erythematosus

Type I interferons (IFNs) may play a critical role in the pathogenesis of systemic lupus erythematosus (SLE)

- Serum IFN-α levels are elevated in patients with SLE\(^1\)
- Increased expression of type I IFN-induced genes in blood and involved tissues in SLE\(^2\)
- Correlation between IFN levels and expression of type I IFN-induced genes and SLE activity\(^1,3\)
- Development of SLE in patients undergoing IFN-α treatment\(^4\)
- Inhibition of IFN-α may provide therapeutic benefit in the treatment of SLE

Anifrolumab Phase II Trial: Primary endpoint: SRI(4) including OCS taper

Anifrolumab vs. Placebo

Delta: 16.7% 11.2% 22.8% 15.0% -1.6% 0.0%
OR: 2.38 1.94 3.55 2.65 0.96 1.04
90% CI: (1.33, 4.26) (1.08, 3.49) (1.72, 7.32) (1.27, 5.53) (0.34, 2.74) (0.37, 2.88)
P: 0.014 0.063 0.004 0.029 0.946 0.953

Day 169

Day 365

Furie R et al. Arthritis Rheumatol 2017
• **Kinome**
  
  - A subset of the genome consisting of the protein kinase genes
  
  - Protein kinases act as key regulators of cell function by catalyzing the addition of a negatively charged phosphate group to proteins
  
  - Regulates protein function in both normal and disease states
  
  - Over 500 kinome genes have been identified
• SYK  (R-333 failed for cutaneous lupus) (GS-9876 in cutaneous lupus trial)
• JAK Tofacitinib trial underway at NIH, JAK 1 and 3 inhibitor, baricitinib in Phase II trial fully enrolled (Lilly), filgotinib for cutaneous lupus
• BTK (Merck Serono, Roche, Lilly, Biogen, et al)—positive results
• PDE4 ( apremilast--Otezla)
• P13K
• TYK (BMS)
Mechanisms of disease reduction by Btk inhibition

iBtk blocks
- BCR signaling
- FcR signaling
- TLR signaling

Adapted from: Int J Mol Sci 2015 Kim JM et al.
Other MOA’s potentially relevant to SLE (I)

• RSLV-B2 in Phase 2a trial—breaks down RNAse as a Rnase-Fc fusion protein
• Toleragens: Lupuzor, Edratide
• Innate immune system: TLR7 and TLR9 blockade
• Anti-BCDA2 monoclonal antibody inhibits plasmacytoid dendritic cells (BIIBo59)
• Iguratimod (Esai) is approved for RA in China and Japan and blocks NkappaB. Being studied in nephritis.
MSCs in SLE Trial Protocol

• A Phase II sequential dose-escalation study evaluating the safety and feasibility of allogeneic umbilical cord derived mesenchymal stem cells (MSC) for the treatment of adults with treatment refractory lupus.

• IND 16377 approved (sponsor: Gary Gilkeson, MD)
• Introduction to SLE Clinical Development

• SLE Clinical Trials Landscape
  – Clinical Domains and Tools – Pros / Cons / Considerations
  – Clinical Trials – Landscape

• How to Design a Successful SLE Trial
  – Lessons Learned
  – Recommendations
Major unmet needs

• Patients with active non organ threatening disease whose disease can only be suppressed with too much steroid Rx and/or are intolerant of or resistant to antimalarials

• A validated surrogate or biomarker, especially for nephritis and CNS lupus

• Pediatric lupus
Learning from recent failures

- Laquinimod (28 joint counts don’t work)
- Dynavax (requiring IFN signature to enter study based on faulty preliminary data)—if you are going to require a positive blood test with a biomarker, do your homework first. Pre-screen patients to see if they carry required biomarker (e.g., ANA).
- Put rheumatologists who see large numbers of lupus patients on Protocol Committees and Advisory Boards
- BILAG does not work outside of the English speaking world, even if the PI is fluent in the language
- Background corticosteroids and CS tapering
- Confusion with defining flare rates
  - BILAG and SELENA-SLEDAI definitions vary widely
  - Flare rates vary by geography and demographics
Large Trials Are No Longer Necessary

- The FDA Guidance document recommendation of two large Phase III trials is not practical.

- Few companies have $1B to do such a trial, and their conclusions are not always as reliable as we wish. Large scale international trials often do not take into account practice patterns (no HCQ in Japan, little MMF outside of US), demographics, socioeconomic levels of attainment, cultural diversities, fluency in English, ability to treat infections differs in different countries, high levels of subjective responses in some countries, variations in stratification.

- Putting all eggs in one basket: Phase I or II trials are not being conducted with some compounds in SLE (e.g., RA) so we don’t learn about MOA (e.g., tabalumab).

- Potential corrosive influence of CROs: extra middle layer of bureaucracy, delays academic sites from joining in favor of private sites and IRBs, use of questionable clinical labs that perform ANA and other serologies.
The paradigm has changed: New approach to designing clinical trials is no longer related to mechanism of action but by what the intent is:

- Prevention of disease development
- Induction therapy for early/active disease
- Maintenance of improvement
- Flare prevention
- Domain (organ system) specific treatment
Smart Cost Effective Small Scale Trials

- Rituximab approval for vasculitis based on <200 patient trial
- Repurposing/repositioning for drugs already approved and shown to be safe can be conducted with <100 patients (e.g., LuCIN)
- Using well characterized lupus phenotypes enriches the protocol; especially in those with more active disease
Suggestions for Improvements in Trial Design

• We need an ACR 20/50/70 for lupus (Forbess, OMERACT, GSK, Lilly) using data mining from completed studies
• We need a Patient Related Outcome (PRO) that is lupus specific with cross-cultural validity (Jolly, LIT; NIH, PROMIS) and not onerous
• Embed SLEDAI and other clinical markers into the EMR (e.g., EPIC) so community rheumatologists will feel comfortable using them which will allow important clinical data to be accrued
• Avoid the perfect trial (2 years to enroll first Biogen patient, NIH Trial took 10 years and then AZA was obsolete and MMF available)
• Need to think outside the box to totally redesign clinical trials from scratch (e.g., withdrawal studies, BOLD design)
• Avoid flare rates or steroid withdrawal as a primary outcome measure
Regional Variations

• Type of patients
  – Severity and Disease manifestations
  – Genetic
• Treatment approach/SOC/Placebo-controlled trials
• Technology platforms
• Health Authorities/Ethics committees
• Patient privacy/Informed consent forms
• Pregnancy prevention
Adjudication

- Not enough adjudication
- Too Much adjudication
Changes in the landscape relevant for Nephritis trials

- Biomarkers: chemokine score, role of C1q/anti C1q, utility of C3B, urinary glomerular podocytes, anti vimentin Ab, urinary MCP, membrane endothelial proteomic receptor (mEPCR), alpha-enolase and annexin-1 antibodies
- Imaging: Ability of MRI/CT/PET to pick up ICOS, PDI, CD20, II-21, Bcl-6
- Is tubulo-interstitial disease more important than glomerular disease? How can we measure it (e.g., ischemia, inflammation, Tfh cognate interactions)?
- Relevance of biopsy, and when should it be done?
- Drugs already studied*: tacrolimus, abatacept, rituximab, leflunomide, blisbimod, mycophenolate for new studies
- Drugs not studied for nephritis*: ACTHar, voclosporin, obinutuzumab (anti CD20), sirilimus (rapamycin), BI655064 (anti CD40), laxomib (proteasome)

*Clinicaltrial.gov 3/1/17
Improving trial design and implementation

- Make the trial attractive to a study center (fewer hassles, unnecessary forms, blood tests, visits)
- Make the trial attractive to patients: chance of getting open label drug, off steroids, appeal to altruism
- Adaptive trial design: Implement of more elastic data analysis and statistics during the trial (FDA Guidance Document 2012)
- Make the trial attractive to the community rheumatologist to refer their patients
- Create a “buzz” through social networking sites
In addition to effects of a specific dose of the drug, the adverse event spectrum ideally should include a composite index which includes:

- A. Organ damage
- B. Hospitalization rates
- C. Direct and indirect costs
- D. Mortality
Recruitment and Retention

• Logistics, logistics, logistics!!!!
  • How long is the visit? How much work is missed?
  • Filling out time consuming, pointless and redundant forms
  • How long is the wait time?
  • How often are the visits? (some studies rely on long trips in traffic for a 5 minute blood draw). Is the visit really necessary? (e.g., reading a TB skin test when a digital photo can suffice) This can be a deal breaker
  • Bonding with the nurse/TLC
  • Is the center open early or late?
    – Hassle time for the investigators to take repetitive, redundant training

• What are the chances of getting drug? Open-label extension?
Conclusions/Concerns

- $10$ billion have been spent on failed efforts
- There is a widespread belief that many of the drugs had a beneficial effect in some patients
- Drugs that ‘work’ (e.g., cyclophosphamide, MMF) are not approved for SLE so cannot be part of placebo or non-inferiority trials
- Lupus is characterized by marked heterogeneity, which makes trial design more complicated
SLE: CLINICAL TRIALS – CHALLENGES, PITFALLS, AND STEPS TOWARDS SUCCESS

Daniel J Wallace MD
Clinical Professor of Medicine
Cedars-Sinai Medical Center
David Geffen School of Medicine at UCLA
Despite Improvements in Survival Rates, SLE Remains a Chronic 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.

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).

SLE Is Associated With Increased Emergency Department Visits and Hospitalization

- Emergency department and hospitalization rates do not improve with increasing SLE duration

Average Healthcare Utilization by SLE Patients

Patients with newly active SLE and 5 years of follow-up data were identified in the MarketScan Medicaid Database (1999–2005), which includes all inpatient, outpatient, emergency department, and pharmaceutical claims for more than 10 million Medicaid beneficiaries. A reference group of patients without SLE was constructed using propensity score matching. Mean age of SLE patients at diagnosis was 44 years, 93% were female, 34% were white, 28% were black, 10% were Hispanic, and 28% were "other" or missing/unknown.

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."

Organ Damage Accrual Rates in SLE Have Not Decreased Substantially Over Time

- No change in the rate of organ damage accrual 1978-1988 and 1989-1999
  - More than 40% of patients in each cohort accrued organ damage over a mean of 3 years
- No improvement in preventing organ damage in patients who had no damage (SDI*<1) at baseline

*The SLICC/ACR Damage Index (SDI) measures permanent organ damage (resulting from SLE or its sequelae, treatments, or comorbid conditions) that has accumulated since the onset of disease.

Prospective cohort study of SLE patients from Montreal General Hospital assessed for organ damage from time of diagnosis. SDI scores prior to 1993 were assigned retrospectively based on chart review. At diagnosis for Cohort 1 (diagnosis/follow-up: 1978-1988) and Cohort 2 (diagnosis/follow-up: 1989-1999), mean age: 36 and 36.5 years; 89% and 94% female; 81% and 72% white, respectively.

One-Third of SLE Patients Accrue Permanent Organ Damage Within 5 Years of Diagnosis

Percentage of Patients With Permanent Organ Damage

<table>
<thead>
<tr>
<th>Percent of Patients With SDI ≥1</th>
<th>1 Year (N=232)</th>
<th>5 Years (N=232)</th>
<th>10 Years (N=232)</th>
<th>15 Years (N=143)</th>
<th>20 Years (N=75)</th>
<th>25 Years (N=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Damage Score</td>
<td>0.11</td>
<td>0.42</td>
<td>0.77</td>
<td>1.01</td>
<td>1.26</td>
<td>2.17</td>
</tr>
</tbody>
</table>

Retrospective analysis of records for patients with ≥10 years of consistent follow-up presenting at the University College London Hospital SLE clinic. Year 0 represents time of diagnosis. Mean age at diagnosis was 31.2 years, 95% of patients were female, 72% were white, 14% were black, 10% were Asian (Indian), and 4% were “other.”

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."
Tolerance Mechanisms: Edratide (XTL)

Reactive to self antigens

Deletion

Anergy

Receptor editing

Bone Marrow

Peripheral lymphoid organs

Self antigen

Follicle

T-cell zone

Deletion

B cell

BCR

Self antigen

B cell

BCR

Self antigen

B cell

BCR

B cell

BCR

B cell

BCR

B cell

BCR

Toleragens

Lupuzor

- **Mechanism:** P140 peptide toleragen that is an immunomodulator, but not immune suppressive via a T cell approach. Derived from RNP U1-70K splicosome and reduces autophagy.

- **Efficacy:**
  - Phase 2 had clinical and statistical improvement in disease activity in patients with SLEDAI ≥6 target population. Using SRI outcome, statistically significant improvement in treatment groups at week 12. Allowed to use standard therapy.
  - Phase 3 has enrolled 100 patients; no safety concerns

Edratide anti ss DNA monoclonal antibody to the 16/6 idiotype

- Met secondary endpoint (SLEDAI) improvement, but not primary (BILAG) in large Phase II trial. Phase III trial to start in 2017

**T-Cell: Co-stimulatory Inhibitor**

- **Abatacept**
  
  **Mechanism**: fully human, soluble fusion protein made of human CTLA-4 linked to IgG1, can selectively modulate the CD80/CD86:CD28 co-stimulatory signal. New arthritis and renal trials ongoing.

  **Efficacy**:
  
  - Studies for SLE with LN and without failed to meet primary endpoint.
  
  - **LN trial**:
    - If they used different definition of clinical success for primary endpoint, post hoc shows a difference. Used ACR 13-14% in treatment vs. 6% in placebo. LUNAR 22-24% vs. 6%.
    - Post hoc suggested that abatacept treatment with fewer major BILAG A flares, as well as improvements in exploratory QOL measures, reductions in dsDNA, and also urinary protein.

  - **Non-LN trial**:
    - Study design issues with high dose steroids. Post-hoc proportions showed significantly less flares (BILAG A and physician assessed).
The roles of ICOS/B7RP-1 in T\(_{FH}\) cell development, humeral immunity and T\(_{h}17\) cell expansion make it a rational target for human autoimmune diseases.

- B7 related protein-1 (B7RP-1) binds to ICOS on activated T cells impacting T cell effector functions and B cell differentiation and function.
- Blockade of B7RP-1 represents a promising strategy for the treatment of SLE and other autoimmune diseases.
- EULAR 2017, Madrid, Lupus arthritis trial of 20 patients with safety established.
IMMU-115 (milatuzumab) - humanized antibody targeting the CD74 antigen present on antigen-presenting cells (APC), including B-cells and dendritic cells.


• When given IV, slowing infusions plus premedication controlled reactions (Grade 1-2) at doses up to 16 mg/kg.

• A concentrated formulation was developed for subcutaneous (SC) injection.

Dysregulation of APCs may also occur in nonmalignant disorders.

• In preclinical studies, IMMU-115 prevented GVH disease, modestly inhibited B-cell proliferation, and enhanced factors underlying lymphocyte recruitment.

• IMMU-115 reduced interferon-α production in stimulated peripheral blood mononuclear cells from healthy donors and SLE patients.

IMMU-115 could thus potentially help control underlying immune responses responsible for autoimmunity.

Wallace et al, EULAR 2016, London