057 - Systemic Lupus Erythematosus: Difficult to Treat Systemic Lupus Erythematosus

Monday, Nov. 9, 2015
4:30 PM - 6:00 PM

Eliza Chakravarty, MD, MS
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Faculty Disclosure

Eliza Chakravarty, MD, MS

E. Chakravarty, Nothing to disclose
057 - Systemic Lupus Erythematosus: Difficult to Treat Systemic Lupus Erythematosus

Eliza Chakravarty, MD, MS

Session Overview:

In this session, participants will learn about and discuss strategies to treat severe manifestations of systemic lupus erythematosus (SLE). A paucity of robust, clinical trial data complicates treatment decisions for many SLE manifestations. In addition, the majority of medications that are used to treat SLE have not been formally approved by the U.S. Food and Drug Administration for this disease.

This case-based session will serve to review the established data and provide expert consensus on the treatment of several SLE manifestations that a clinician might see in his/her practice. The session will be very interactive with a mixture of presented case studies and questions from participants. Prepared cases will include patients from Dr. Dall’Era’s Lupus Clinic with refractory cutaneous lupus, challenging lupus nephritis, and severe thrombocytopenia.

Upon completion of this session, participants should be able to:

- review established data from the medical literature in order to improve clinical practice related to the treatment of SLE
- examine management strategies for refractory cutaneous manifestations of systemic lupus erythematosus
- discuss management of progressive or relapsing lupus nephritis
- discuss management of severe cytopenias
OBJECTIVES:
Review current guidelines for treatment of SLE
Gaps in knowledge
Approaches to the refractory patient
- Nephritis
- Cutaneous LE
- Cytopenias

DIFFICULT TO TREAT LUPUS: ACR MEET THE PROFESSOR

No conflicts of interest to disclose

We will be discussing off-label use of almost all medications
- This is lupus, after all

SYSTEMIC LUPUS ERYTHEMATOSUS
Heterogeneous disease
Can effect any organ
Heavy burden from constitutional symptoms
Active disease vs. damage
Fibromyalgia/ Chronic pain

MEECHANISMS OF SLE IMMUNOPATHOLOGY

Incurable disease

Goals of treatment:
- Manage symptoms and improve function/QOL
- Reduce inflammation
- Prevent organ damage
- Prevent damage from medications
- Reduce co-morbidity
- Minimize disability
- Pharmacological and non-pharmacological options

Patient Satisfaction With Conventional Treatments
Survey of 914 patients by Lupus Europe and the LFA

<table>
<thead>
<tr>
<th>% Female</th>
<th>% Age 20-50</th>
<th>% fatigue</th>
<th>% with active joints/mob</th>
<th>% where Rx affects ADL</th>
<th>% on steroids</th>
<th>% dissatisfied w/current Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>95</td>
<td>80</td>
<td>85</td>
<td>83</td>
<td>82.1</td>
<td>51.2</td>
<td>51.7</td>
</tr>
</tbody>
</table>

Published standards of Care
Absence of FDA approved therapies
Based upon evidence based studies and consensus from SLE experts
Quality indicators

Treatments for SLE that Are Not New Biologics AND Are Approved for Lupus

<table>
<thead>
<tr>
<th>Most Common</th>
<th>Used For</th>
<th>Evidence Base</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most Common</td>
<td>Used For</td>
<td>Evidence Base</td>
</tr>
<tr>
<td>NSAIDS</td>
<td>ASA</td>
<td>Symptomatic</td>
</tr>
<tr>
<td>NSAIDS</td>
<td>Cox 1-2 Inh</td>
<td>Symptomatic</td>
</tr>
<tr>
<td>Anti-Materials</td>
<td>Hydroxychloroquine</td>
<td>Mild LE/ prevention</td>
</tr>
<tr>
<td>Steroids</td>
<td>Prednisone</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Immune Suppressants</td>
<td>MMF Methotrexate</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Cytotoxics</td>
<td>Cyclophosphamide</td>
<td>Severe</td>
</tr>
<tr>
<td>Anti-Coagulants</td>
<td>Coumarins</td>
<td>Prevention</td>
</tr>
</tbody>
</table>

Treatments for Lupus in 503 Patients Across US in 2010

Survey of 531 people with lupus, 93% women; 86% 20–50 years old

Treatment Considerations

Does This Patient Have the Problem the Treatment Solves?
When to Add on? When to Replace?
When to Add on? When to Replace?
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When to Add on? When to Replace?
Lupus Nephritis

Many large randomized clinical trials and meta-analyses

“Hard” outcomes

Easiest of SLE manifestation to generate evidence based guidelines

Guidelines for the treatment of Lupus Nephritis

Use of HCQ (in all SLE patients)

Use of ACE/ARB in patients with proteinuria (reduction by ~30%)

Aggressive control of HTN

Addition of Statins (level C evidence)

IV cyclophosphamide:
- Low dose: 500 mg IV Q 2 weeks x 6 doses
- High dose: 500-1,000g/m² IV Q month x 6 doses


Low-Dose (Euro-lupus) Cyclophosphamide

- Mainly Caucasian
- Mild to moderate LN
- Proteinuria: 3g/d; SCr: 1.15 mg/dl
- Trend toward fewer infections in the Low-Dose group
- Premature ovarian failure low in both

Response Rate by Race: ALMS Trial: Induction

Response rates with ideal treatment remain at ~50%
Almost half of LN patients will be non-responders

Accept partial response?
- If one induction method fails, try the other
- What to do if both fail?
- Role of repeat biopsy

Look for other reasons for failure:

- Not taking medications
  - Side effects
  - Access to expensive therapies
  - Too many medicines
- Progressive damage
  - Uncontrolled hypertension
  - Uncontrolled hyperglycemia

Alternative Therapies

- Rituximab
- Tacrolimus/calcineurin inhibitors
- Combination therapy
- Plasma exchange
- IVIG
- Immunoablation
- Stem cell transplantation
- Plasma cell inhibitors (borotizumab)

Rituxilup: A Steroid-Free Protocol

<table>
<thead>
<tr>
<th>Class III, IV, V</th>
<th>LN</th>
<th>Non-Inferiority Trial</th>
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<tbody>
<tr>
<td>Total</td>
<td>37</td>
<td>16</td>
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<tr>
<td>Class III</td>
<td>(83%)</td>
<td>(64%)</td>
</tr>
<tr>
<td>Class IV</td>
<td>(63%)</td>
<td>(54%)</td>
</tr>
<tr>
<td>Class V</td>
<td>(54%)</td>
<td>(54%)</td>
</tr>
</tbody>
</table>

Preliminary Rituxilup Data-Single Center

- Remission
- Median time to remission: 3 months (1-18)
The LN Therapeutics Landscape

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type</th>
<th>Target</th>
<th>Clinical Trial Status</th>
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</thead>
<tbody>
<tr>
<td>Abatacept</td>
<td>CTLA4-Ig</td>
<td>CTLA4-B7 Interaction</td>
<td>Two Phase 2/3 Trials FAILED but ENCOURAGING</td>
</tr>
<tr>
<td>Laquinamod</td>
<td>Small Molecule</td>
<td>Inflammation</td>
<td>Phase 2-ENCOURAGING</td>
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<tr>
<td>Rituximab</td>
<td>Monoclonal Antibody</td>
<td>CD20</td>
<td>Phase 3-FAILED</td>
</tr>
<tr>
<td>Sirukumab</td>
<td>Monoclonal Antibody</td>
<td>IL-6</td>
<td>Phase 2-FAILED</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Proteosome Inhibitor</td>
<td>Plasma Cells</td>
<td>Phase 4-STOPPED</td>
</tr>
<tr>
<td>Anti-CD40 Ligand</td>
<td>Monoclonal Antibody</td>
<td>CD40 Ligand</td>
<td>Phase 2-STOPPED</td>
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<tr>
<td>Belimumab</td>
<td>Monoclonal Antibody</td>
<td>Blys</td>
<td>Phase 3-Underway</td>
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<td>Anti-TWEAK</td>
<td>Monoclonal Antibody</td>
<td>TWEAK</td>
<td>Phase 2-Underway</td>
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<tr>
<td>Medi-546</td>
<td>Monoclonal Antibody</td>
<td>INF-α Receptor</td>
<td>Planned</td>
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<tr>
<td>Ecolizumab</td>
<td>Monoclonal Antibody</td>
<td>C5</td>
<td>Proposed</td>
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</tbody>
</table>

Pankh and Rovin, AJK, 2014

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Cutaneous Lupus

Cutaneous lupus: classification

<table>
<thead>
<tr>
<th>SLICC Clinical Criteria</th>
<th>ACR Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Acute cutaneous LE, including butterfly rash, (do not count: facial discoid), discoid lupus; toxic epidermal necrolysis variant of SLE; maculopapular lupus rash; photosensitive lupus rash in the absence of dermatomyositis or subacute cutaneous lupus (manifestation of palisading and/or annular polyangiitis that resolves without scarring, although occasionally with post inflammatory dyspigmentation or telangiectasias)</td>
<td>1. Malar Rash</td>
</tr>
<tr>
<td>2. Chronic cutaneous lupus, including classical discoid rash localized (above the neck) of generalized (above and below the neck); hypertrophic (potentiated) lupus panniculitis (potentially); discoid lupus, lupus erythematosus profundus, chilblains lupus, discoid lupus with palm planar overlap</td>
<td>2. Photosensitivity</td>
</tr>
<tr>
<td>3. Oral ulcers, palate, buccal, lingual or nasal ulcers in the absence of other causes such as vasculitis, Behcet, infection,ngo, or other causes of oral ulcers, or oral ulcers in the absence of the causes such as systemic lupus erythematosus, drugs, iron deficiency and androgenic alopecia</td>
<td>3. Discoid Rash</td>
</tr>
<tr>
<td>NA</td>
<td>4. Oral Ulcers</td>
</tr>
</tbody>
</table>

Cutaneous Lupus

Guidelines/Standard of care:

- Antimalarials
- Topical glucocorticoids
- Systemic glucocorticoids
- Methotrexate

Non-pharmacologic measures:

- Sun avoidance
- Smoking cessation
**Immunopathology: clues to treatment options**

Possible mechanisms of CLE
- TLR 7/9 → plasmacytoid DCs → IFN alpha
- UV light exposure → apoptosis of keratinocytes, increased pro-inflammatory cytokines
  - IFN-gamma
  - TNF alpha
  - BLyS (BAFF)
  - IL-6
  - IL-10 (pro-inflammatory in some circumstances)
  - IL-17
  - CXCL10 (chemokine recruiting immune cells to skin)

**Potential reasons for failure**

Medications just not working
- Non adherence
- Low blood/serum levels of drug
- Post inflammatory hyperpigmentation/scarring
- Transformation to Squamous Cell Ca

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**Hydroxychloroquine efficacy may be concentration dependent**

- French study of 300 CLE patients
  - 160 DLE, 86 SCLE, 94 other CLE
  - All treated with HCQ >3 months
  - Whole blood HCQ concentrations by HPLC

<table>
<thead>
<tr>
<th>Variable</th>
<th>Complete remission</th>
<th>Partial remission</th>
<th>Treatment failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%)</td>
<td>114 (38%)</td>
<td>86 (29%)</td>
<td>100 (33%)</td>
</tr>
<tr>
<td>Median (range) blood HCQ concentration (ng/mL)</td>
<td>910 (&lt;50-3057)</td>
<td>692 (&lt;50-2843)</td>
<td>569 (&lt;50-2242)</td>
</tr>
<tr>
<td># with HCQ &lt; 200 ng/mL (non-adherent)</td>
<td>8</td>
<td>8</td>
<td>14</td>
</tr>
</tbody>
</table>

**Factors associated with HCQ concentrations**
- Univariate: dose (mg/Kg), missing tablets, BMI, weight
- Multivariable: Dose, missing tablets
- NO correlation with: subtype of CLE, dose by ideal body weight, height, smoking, alcohol use

**Factors associated with complete remission**
- Univariate: DLE (negative), and HCQ concentration
- Multivariate: HCQ concentration, DLE (negative)
- NO correlation with: daily HCQ dose, missing tabs, presence of SLE, BMI, smoking, alcohol use

**HCQ levels and clinical response**

**Alternative Therapies**

- Combination anti-malarials
  - HCQ + quinacrine (100 mg/day)
- Topical immunmodulators
  - Tacrolimus 0.1% ointment
- Classic “SLE” medications
  - MTX
  - Azathioprine, mycophenolate mofetil
  - Calcium inhibitors
  - Rituximab, belimumab
- Others
  - Dapsone (25-150 mg/d; avoid in G6PD deficiency)
  - Oral retinoids (Acitretin, isotretinoin)
  - Thalidomide (need to be an approved provider)

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*Kirschhof, MG, Dutz JP. Rheum Dis Clin NA 2014;14:455*


*Oksan LG, Werth VP. Best Pract Res Clin Rheumatol 2013;27:391*
**Belimumab: Combined results from phase III studies**

**Baseline SELENA-SLEDAI Organ Involvement**

- More than 94% of patients had 2 or more organ systems involved at baseline.


**Rituximab**

Case series of 17 SLE patients with CLE
- All failed HCQ, topicals, and standard IS
- Received Ritux 1g iv X 2 Q2weeks + 750 mg IV cyclophosphamide X 1 the day after the first rituximab dose


**Rituximab**

Case series of 17 SLE patients with CLE
- All failed HCQ, topicalis, and standard IS
- Received Ritux 1g iv X 2 Q2weeks + 750 mg IV cyclophosphamide X 1 the day after the first rituximab dose
  - 53% response after 1st course
  - 71% relapse after mean time 10 months
  - 78% response after 2nd course
  - Sustained remission -18 (9-24) months
  - B-cell repopulation at 7 (6-60) months


**Rituximab in CLE**

- 26 of 82 SLE patients receiving rituximab had active CLE
  - Bilag A or B disease, failed other therapies
  - Baseline HCQ and immunosuppressants continued
  - Low rate of mucocutaneous response (35%) at 6 months
    - 43% (6/14) response in ACLE
    - 0 of 8 patients responded with CCLE
    - Flares in 12 patients (prior no disease or ACLE)


**More alternative therapies → Less Data**

Most described in case reports or small series
- Tacrolimus lotion [JAMA derm 2015]
- Imiquimod cream [ACTA Dermatovenerol Croat 2014]
- Aprimilast [J Drugs Dermatol 2012]
- Fumaric acid esters [JAAD 2013]
Case….Discoid Lupus

Expert Consensus Treatment Algorithm for SLE

<table>
<thead>
<tr>
<th>Organ</th>
<th>1st Line</th>
<th>2nd Line</th>
<th>3rd Line</th>
<th>Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional</td>
<td>GC/HOQ16</td>
<td>MMF</td>
<td>RTX/BLM</td>
<td>60%</td>
</tr>
<tr>
<td>Widespread DLE</td>
<td>HCO ± GC</td>
<td>AZA/Antimalarial</td>
<td>AZA/MMF or MTX</td>
<td>70%</td>
</tr>
<tr>
<td>Polyarthritis</td>
<td>HCO ± GC</td>
<td>MTX</td>
<td>RTX</td>
<td>80%</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>GC ± HCO</td>
<td>MMF/AZA/MTX</td>
<td>RTX/BLM</td>
<td>75%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>HCO ± GC</td>
<td>AZA/MMF</td>
<td>RTX/IVIG/IV CYC</td>
<td>50%</td>
</tr>
<tr>
<td>CNS Lupus</td>
<td>GC + IV CYC</td>
<td>RTX/IVIG/Pherasis</td>
<td>N/A</td>
<td>60%</td>
</tr>
<tr>
<td>Nephritis (III/IV)</td>
<td>GC+ MMF</td>
<td>IV CYC</td>
<td>RTX</td>
<td>70%</td>
</tr>
</tbody>
</table>


Thrombocytopenia

Often associated with aPL antibodies

Usually asymptomatic and does not require specific therapy (>50,000)

Independently associated with poor survival and poor prognosis in SLE
  - Even in the absence of hemorrhagic complications
  - Associated with hemolytic anemia, renal disease, NPSLE, and antiphospholipid antibody syndrome


Thrombocytopenia—Immediate Treatment

- Glucocorticoids offer rapid response in the setting of dangerously low platelets
  - Mean time to PLT>50k→7.2 days
  - Sustained response very rare

- IVIG—Transient response in ~65%
  - Mean time to PLT>50k was 4.6 days
  - No sustained response


Thrombocytopenia—Long term treatment

- HCQ—only studied in 11 patients
  - 7/11 had sustained response and lower prednisone requirement

- Danazol—weak adrogenic steroid
  - Add on to steroids
  - Doses 400-800 mg daily
  - Sustained response seen in many
  - Slow onset of efficacy


**Immunosuppressants**
- Aza
- Cyclosporine
- Cyclophosphamide
- Vincristine
- MMF
  - Response rates vary

**Dapsone**
- Second line therapy for ITP (after steroids)
- Good sustained response
- Slow onset of action
- Must check G6PD

**Rituximab**
- Total of 6 cohort studies of Ritux in SLE thrombocytopenia
  - 50-92% response rate
  - Rituximab found to be a useful salvage therapy

**Splenectomy**
- Last resort, concern for infectious complications
- Good, but not universal response rates
- VACCINATE prior to procedure

**Thrombotic Thrombocytopenia Purpura**
- Classic pentad:
  - Thrombocytopenia
  - Microangiopathic hemolytic anemia
  - Fever
  - Neurological deficits
  - Renal dysfunction
- Even in the era of PEx...
  - 34-62% mortality in SLE + TTP
  - Vs. >20% in non-SLE TTP
- Differential diagnosis of TTP in SLE
  - Catastrophic APS
  - Malignant hypertension

**TTP and SLE**
- Associated with numerous autoantibodies, endothelial damage, & platelet aggregation
  - Anti endothelial-cell antibodies
  - Antiplatelet antibody
  - Anti-ADAMTS13 antibodies
- Role of ADAMTS13 deficiency less clear in SLE-associated TTP

**Laboratory abnormalities**
- 100% blood smears + Schistocytes
- 78% Coombs negative
- ADAMTS13 activity: 41% severe deficiency; 6.3% moderate deficiency; 37% mild deficiency
- 8% Coombs negative
- Anti-ADAMTS13 antibodies + in 97% of 22 cases tested

**TTP and SLE: treatment**
- Plasma exchange
- Pulse glucocorticoids
- Cytotoxics
  - Cyclophosphamide
  - MMF
  - Vincristine
  - Cyclosporine A
- Rituximab
- Other therapies
  - IVIG
  - Anticoagulants
  - Bilateral nephrectomy (1 case)
Eculizumab

- Targets C5 and prevents formation of the membrane attack complex
- Approved for the treatment of paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome
- Case report of successful use in refractory TTP/SLE

TTP & SLE

- Key lies in early diagnosis
- Schistocytes on peripheral smear
- Neurologic symptoms due to small vessel cerebral ischemia
- ADAMTS13 tests take days to weeks to come back
- Early initiation of plasma exchange and other aggressive therapies

Case….SLE

Thrombocytopenia

Conclusions

- Lupus can be really hard to treat
- Heterogeneous clinical manifestations/heterogeneous immunopathologies
- Balance medication toxicies with efficacy Adherence
- How long before considering non-response
- Little evidence to base treatment decisions beyond first line therapies

Questions
Discussion
Additional Cases

Thank you!
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