Outcome Measures in Lupus Nephritis Trials

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Background and Significance

• There is a lack of clarity about choice of outcome measures for lupus nephritis trials

• Variability in outcome measures influences clinical trial results and slows development of safe and effective therapies for lupus nephritis

• Standardized, evidence-based outcome measures would be highly beneficial in the conduct of clinical trials, particularly given high cost of trials and scarcity of trial subjects
Overarching Project Goals

• Develop a set of renal response outcome measures for use in lupus nephritis trials that correlate with long-term preservation of renal function and reduction in lupus nephritis flares

• FDA acceptance of these outcome measures for use in lupus nephritis trials
Additional Project Goals

• Determine the renal response outcome measures that best differentiate between experimental and control arms in lupus nephritis trials

• Provide definitions for commonly used terms such as “severe lupus nephritis” and “refractory lupus nephritis”
Study Design: Three Phases of Project

I. Review of lupus nephritis clinical trial literature (each trial reviewed by two investigators and data entered into Excel spreadsheet)

II. Analyses of primary data from large datasets (randomized clinical trials and longitudinal cohorts)

III. Derivation of consensus recommendations for clinical trial outcome measures and definitions of terms
Phase I Literature Review

- Pub-Med search for randomized, controlled lupus nephritis trials with > 50 subjects resulted in 31 trials
- LNTN investigators who participated in review:
  - Cynthia Aranow
  - Eduardo Borba
  - Maria Dall’Era
  - Michelene Hearth-Holmes
  - Annette Jacobi
  - Meenakshi Jolly
  - Ken Kalunian
  - Hilda Fragoso Loyo
  - Meggan Mackay
  - Ana Malvar
  - Elena Massarotti
  - Thomas Rauen
  - Brad Rovin
  - Dawn Smilek
  - Laura Straub
  - Y.K.O. Teng
Phase I Literature Review

- Published trial dates ranged from 1978-2013
- # subjects per trial ranged from 50-370
- Induction trials and maintenance trials were represented
- Blinded and open-label trials were represented
- Variability in treatment regimens, trial duration, outcome measures
Phase I Literature Review

- Shift in emphasis of primary outcome measures
  - Early studies emphasized treatment failure, loss of renal function
    - Time to end stage renal failure
    - Doubling of SCr
    - Death/renal failure/start of dialysis
    - Treatment failure
  - Later studies emphasized good renal response to treatment (complete and partial response)
<table>
<thead>
<tr>
<th></th>
<th>Complete Renal Response</th>
<th>Partial Renal Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proteinuria</strong></td>
<td>• &lt;0.2g/d; 0.3g/d; 0.33g/d; &lt;0.5g/d; &lt;1.0g/d</td>
<td>• &gt;50% reduction</td>
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<tr>
<td></td>
<td>• UP/C &lt; 3 if nephrotic or &gt;50% reduction if subnephrotic</td>
<td>• &gt;50% reduction to &lt;3g if nephrotic or to &gt;1g if non-nephrotic</td>
</tr>
<tr>
<td></td>
<td>• Within 10% of normal</td>
<td>• &gt;50% reduction to 0.3-3.0 g/d</td>
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<tr>
<td></td>
<td></td>
<td>• &gt;50% reduction to &lt; 1.5g/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• &gt;50% reduction to &lt; 1.5g if baseline &lt; 3g or to &lt; 3g if baseline &gt; 3g</td>
</tr>
<tr>
<td><strong>SCr or eGFR</strong></td>
<td>• &lt;1.2mg/dl; &lt; 1.4mg/dl</td>
<td>• No doubling of SCr</td>
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<tr>
<td></td>
<td>• &lt;130% of lowest level</td>
<td>• &lt; 150% of lowest level of SCr</td>
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<tr>
<td></td>
<td>• “Stable or improved renal function”</td>
<td>• &lt; 10% increase in SCr</td>
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<tr>
<td></td>
<td>• &lt;15% worsening of SCr</td>
<td>• &gt; 50% improvement in SCr</td>
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<td>• Within 10% of normal of SCr</td>
<td>• &lt; 25% increase in SCr</td>
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<td></td>
<td>• &lt; 130% lowest SCr</td>
<td>• &lt; 130umol/L if baseline 130-260umol/L</td>
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<td></td>
<td>• No doubling of SCr</td>
<td>• &lt; 115% of baseline SCr</td>
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<tr>
<td><strong>Urinalysis</strong></td>
<td>• &lt; 10 dysmorphic RBC/hpf + no cellular casts</td>
<td>• &gt; 50% reduction in dysmorphic RBCs and cellular casts</td>
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<tr>
<td></td>
<td>• &lt; 5 RBCs, &lt; 2+ dipstick, no RBC casts</td>
<td>• &gt; 50% improvement in sediment</td>
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<td></td>
<td>• &lt; 5 RBCs + &lt; 5 WBCs/hpf</td>
<td>• RBCs/hpf ≤ 50% above baseline and no RBC casts</td>
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<tr>
<td></td>
<td>• RBCs &lt; 50% above baseline + no RBC casts</td>
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</tr>
<tr>
<td></td>
<td>• &lt; 5 RBCs/hpf + no RBC casts</td>
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<tr>
<td></td>
<td>• &lt; 10 RBCs/hpf</td>
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</tbody>
</table>
Study Design: Three Phases of Project

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<table>
<thead>
<tr>
<th>Controlled Trials</th>
<th>Longitudinal Cohorts</th>
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<tbody>
<tr>
<td>ALMS</td>
<td>LUMINA</td>
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<tr>
<td>LUNAR</td>
<td>Hopkins Lupus Cohort</td>
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<tr>
<td>ACCESS</td>
<td>Euro-Lupus Nephritis Cohort</td>
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<td></td>
<td>Ohio State University Cohort</td>
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<td></td>
<td>Miami Cohort</td>
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<td>Toronto Cohort (pediatrics)</td>
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<td></td>
<td>Karolinska Cohort</td>
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<td>UCLA Cohort</td>
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<td>Pittsburgh Cohort</td>
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<td>Rome Cohort</td>
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<td>Barcelona Cohort</td>
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Phase II Analyses

Potential response measures (6, 12, 18 months)
- Proteinuria
- SCr or eGFR
- Urine sediment
- Serologies
- Blood pressure
- Lipids
- Serum albumin

Long-term outcomes (3, 5, 10 years)
- ESRD
- Doubling SCr
- 50% increase in SCr
- Chronic kidney disease
- Renal flares
- Death
Additional Questions

• Potential interaction between race/ethnicity and outcome measures
  - Do outcome measures perform differently in different racial/ethnic groups?
  - In different racial/ethnic groups:
    - Should there be different goals in terms of proteinuria reduction and improvement in renal function?
    - Do any of the individual components of an outcome measure (proteinuria, SCr, urine sediment) have more/less utility?
    - Are certain combinations of the components of the outcome measures more important in predicting long-term outcome?
Next Steps

• Complete Phase I

• Create web-based system to store and manage the large patient data sets (with ASN)

• Begin analyses on primary data received from trials and longitudinal cohorts

• Consider setting aside subset of data as validation cohort

• Continue to enlist participation of trials and cohorts
Thank you

- Questions and Discussion