# 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)

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

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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)**

| | Complete Renal Response | Partial Renal Response |
|---|---|---|
| **Proteinuria** | • <0.2g/d; 0.3g/d; 0.33g/d; <0.5g/d; <1.0g/d<br>• UP/C < 3 if nephrotic or >50% reduction if subnephrotic<br>• Within 10% of normal | • ≥50% reduction<br>• ≥50% reduction to <3g if nephrotic or to >1g if non-nephrotic<br>• ≥50% reduction to 0.3-3.0 g/d<br>• ≥50% reduction to < 1.5g/d<br>• ≥50% reduction to ≤ 1g if baseline ≤ 3g or to ≤ 3g if baseline > 3g |
| **SCr or eGFR** | • <1.2mg/dl; < 1.4mg/dl<br>• <130% of lowest level<br>• "Stable or improved renal function"<br>• ≤15% worsening of SCr<br>• Within 10% of normal of SCr<br>• < 130% lowest SCr<br>• No doubling of SCr | • No doubling of SCr<br>• < 150% of lowest level of SCr<br>• ≤ 10% increase in SCr<br>• ≥ 50% improvement in SCr<br>• ≤ 25% increase in SCr<br>• < 130umol/L if baseline 130-260umol/L<br>• ≤ 115% of baseline SCr |
| **Urinalysis** | • < 10 dysmorphic RBC/hpf + no cellular casts<br>• < 5 RBCs, < 2+ dipstick, no RBC casts<br>• < 5 RBCs + < 5 WBCs/hpf<br>• RBCs < 50% above baseline + no RBC casts<br>• < 5 RBCs/hpf + no RBC casts<br>• < 10 RBCs/hpf | • ≥ 50% reduction in dysmorphic RBCs and cellular casts<br>• ≥ 50% improvement in sediment<br>• RBCs/hpf ≤ 50% above baseline and no RBC casts |

# 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 II Trials and Cohorts

| Controlled Trials | Longitudinal Cohorts |
| --- | --- |
| ALMS | LUMINA |
| LUNAR | Hopkins Lupus Cohort |
| ACCESS | Euro-Lupus Nephritis Cohort |
| | Ohio State University Cohort |
| | Miami Cohort |
| | Toronto Cohort (pediatrics) |
| | Karolinska Cohort |
| | UCLA Cohort |
| | Pittsburgh Cohort |
| | Rome Cohort |
| | Barcelona Cohort |

# Phase II Analyses

**Potential response measures (6,12,18 months)**

- Proteinuria
- SCr or eGFR
- Urine sediment
- Serologies
- Blood pressure
- Lipids
- Serum albumin

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**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**