

## Biennial report

### Study Groups

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#### Title of the study group: EULAR Lupus Nephritis Trials Study Group

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Date of annual report submission: March 23, 2018

#### Summary of last year's activities

The Lupus Nephritis Trials Network (LNTN) launched in July 2012. As articulated in its original mission statement, the goal of the LNTN "is to improve outcomes for patients with lupus nephritis through: (1) the conduct of clinical trials designed to prevent chronic kidney disease and end-stage kidney failure, and (2) the development of clinical trial methodologies that improve and simplify the assessment of therapeutic agents." Membership in the LNTN has grown steadily since its inception to the point that it now includes 202 member investigators (including adult and pediatric rheumatologists, nephrologists, internists, and immunopathologists) from 40 countries on 5 continents.

As summarized below, during its first five years the LNTN has launched major trials on both sides of the Atlantic, has competed successfully to participate in important new NIH-sponsored projects, and has generated informative data to address key unanswered questions about trial design and interpretation.

#### Major Research Achievements

- 1) Evidence-Based Recommendations for Outcome Measures in Lupus Nephritis – The inaugural project of the LNTN was designed to address two key unanswered questions that have led the FDA to be skeptical of proposed clinical trial designs. The FDA has been concerned about the lack of evidence that could link outcome measures used in lupus nephritis trials with the long-term outcomes that are most important to people with lupus nephritis – specifically, preservation of renal function and prevention of end-stage renal disease. There also has been considerable controversy about the interpretation of data used to assess renal disease activity, especially microscopic hematuria. In large part for these reasons, the FDA withdrew its guidance document for lupus nephritis trials and has been hesitant to issue a new one until better data are available to address their concerns. The absence of such guidance has been a serious impediment to the development of lupus nephritis trials.

In order to address the FDA's concerns with data, the LNTN undertook a transatlantic collaboration to examine long-term outcome data from the Euro-Lupus Nephritis Trial and the MAINTAIN Trial. In two publications based on independent data sets, LNTN showed that: (i) improvement in proteinuria during the course of a clinical trial correlates strongly with long-term preservation of renal function; (ii) inclusion of microscopic hematuria actually undermines the predictive value of the trial outcome measure; (iii) complete response correlates better with long-term preservation of renal function than total (complete plus partial) response; (iv) trial results at 12 months correlate better with long-term outcome than trial results at 3 or 6 months; and (v) a proteinuria cut-off of 0.7–0.8 gm/day at 12 months correlates best with long-term outcome (Arthritis Rheumatol 2015; 67:1305-13 and Lupus Sci Med 2015;e000123. doi: 10.1136/lupus-2015-000123). The ability to demonstrate, and then to confirm, these findings using independent patient populations illustrates the impact that can be achieved through the collaborative spirit of the LNTN investigators. This outcome measure has since been independently validated by two other groups (Ugolini-Lopes MR, Seguro LPC, Castro MXF, *et al.* Lupus Sci Med 2017;4. doi:10.1136/lupus-2017-000213; and Fung WA, Su J, Touma Z. Biomed Res Int 2017; 2017: 5312960).

2. Analysis of Longitudinal Lupus Nephritis Cohorts – Ultimately, the most important outcomes in lupus are the long-term outcomes that occur in the course of actual practice rather than outcomes that occur in the context of tightly controlled drug trials. Therefore, we are in the process of validating our analysis of trial results (see above) by analyzing data from numerous longitudinal lupus nephritis cohorts worldwide. This analysis is currently underway and includes cohorts from Mexico, Canada, Japan, Italy, Eastern Europe, Hong Kong, Scandinavia, and the United States (Ohio State University, Johns Hopkins University, University of North Carolina, LUMINA). This remarkable degree of worldwide collaboration is a central feature of LNTN. It will enable us to evaluate subjects from diverse racial, ethnic, and geographic groups. A manuscript describing a risk model based on these data is currently under review.
3. Clinical Trials – Two major therapeutic trials have been launched by the LNTN. Together, they constitute a coordinated approach to understanding a confusing paradox that has emerged regarding the role of rituximab in the treatment of lupus nephritis: specifically, how can we reconcile the apparent value of rituximab in case series with the failure of rituximab in controlled trials. Our trials address distinct hypotheses regarding this issue:
  - a) The RING Trial – tests the hypothesis that rituximab is effective in the treatment of lupus nephritis that has been refractory to other therapeutic approaches. This multinational trial is currently enrolling subjects.
  - b) The CALIBRATE Trial – tests the hypothesis that maintenance therapy with anti-BAFF can prevent repopulation with autoreactive B cells following rituximab treatment. This NIH-funded, US-based trial has completed enrollment ahead of schedule. Results will be forthcoming during the second quarter of 2018.