COMPARING DISEASE FEATURES AND OUTCOMES IN PATIENTS WITH MEMBRANOUS AND PROLIFERATIVE LUPUS NEPHRITIS

BACKGROUND

Lupus nephritis (LN) is one of the most severe manifestations of Systemic Lupus Erythematosus (SLE). A recently published international inception cohort study demonstrated renal involvement in 38.3% of patients with SLE (1). As well as being associated with end-stage renal disease (ESRD) and death, severe renal involvement is also associated with poorer quality of life (1).

LN is currently classified according to the 2003 *International Society of Nephrology/Renal pathology Society* (ISN/RPS) classification system, which is based on histopathology (2). Most patients have proliferative lupus nephritis (PLN), which has been the most studied type of LN. Membranous lupus nephritis (MLN) is less frequent, accounting for 10-20% of the cases (3). In some patients, there is a combination of the two types – mixed LN.

Recently, our group conducted a single-centre retrospective observational study, analysing the University College London Hospital LN cohort. The results, not yet published, were presented at the "XX Congresso Português de Reumatologia". From a cohort with 209 patients with biopsy-proven LN, 187 patients were included: 135 with proliferative, 38 with membranous and 14 with mixed LN. The groups differ regarding ethnicity (p=0.044) - higher proportion of Caucasians with PLN versus higher proportion of Afro-Caribbeans with MLN. Patients with MLN present with higher C3 levels (median of 0.81 in MLN versus 0.61 in PLN and 0.64 in mixed LN; p=0.002) and considerably lower anti-dsDNA levels than the ones with proliferative changes (median of 80 in MLN versus 863 in PLN and 296 in mixed LN; p=0.000). Interestingly, levels of proteinuria at the time of the renal biopsy did not differ significantly between groups. Thirty-four patients with PLN, 3 with MLN and 2 with mixed nephritis, progressed to ESRD. Cumulative renal survival rates at 5, 10, 15 and 20 years were 91, 81, 75 and 66% for PLN and 100, 97, 92 and 84% for MLN, respectively, with a significant difference between groups (p=0.029).

Our hypothesis is that the Portuguese cohorts of membranous and proliferative LN also show significant differences regarding clinical and serologic features and outcomes.

OBJECTIVES

1. To compare membranous and proliferative lupus nephritis patients regarding:

    a) Clinical and laboratory presentation

    b) Serologic profiles (autoantibodies and C3)

    c) Renal and overall survival

2. To identify predictors of:

    a) ESRD

    b) Remission

    d) Chronic kidney disease (CKD)

    e) Death

METHODS

1. Study design

Multi-centre observational study, with retrospective analysis of a prospective cohort, using data from the Portuguese registry of rheumatic diseases – Reuma.pt.

Inclusion criteria:

a) SLE classified according to ACR(4) or SLICC(5) criteria;

b) Biopsy-proven lupus nephritis classified according to the ISN/RPS 2003 classification system (2).

Ethical considerations:

We have ethical approval from the *Institute of Child Health / Great Ormond Street Hospital Research Ethics Committee.*

The research will be conducted in accordance with the Helsinki Declaration as revised in 2013.

2. Variables

Demographic data: year of birth, sex, ethnicity

Clinical data:

a) Year of diagnosis of SLE, classification criteria fulfilled;

b) Date of diagnosis of nephritis (month and year), number of renal biopsies, date of each renal biopsy (month and year), class of LN in each biopsy, development of ESRD (yes/no) and date (year), renal transplant (yes/no), recurrence of nephritis in the allograft (yes/no);

c) SLEDAI at the time of LN diagnosis and at 12 months after diagnosis.

d) Year of last visit, year and cause of death (if occurred);

e) Treatment with antimalarials, immunosupressants, corticosteroids, renin–angiotensin–aldosterone system blockers and non-steroidal anti-inflammatory drugs.

f) Comorbidities: antiphospholipid syndrome, diabetes mellitus, arterial hypertension

Laboratory data:

a) Autoantibody profile: ever-positive ANA, anti-dsDNA, anti-Sm, anti-RNP, anti-Ro, anti-La; antiphospholipid antibodies (anti-cardiolipin, anti-beta2glicoprotein1, lupus anticoagulant);

c) Ever-low C3

d) Urinary protein/creatinine ratio (PCR) or 24h-proteinuria, serum creatinine, albumin, anti-dsDNA and C3, ESR and CRP - all at the time of biopsy, 6, 12 and 24 months afterwards, and at the time of last visit. These data may be collected only for class III, IV, V and mixed.

e) Estimated GFR < 60 mL/min/1.73 m2 for at least 3 months (yes/no), date when this occurred.

3. Outcomes

The following variables will be determined:

a) Time and predictors to develop ESRD

b) Time and predictors to develop CKD

c) Time and predictors to achieve remission

d) Time and predictors to death

We define remission as follows:

Complete remission - urinary PCR of not more than 30 mg/mmol (or 24h-proteinuria of not more than 300mg), normal serum creatinine and normal serum albumin.

Partial remission – decrease in urinary PCR or 24h-proteinuria by at least 50%, serum albumin of at least 30 g/L, and either normal serum creatinine if the baseline creatinine was less than 260 µmol/L (2.95 mg/dL) or a 50% decrease in creatinine if the baseline creatinine was 260 µmol/L (2.95 mg/dL) or more.

We define CKD as decreased GFR of less than 60 mL/min/1.73 m2 for at least 3 months, according to Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. GFR will be estimated according to the CKD-EPI creatinine equation.

4. Statistical analysis

Descriptive analysis of the cohort: we will present categorical variables using absolute and relative frequencies. For numerical variables, we will present central tendency (mean or median) and dispersion measures (standard deviation or interquartile range).

Comparison between membranous and proliferative nephritis: categorical variables will be compared using Pearson's Chi Square test. Numerical variables will be compared using parametric or non-parametric tests.

We will use the Kaplan-Meier method to perform the survival analyses and multivariable COX regression analysis to investigate predictors of survival.

STUDY LIMITATIONS

Because this is a retrospective analysis, there might be some limitations related to underreporting and missing data. We will try to overcome this by having collaborators in each centre who will, whenever possible, complete the registry with data from patients' clinical files.

STUDY TIMELINE

Data collection: January – April 2019

Data analysis: May 2019

Abstract preparation and submission to ACR annual meeting 2019: June 2019

Manuscript preparation: June – October 2019

RESEARCH TEAM

Proponent: Filipa Farinha – PhD student at University College London (UCL)

Research team: Anisur Rahman, PhD – UCL Centre for Rheumatology; Ruth Pepper, PhD – UCL Centre for Nephrology

Collaborators: all Portuguese rheumatology centres are invited to participate. Clinicians who actively collaborate in this study will be co-authors, according to ICMJE recommendations, up to two co-authors for each centre.

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We have no conflicts of interest to declare.

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