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Concise report

# Assessment of long-term remission in lupus nephritis patients: a retrospective analysis over 30 years

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## Abstract

**Objective.** To review the likelihood of very long-term remission in patients with biopsy-proven LN attempting to identify good prognostic features.

**Methods.** We reviewed patients with LN whose renal biopsies showed World Health Organization (WHO) classes III, IV and V and who had a follow-up of at least 5 years between 1973 and 2008. We analysed demographic, clinical, laboratory and therapeutic parameters comparing those patients with (group A) and without (group B) 5 year remission.

**Results.** Of 191 LN patients followed, 105 patients met the strict inclusion criteria. Ninety-five patients were female. Mean age at diagnosis of lupus was 24.1 years (S.D. 10.7). ean age at diagnosis of LN was 28.4 years (S.D. 11.3). The mean duration of follow-up was 13.7 years (S.D. 14.1). Forty (38%) patients achieved 5 year remission, of whom 17 (16.2%) had remission for $\geqslant$15 years. The incidence of flares per year from 5 to 15 years was 7.9%; however, no flares were observed after 15 years of remission. The only distinguishing feature found in this study was the association of WHO class IV on kidney biopsy with LN progression ($P = 0.03$).

**Conclusion.** Renal histology with WHO class IV predicted a poor long-term remission rate. Age, sex, ethnicity, serological parameters and treatment received did not predict long-term remission. Renal flares can occur up to 15 years after a patient has gone into remission.

**Key words:** systemic lupus erythematosus, lupus remission, lupus flares, renal biopsy in lupus.

**Rheumatology key messages**

- Patients with LN who achieve long-term remission (>5 years) have a better outcome.
- LN with WHO class IV on renal biopsy is associated with a reduced probability of long-term remission.
- Patients who remain in remission for $\geqslant$15 years are very unlikely to flare.

## Introduction

SLE is a systemic autoimmune rheumatic disease that is highly heterogeneous in terms of its manifestations, severity and progression. LN occurs in 30–50% of patients [1] and is the most important predictor of long-term morbidity and mortality [2], leading to end-stage renal disease in 5–10% after 10 years [3]. Achieving early and sustained remission is important in preventing long-term complications and death. Various factors, including ethnicity and chronicity index on renal biopsy, help to determine the initial response to therapy. Many therapeutic studies report short- or medium-term remission status. However, we are only aware of three studies and one case report providing data on very long-term LN follow-up (>10–15 years) [4–7]. The primary objective of our study was to identify the number of patients achieving complete and long-term remission (minimum of 5 years) in a single cohort of patients followed carefully for periods of

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up to 35 years. Secondary objectives were to identify factors associated with long-term remission.

## Patients and methods

Patients fulfilling the SLICC criteria for SLE [8] with biopsy-proven LN were retrospectively assessed. The patients included had a kidney biopsy assessed according to the World Health Organization (WHO) classes of III, IV, V or III/IV with V. They were managed principally at University College Hospital from 1978 until December 2013 with follow-up of at least 5 years after initiating induction therapy. Data from patients transferred to other centres were also included if available. As such, this study is an audit and University College London does not require patient consent for studies of this type.

The study variables included demographic details of the patient's gender, ethnicity, age at onset of lupus, age at onset of renal disease, clinical manifestations, laboratory results [notably anti-dsDNA, aCL, anti-ENA, complement C3, serum creatinine, 24 h urine protein or spot urine protein creatinine ratio, estimated glomerular filtration rate (GFR) and serum albumin], renal histology (WHO classification), induction therapy [CYC according to the National Institutes of Health [9] or the European Lupus Nephritis Trial (ELNT) protocol] [10], MMF, rituximab (RTX) or other drugs (including steroids, AZA and ciclosporin) and follow-up data (time to achieve remission, duration of remission, number of flares, infectious and non-infectious complications requiring hospital admission and associated co-morbidities).

### Outcome measures

The primary objective was to assess the long-term renal remission rate in our LN patients. Other assessed outcomes were LN flares, chronic kidney disease, end-stage renal disease, patient survival and adverse events and chronic complications. Long-term remission was considered to have occurred in patients with a 5 year remission defined by the absence of proteinuria on urine dipstick, 24 h urine protein $<$200 mg or spot urine protein $<$0.20, negative anti-dsDNA antibodies, normal complement C3 and normal serum creatinine for 5 consecutive years. As we and others have shown that serologically active clinically quiescent patients will flare [11], anti-dsDNA antibodies had to be negative to ensure that the patients in this group were in remission.

A complete response was noted if inactive urinary sediment, a decrease in proteinuria to $\leqslant$0.2 g/day and normal serum creatinine lasted for 5 years. A partial response was considered to have been achieved given a major level of improvement, usually defined as inactive sediment, proteinuria $\leqslant$0.5 g/day, with normal (GFR $>$90 ml/min) or stable ($<$10% deterioration from baseline if GFR was previously abnormal) renal function. Nephritic flare was defined as an increase or recurrence of active urinary sediment and/or proteinuria with an increase $\geqslant$25% in serum creatinine. Proteinuric flare was characterized by a persistent increase in proteinuria to values $>$0.5–1.0 g/day after a complete response has been achieved or a doubling of proteinuria, with values $>$1.0 g/day, after achieving a partial response.

Based on 5 year remission, the patients were divided into two groups, those achieving complete remission for 5 years (group A) and those with partial/no remission (group B), and were compared for significant differences in demographic, clinical and serological features or treatment received. Patients were considered to have serious non-renal complications if they developed infections requiring hospitalization, myocardial infarction/stroke or cancer.

### Statistical analysis

Data were compiled in Excel (Microsoft, Redmond, WA, USA) spreadsheets and basic analysis including means and S.D.s were noted. Continuous variables were analysed using unpaired *t*-test and categorical variables were analysed using Fisher's exact test as required to compare the remission and non-remission groups. A $P$-value $<0.05$ was considered to be significant.

## Results

Of 191 LN patients identified in our cohort, 105 patients met the strict inclusion criteria for the study. Their baseline parameters are shown in Table 1. Those who had nephritis but were not analysed included those who had not had a biopsy or whose biopsy result was not available (17 patients), had WHO class I or II (11 patients), were lost to follow-up in too short a time (23 patients) or where the data were incomplete (35 patients), often because the patient had moved overseas or was lost to follow-up.

In 37 patients (35.2%) nephritis was diagnosed at presentation. Mean duration between onset of lupus and nephritis was 4 years (S.D. 5.4), with 76 patients (72.4%) diagnosed within 5 years of onset of lupus.

CYC was given according to the National Institutes of Health protocol in 40 patients and according to the ELNT protocol in 3 patients. MMF was administered to 16 patients and RTX to 4 patients. Forty-two patients were initially managed with a combination therapy of steroids and AZA, ciclosporin or tacrolimus. Re-induction was necessary in six patients in group A and all received RTX. In group B, re-induction therapy consisted of CYC in 9 patients, RTX in 15, ciclosporin in 2, MMF in 3 and ocrelizumab in 1. Maintenance therapy immediately following induction consisted of the following: in group A, 27 of 40 received AZA, 8 received MMF and 5 received only steroids; in group B, 35 received AZA, 22 received MMF, 2 received MTX, 3 received RTX and 3 received only steroids. In group A, four patients were able to stop their immunosuppression or steroids.

Forty (38.1%) patients achieved 5 year remission (group A) and 65 (61.9%) had either partial or no remission (group B). A comparison of clinical parameters of patients with and without 5 year remission is shown in Table 2. The main distinguishing feature is WHO class on kidney biopsy: class IV was more frequent in group B ($P=0.03$),

TABLE 1 Baseline parameters of 105 LN patients

| Parameter | Value |
|---|---|
| Age, mean (S.D.), years | 24.1 (10.7) |
| Gender, *n* (%) | |
| Female | 95 (90.5) |
| Male | 10 (9.5) |
| Age at diagnosis of SLE, mean (S.D.), years | 24.1 (10.7) |
| Age at diagnosis of LN, mean (S.D.), years | 28.4 (11.3) |
| Duration of follow-up, mean (S.D.), years | 13.7 (14.1) |
| Ethnicity, *n* (%) | |
| Caucasian | 41 (39) |
| Indian, Pakistani, Bangladeshi | 24 (22.9) |
| Afro-Caribbean | 23 (21.9) |
| Other | 17 (16.2) |
| Renal histology WHO class, *n* (%) | |
| Class III | 17 (16.2) |
| Class IV | 62 (59) |
| Class V | 21 (20) |
| Mixed V + III/IV | 5 (4.8) |
| RPGN presentation | 25 (23.8) |
| Nephrotic syndrome presentation | 25 (23.8) |
| Raised anti-dsDNA antibodies | 94 (89.5) |
| Low C3 | 64 (61) |
| aCL | 39 (37.1) |
| Antibodies to ENA | 54 (51.4) |
| 24 h urine protein, mean (S.D.), normal 0–0.15 g | 3.37 (2.83) |
| Serum creatinine, mean (S.D.), normal 50–110 μmol/l | 112 (74.1) |
| Serum albumin, mean (S.D.), normal 35–50 g/l | 30.6 (7.22) |
| Estimated GFR, mean (S.D.), normal >90 ml/min/1.73 $m^2$ | 66.5 (27) |

GFR: glomerular filtration rate; RPGN: rapidly progressive GN; WHO: World Health Organization.

and among these was even more frequent in those without partial remission ($P = 0.017$).

In group A, 13 had nephritis at onset of lupus and 30 had it within the first 5 years following diagnosis. In group B, 24 of 65 had nephritis at onset, while 46 developed it within 5 years (not significant).

The incidence of flares per year from 5 to 15 years was 7.9%; however, no flares were observed after 15 years of remission. Seventeen (42.5%) patients had persistent remission for $\geqslant$15 years.

In group A at the last visit to hospital, 39 patients were in remission, of whom 32 had normal renal function and 7 had chronic kidney disease. In group B, 17 patients were in remission, 12 had chronic kidney disease and 25 had end-stage renal disease, of whom 13 had undergone renal transplant. No deaths occurred in group A, whereas 14 deaths occurred in group B ($P = 0.0009$). The number of deaths was significantly lower among those in group B who achieved partial remission ($P = 0.0084$). Infectious ($P = 0.0001$) and non-infectious ($P = 0.0031$) serious non-renal complications were significantly more frequent in group B.

## Discussion

This is a single-centre retrospective study of the lupus cohort from University College London Hospital with biopsy-proven class III/IV and/or V LN over the past 35 years. Many studies have tried to determine the prevalence of remission, but comparisons are difficult due to different criteria. Approximately 60–90% of patients achieve remission after treatment [12]. The renal response rate in the ELNT was 71%, which persisted for up to 10 years. In our study with stringent criteria for remission (normal renal function, absent protein in urine dipstick and 24 h urine protein <0.2 g), a 5-year remission rate of 38.1% was seen. Seventeen per cent of the patients had a remission of $\geqslant$15 years. Flares occurred up to 15 years after going into remission.

Several features at baseline have been found to be predictive of renal remission, including race [13], age, serum creatinine and chronicity index. In addition, compliance with therapy is essential. In this study, no features predicted which patients were more likely to sustain a long-term complete remission apart from renal histology. We and others have previously reported that black subjects with SLE have poorer patient and renal survival compared with white subjects [14]. These differences in survival are probably due to genetic factors. In the cohort of 105 patients with class III, IV or V LN, 42 were initially managed with a combination therapy of steroids, AZA, ciclosporin or tacrolimus. We have also previously reported on a group of patients with LN type III, and in some cases type IV, who responded well to treatment with steroids and AZA alone i.e. they did not receive i.v. CYC or MMF [15]. However, amongst the 42 patients, twelve 12 later received cyclophosphamide CYC or MMF as re-induction therapy (all in the non-remission group).

We found that 40 of 105 patients (38.1%) went into remission (group A) for at least 5 consecutive years. Seventeen patients (16.2%) remained in remission for $\geqslant$15 years. A comparison of groups A and B showed that the presence of WHO class IV LN was the single most important negative predictor of long-term remission. Age at diagnosis of lupus, duration between renal disease and onset of lupus, ethnicity, baseline dsDNA antibody complement levels, aCL antibodies, serum creatinine, GFR, 24 h urine proteinuria and serum albumin and the therapy received did not affect the long-term response.

Three previous studies of long-term (10–15 years) follow-up have been reported. Moroni *et al.* [6] described a cohort of 25 patients with LN followed up for >10 years, with remission or not, and noted that the incidence of flares decreased significantly after the 10th year. Donadio *et al.* [4] and Bono *et al.* [5] studied cohorts of 439 and 110 patients, respectively, with LN and showed a progressive decrease in survival free of renal failure: 83–84%, 72–74% and 61–64% at 5, 10 and 20 years of follow-up, respectively. Donadio *et al.* [4] noted that survival was negatively influenced by progressive WHO class, hypertension, kidney failure, proteinuria in nephrotic range, hypoalbuminaemia and anaemia. Bono *et al.* [5]

**Table 2** Comparison of clinical parameters of patients with (group A) and without (group B) 5 year remission

| Parameter | Group A ($n = 40$) | Group B ($n = 65$) | *P*-value |
|---|---|---|---|
| Female:male, *n*:*n* | 37:3 | 58:7 | 0.43 |
| Age at diagnosis of SLE, mean (S.D.), years | 25 (2.8) | 24.2 (10.8) | 0.50 |
| Age at diagnosis of LN, mean (S.D.), years | 29.6 (1.4) | 27.7 (9.2) | 0.38 |
| Ethnicity, *n* (%) | | | |
| Caucasian | 19 (47.5) | 22 (33.8) | 0.31 |
| Afro-Caribbean | 6 (15) | 18 (27.7) | 0.16 |
| Indian, Pakistani, Bangladeshi | 10 (25) | 13 (20) | 0.63 |
| Other | 5 (12.5) | 12 (18.5) | 0.59 |
| WHO class, *n* (%) | | | |
| Class III | 8 (20) | 9 (13.8) | 0.43 |
| Class IV | 18 (45) | 44 (67.7) | 0.03 |
| Class V | 13 (32.5) | 8 (12.3) | 0.02 |
| Mixed V + III/IV | 1 (2.5) | 4 (6.2) | 0.65 |
| Raised anti-dsDNA antibodies, *n* (%) | 38 (95) | 58 (89.2) | 0.29 |
| Low C3, *n* (%) | 24 (60) | 40 (61.5) | 1.00 |
| aCL, *n* (%) | 12 (30) | 27 (41.5) | 0.20 |
| Anti-Ro antibodies, *n* (%) | 9 (22.5) | 26 (40) | 0.06 |
| Anti-La antibodies, *n* (%) | 6 (15) | 13 (20) | 0.70 |
| Anti-RNP antibodies, *n* (%) | 11 (27.5) | 22 (34.4) | 0.60 |
| Anti-Sm antibodies, *n* (%) | 7 (18.4) | 11 (17.4) | 0.88 |
| Mean baseline 24 h urine protein, g | 2.49 | 2.95 | 0.83 |
| Mean baseline serum creatinine, mmol/l | 89 | 96 | 0.54 |
| Mean baseline serum albumin, g/dl | 31 | 30 | 0.47 |
| RPGN, *n* | 10 | 15 | 0.26 |
| Nephrotic syndrome, *n* | 10 | 15 | 0.26 |
| Treatment, *n* | | | |
| NIH protocol | 17 | 23 | 0.84 |
| MMF | 4 | 12 | 0.18 |
| ELNT protocol | 2 | 1 | 0.56 |
| Rituximab | 1 | 3 | 1 |
| Other[a] | 16 | 25 | 1 |
| Patients on HCQ, *n* | 20 | 30 | 0.84 |
| Patients on ACE inhibitors, *n* | 24 | 57 | 0.004 |
| Deaths[b], *n* | 0 | 14 | 0.0009 |

[a]Other medications were steroids, AZA, ciclosporin and tacrolimus. [b]Deaths occurred due to sepsis (seven patients), carcinoma of the anus (two patients), bacterial peritonitis (one patient), myocardial infarction (one patient), heart failure (one patient) and renal disease (two patients). ACE: angiotensin-converting enzyme; ELNT: European Lupus Nephritis Trial; NIH: National Institutes of Health; RPGN: rapidly progressive GN; WHO: World Health Organization.

noted that no patients with normal kidney function had new-onset renal failure after the 10th year of follow-up.

Infectious and non-infectious complications were more common in group B. There were no deaths in group A, whereas 16 deaths occurred in group B. This reiterates the importance of remission.

As our data were collected over the past 30 years, the evolving changes in treatment may have influenced patient outcomes. However, we could not identify any significant differences between various therapies

In conclusion, renal histology with WHO class IV predicted a decreased long-term remission rate. Age, sex, ethnicity, serological parameters and treatment received did not predict long-term remission. Renal flares can occur up to 15 years after a patient has gone into remission. The incidence of infectious and non-infectious complications was increased in patients who did not achieve sustained complete remission.

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