Systemic lupus erythematosus : from diagnosis to prognosis

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Chapter 4

Long-term Preserved Renal Function in Patients with Class III or IV Lupus Nephritis Undertreated According to Guidelines: Recognition of a Subgroup with a Favourable Natural History

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Submitted

ABSTRACT

Background

Present guidelines for lupus nephritis (LN) recommend that all patients with class III or IV LN receive cytotoxic immunosuppression. Scarce data from the past suggest that some patients with class III or IV LN maintained renal function without such therapy in clinical trials. In this study, we aimed to study the natural history of class III or IV LN and explore a subgroup of patients for whom treatment without cytotoxic drugs could suffice.

Methods

All patients were included with a renal biopsy showing class III or IV LN between 1983–2011 and with clinical follow-up at the Leiden University Medical Center. Evolution of eGFR during 10 years follow-up was compared between all consecutive patients who did and did not receive guideline-recommended cytotoxic immunosuppression.

Results

Three patients were identified with class III or IV LN presenting with relatively preserved renal function who did not receive cytotoxic immunosuppression, in defiance of current guidelines. Follow-up of 9–24 years revealed that these patients achieved remission with stable renal function and without LN flares, despite mild non-nephrotic proteinuria in the absence of erythrocyturia. Their eGFR evolution over 10 years did not differ from that observed in 98 patients from the same cohort who received cytotoxic immunosuppression (P=0.56).

Conclusions

The three cases undertreated according to guidelines represent a subgroup of patients with class III or IV LN for whom milder therapy regimens without cytotoxic immunosuppression appear sufficient. These findings signal a need to study similar patients in future studies.

INTRODUCTION

For patients with class III or IV lupus nephritis (LN), standard care includes intravenous cyclophosphamide or mycophenolate mofetil (MMF) in combination with corticosteroids.[1-5] However, such treatment is associated with severe side effects, including sepsis, avascular bone necrosis, gonadal dysfunction, and malignancy.[6] Even with these therapies, LN carries considerable risks of end-stage renal disease (ESRD) and death.[7-13] Randomised controlled trials (RCTs) have focused on treatment strategies to improve prognosis focusing on patients at high risk of these adverse outcomes. As a consequence, a subgroup of patients with class III or IV LN who might have a lower risk of adverse outcomes has been overlooked in these trials. Yet, it has always been clear from the landmark trials performed at the National Institute of Health (NIH), that about 10–40% of patients who received prednisolone therapy alone did not reach ESRD during 10 years follow-up.[8] Unfortunately, the clinical course of these patients has never been detailed; thus, little is known about the natural history of class III or IV LN. Treating patients with prednisolone therapy alone is no longer recommended.[1-5] Therefore, it is presently unknown whether a conceivably lower-risk subgroup of patients with class III or IV LN could be treated with milder regimens omitting cytotoxic immunosuppression.

In this study, we aimed to explore the existence of a subgroup of patients with class III or IV LN for whom milder immunosuppressive regimens could suffice. We report the results of a retrospective study in which we identified patients with class III or IV LN as registered in the pathology archives of the Leiden University Medical Center between 1983–2011 who did and did not receive guideline-recommended cytotoxic immunosuppression. We present the clinical characteristics, therapeutic strategies, and clinical outcomes in all consecutive patients with class III or IV LN who did not receive guideline-recommended cytotoxic immunosuppression in this cohort. The evolution of eGFR during 10 years follow-up was compared between these patients and patients from the same cohort who did receive cytotoxic immunosuppression in accordance with the guidelines.

METHODS

Identification of cases

The pathology archives at the Leiden University Medical Center were searched for all patients biopsied between 1983–2011 with class III or IV LN. Patients were included if they had a renal biopsy available for re-evaluation, fulfilled ≥4 American College of Rheumatology (ACR) or ≥4 Systemic Lupus International Collaborating Clinics (SLICC) criteria for systemic lupus erythematosus (SLE),[14] and had clinical follow-up at our centre.

Biopsies were reclassified according to the ISN/RPS 2003 classification.[15] Medical records were evaluated for history of immunosuppressive medication prior to biopsy and during follow-up. The glomerular filtration rate was estimated using the Cockcroft-Gault formula (eGFR). eGFR was recorded at the time of renal biopsy, as well as at 1, 2, 3, 4, 5, and 10 years of follow-up. In accordance with the ethics committee of Leiden University Medical Center, all patient data were coded and kept anonymously throughout the study.

Statistical analysis

Normally distributed data are expressed as means ± standard deviation and non-normally distributed data are presented as median values and interquartile range. Normally distributed data were compared with *t*-tests and categorical data with Fisher's exact tests or chi-square tests. To compare non-normally distributed data, Mann-Whitney U tests were used.

A random intercept/random slope mixed model was used to compare the course of eGFR between patients. In the mixed model, "treatment according to guidelines" was analysed as fixed effect. Visual inspection of residuals was performed to assess normality assumptions. All analyses were performed using SPSS Statistics 23.0 (IBM, Armonk, New York).

RESULTS

We included 101 patients who had biopsy-confirmed class III or IV LN between 1983–2011. Of these, 98 received cytotoxic immunosuppression according to guidelines: corticosteroids in combination with intravenous cyclophosphamide (NIH protocol[12] [n=26]; Euro-Lupus protocol[13] [n=30]), azathioprine (n=33), or MMF (n=9). We identified three consecutive patients who – in defiance of treatment guidelines – did not receive any of the aforementioned regimens prior to biopsy and during follow-up for LN. Clinical and histopathologic characteristics at the time of diagnostic renal biopsy of the latter three patients, as well as of the other 98 patients in the cohort, are shown in **Table 1**. No differences in biopsy findings and clinical presentation were noted between the two groups. The case descriptions of the three patients undertreated according to the guidelines are detailed below.

Table 1 Clinical and histopathologic characteristics of patients at time of diagnostic renal biopsy.

Characteristic	Case 1	Case 2	Case 3	Patients with guideline-recommended immunosuppression (n=98)	P†
Age, y	23	33	32	30 ± 13	0.2
Sex	Female	Female	Male	20 Male 78 Female	0.6
ISN/RPS class of LN	III (A/C)	IV-G (A)	III (A/C)	23 III 24 IV S 45 IV G 6 III/IV + V	0.7
Time since diagnosis of SLE, y	0.3	0	0	3.7 ± 5.0	0.1
Glomeruli without abnormalities	14% (5/36)	0% (0/20)	30% (3/10)	10%	0.9
Glomeruli with proliferative lesions	33% (12/36)	95% (19/20)	10% (1/10)	55%	0.8
Glomeruli with global sclerosis	0% (0/36)	0% (0/20)	10% (1/10)	7%	0.4
NIH Activity Index[16]	7	6	4	10 (6–12)	0.1
NIH Chronicity Index[16]	1	0	4	1 (0–3)	0.8
Serum creatinine, µmol/L	88	74	90	144 ± 135	0.3
eGFR, mL/min	72	86	92	73 ± 35	0.1
Proteinuria, g/24h	3.9	3.1	1.6	4.4 ± 3.8	0.7
ANA	+	+	+	97% (n=98)	1.00
Anti-dsDNA	+	not tested	-	80% (n=96)	0.5

Data are expressed as mean ± standard deviation or median (interquartile range). ANA, antinuclear antibody; anti-ds-DNA, anti-double stranded DNA antibodies. † Patients with guideline-recommended immunosuppression (n=98) versus cases 1–3.

Case descriptions

Case 1

In 1993, a 22-year-old Caucasian woman was diagnosed with SLE based on a malar rash, pleuropericarditis, Libman-Sacks endocarditis, photosensitivity, pancytopenia, hypocomplementaemia, positive antinuclear, anti-dsDNA anti-(double stranded DNA), and antiphospholipid antibodies. Shortly after diagnosis, she experienced an epileptic insult and MRI showed multiple white matter lesions consistent with cerebral SLE involvement. Simultaneously, proteinuria increased (**Figure 1A**) and renal biopsy indicated LN class III (A/C) with endocapillary hypercellularity, fibrinoid necrosis, and cellular crescents. Virtually no chronic damage was present, except for one fibrous crescent.

The patient was started on 40 mg prednisolone and anti-proteinuric treatment with 5 mg enalapril. Due to the patient's stable renal function with class III LN (**Figure 1A**), conservative therapy was maintained and no additional immunosuppressive therapy was initiated. Two years later, the patient experienced two exacerbations of cutaneous SLE with secondary impetiginisation, for which she received 200 mg hydroxychloroquine. Four years after renal biopsy, SLE was in remission, and prednisolone treatment was discontinued.

The patient was followed in our centre for nine years, with her last follow-up showing no symptoms of active LN, despite persisting mild proteinuria of 1–2 g/24h (**Figure 1A**).

Case 2

In 1994, a 33-year-old Caucasian woman with a history of HLA-B27-positive oligoarthritis and preeclampsia presented with fluid retention in her fingers and macroscopic haematuria, anaemia, leukocytopenia, and proteinuria. One year later, she was diagnosed with post-streptococcal glomerulonephritis based on hypocomplementaemia, elevated anti-streptolysin O, erythrocyturia, nephrotic-range proteinuria (4–5 g/24h), hypertension (RR 150/90 mmHg), and a history of pharyngitis. Her renal function was normal (eGFR ± 90 mL/min). She was started on 20 mg enalapril with close follow-up, during which hypocomplementaemia, proteinuria (3–4 g/24h), and erythrocyturia persisted.

In 1996, renal biopsy revealed a membranoproliferative pattern with full house immunofluorescence, which was retrospectively classified as LN class IV-G (A). She had no other systemic symptoms of SLE, but additional testing showed a positive antinuclear antibody (ANA). At the time, the patient fulfilled 4 SLICC criteria: leukocytopenia, hypocomplementaemia, nephritis, and ANA. Due to the patient's wish for pregnancy, she declined immunosuppression and enalapril was switched to methyldopa. Her subsequent pregnancy 3 months later was complicated by preeclampsia (i.e. hypertension with proteinuria of 10 g/24h) in the first trimester, and was therefore terminated. Enalapril treatment was restarted, with the addition of 12.5 mg hydrochlorothiazide. In the following years, she showed stable normal renal function, but persisting proteinuria and erythrocyturia. Four years after renal biopsy, the patient was formally diagnosed with SLE based on the serial occurrence of haematologic disturbances, hypocomplementaemia, positive ANA, and LN.

Eleven years after renal biopsy, while LN was in remission, the patient presented with psychosis, which was diagnosed as cerebral SLE based on cerebellar atrophy on MRI. She was started on 60 mg prednisolone, antipsychotics, and intravenous cyclophosphamide following the NIH scheme. Her condition quickly improved. Within eight months, cerebral SLE was in remission and prednisolone treatment was discontinued. At her last follow-up in our centre, 19 years after renal biopsy, SLE was in complete remission with minimal proteinuria, absent erythrocyturia, and normal eGFR (**Figure 1B**).

Case 3

In 1990, a 31-year-old Caucasian man presented with erythema and arthralgia of his lower legs, for which he received a non-steroidal anti-inflammatory drug. Two months later, laboratory analyses revealed a strongly positive ANA, together with proteinuria and erythrocyturia, with a normal eGFR (**Figure 1C**). Renal biopsy revealed LN class III (A/C) with concomitant thrombotic microangiopathy. The diagnosis of SLE was confirmed based on LN, arthritis, positive ANA, and antiphospholipid antibodies. Therapy was initiated with hydroxychloroquine. For unknown reasons, no additional immunosuppressive therapy was

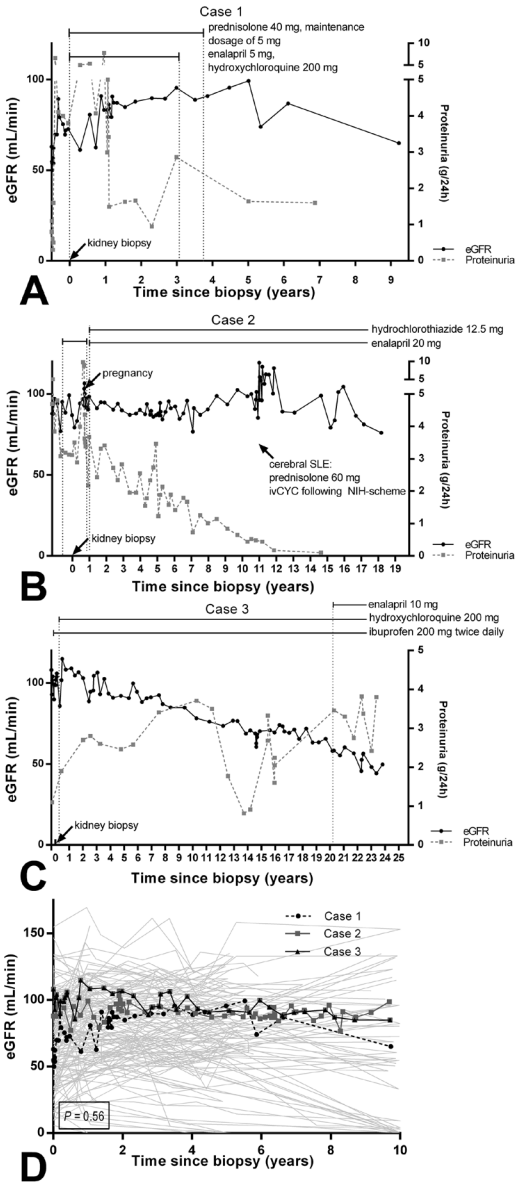
started. Over the following years, SLE was in remission, although mild sediment disturbances and proteinuria persisted (**Figure 1C**).

Fifteen years after renal biopsy, SLE activity increased, with myalgias, arthralgias, and maculous skin lesions of the buttocks and legs. These symptoms resolved after increasing the hydroxychloroquine dosage. Over the following years, eGFR was 55–75 mL/min, proteinuria 2–3.5 g/24h, and erythrocyturia was absent. In 2011, the patient was started on 10 mg enalapril due to persisting proteinuria. In 2013, a second renal biopsy was performed because of a temporarily raised serum creatinine (eGFR ±45 mL/min) together with longstanding proteinuria without erythrocyturia. The biopsy showed one glomerulus with perihilar focal segmental glomerulosclerosis, but no active lesions. There were no chronic lesions, apart from one glomerulus showing global sclerosis. Immunofluorescence was negative, but electron microscopy revealed a limited number of transmembrane and subepithelial deposits. At the last follow-up in our centre, 24 years after initial renal biopsy, the patient showed a stable renal function (**Figure 1C**) without erythrocyturia and with adequate blood pressure (RR 130/80 mmHg).

Renal function in patients with and without guideline-recommended immunosuppression compared

The evolution of eGFR was compared between the 98 patients who did and the three patients who did not receive guideline-recommended cytotoxic immunosuppression during 10 years follow-up. A random intercept/random slope mixed model revealed that the evolution of the eGFR did not significantly differ between the two groups (P=0.56). **Figure 1D** shows the course of eGFR among the patients treated with and without cytotoxic immunosuppression, demonstrating the lack of notable differences in trend for the three patients without cytotoxic immunosuppression compared to the other 98 patients in the cohort.

Figure 1 Clinical course of patients undertreated according to current guidelines.



A: case 1. B: case 2. C: case 3. D: course of eGFR during 10 years follow-up of patients who were undertreated according to current guidelines (cases 1−3; highlighted) in relation to patients from the same cohort who received cyclophosphamide, MMF, or azathioprine (n=98; in grey).

DISCUSSION

We studied consecutive patients from the Leiden University Medical Center with class III or IV LN diagnosed between 1983 and 2011 who did not receive guideline-recommended cytotoxic immunosuppression. We found three patients with class III or IV LN who were undertreated according to current guidelines, having received prednisolone alone or no immunosuppressive therapy. During long-term follow-up, these patients maintained a relatively preserved renal function without LN flares. Their eGFR evolution over 10 years follow-up did not differ from that observed in patients from the same cohort who received guideline-recommended cytotoxic immunosuppression. To our knowledge, this is the first detailed analysis of patients belonging to the understudied subgroup of class III or IV LN who could benefit from a therapeutic approach omitting cytotoxic drugs for their renal manifestations, in disagreement with current treatment guidelines. The three patients described herein may signal a need to more closely investigate similar patients in future prospective studies.

Large RCTs have clearly demonstrated the benefits of various cytotoxic regimens for the pooled group of patients with class III or IV LN, upon which the current LN treatment guidelines are based. Attempts to identify prognostic subgroups of patients with class III or IV LN have focused on patients in high-risk groups. In the trial by Austin e*t al*. performed at the NIH,[8] high-risk patients identified by the presence of a chronicity index ≥1 had a significantly increased risk of ESRD as compared to the patients who had no chronic lesions. In the high-risk group, little over 10% of patients in the prednisolone arm did not reach the end-point ESRD after 10 years follow-up, whereas this percentage increased to nearly 40% in the total group of patients receiving prednisolone including low-risk patients with absent chronic lesions. Although there were only 28 patients in the prednisolone arm, these data suggest that improvement in the qualification of the subgroup of patients for whom milder therapy could suffice is attainable. Focusing on high-risk subgroups in RCTs is profitable, since a treatment effect – if present – is anticipated to be greater among these patients. However, separate analyses of lower-risk patients may reveal under which conditions milder therapies with less harmful side effects may suffice.

Interestingly, the same focus on high-risk patients is observed in the way eligibility criteria for RCTs are defined. Inspection of the inclusion criteria of landmark RCTs, upon which treatment guidelines are based, reveals that patients with a mildly disturbed eGFR and/or mild proteinuria were frequently excluded, as their smaller deviation from normal renal function is reasonably anticipated to be accompanied by a smaller treatment effect.[7-12] Consequently, results of these RCTs cannot be unequivocally applied to all patients with LN in a clinical setting, creating a gap in the guidelines for patients with relatively preserved renal function and a possibly favourable prognosis. Currently, more and more patients with class III or IV LN with preserved renal function and mild proteinuria are

encountered, since current guidelines recommend a renal biopsy for patients with SLE and any sign of renal involvement, particularly reproducible proteinuria of >0.5 g/24h.[1-5] Without supporting evidence, the EULAR/ERA-EDTA guideline[2] attempts to close this gap, proposing that patients with preserved renal function and without adverse histopathologic findings could be considered candidates for milder therapy regimens (e.g. azathioprine). The three patients described here showed relatively preserved renal function at the time of renal biopsy, notwithstanding that they are not typically mild cases unfulfilling the eligibility criteria of some large RCTs. Moreover, these patients' histopathologic findings would probably not be designated as "non-adverse," although this is uncertain since there is no specific definition for this entity. There remains a need for a clear definition of the specific histopathologic lesions and clinical parameters that characterise patients eligible for milder therapy regimens.

Further specification of this subgroup will be challenging. Previous studies showed that neither histopathologic nor clinical parameters are optimal prognosticators in LN. Patients with the same LN class may experience heterogeneous clinical courses, and clinical features alone are poor predictors of histopathologic findings. Most telling, in a recent study by Wakasugi *et al.*, protocolised biopsies of SLE patients without clinical renal involvement revealed class III or IV LN in 13 of 86 cases.[17] Those 13 patients were followed for a median duration of 30 months, and only two patients with class III LN experienced exacerbated LN associated with pregnancy and malignancy. Remarkably, the remaining 11 patients showed no LN flares and had a good prognosis with prednisolone therapy alone. These findings underline three important points: the lack of coherence between clinical findings and histology, the difficulty of determining treatment purely based on LN class, and the challenge of predicting clinical course.

In the present guidelines, no prognostic subgroups of patients with class III or IV LN are recognised: treatment decisions are based solely on the histopathologic classification with no regard of clinical parameters. Here we have shown that these guidelines are at risk of overtreatment, as we demonstrate the existence of a subgroup of patients with class III or IV LN for whom therapy without cytotoxic drugs could suffice. Since we found only three consecutive patients who retrospectively appeared to have been unexposed to cytotoxic immunosuppression, a limitation of our study is that we were hampered by a lack of power to identify features characterising these patients. We speculate that the three patients had (combinations of) the following features in common which may give clues as to why they had a favourable prognosis in the absence of cytotoxic immunosuppression: newly or very recently diagnosed SLE at the time of renal biopsy, a relatively preserved and stable renal function at presentation (only gradual decline in eGFR during the month preceding the renal biopsy of 0–3 mL/min), and a relatively low percentage of proliferative lesions (cases 1 and 3). Awaiting the results of further studies investigating the specific subgroup of patients with yet undefined combinations of clinical and histopathologic manifestations, the following could be deliberated. For selected patients with class III or IV LN, it may be

advisable to institute a window of "watchful waiting" following renal biopsy during which patients are closely monitored, paralleling the strategy in other renal diseases like idiopathic membranous nephropathy.[3] Tailored treatment may be optimal, with a tentative approach involving watchful waiting, and possible introduction of anti-inflammatory treatment with corticosteroids followed by suppression of autoimmunity using cytotoxic immunosuppressive drugs only if deemed necessary. Indeed, older studies have demonstrated that anti-inflammatory doses of corticosteroids alone were as effective as corticosteroids plus cyclophosphamide in the early phase of LN treatment.[8, 18] Obviously, appropriate cases must be selected with extreme caution, as patients with class III or IV LN who are undertreated due to non-adherence to treatment may show a detrimental disease course.[19] Also, SLE is a systemic disease and successful conservative treatment for LN does not imply that this approach can be extrapolated to all extrarenal SLE manifestations. Nevertheless, an approach involving watchful waiting was successful in the three presently described cases and could possibly decrease the burden of cytotoxic regimens in more patients.

ACKNOWLEDGEMENTS

The authors are most grateful to Dr. David Jayne (Vasculitis and Lupus Clinic, Addenbrooke's Hospital, Cambridge) for stimulating discussions and critical reading of the manuscript. Wouter Beck is kindly acknowledged for assistance with figure preparation.

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