EXTENDED REPORT

Improved clinical outcome of lupus nephritis during the past decade: importance of early diagnosis and treatment

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Objective: To evaluate the differences in the outcome of lupus nephritis diagnosed either in the 1980s or the 1990s in Heidelberg, Germany.
Methods: Fifteen patients with biopsy confirmed lupus nephritis (LN) were followed up between 1980 and 1989 and 41 patients were followed up between 1990 and 2000. Their status at diagnosis and their treatment schedules and outcome were analysed. 68% had WHO IV nephritis.
Results: In the decade from 1990 to 2000 there was significantly less proteinuria (46 *v* 17 g/l, p=0.008), significantly lower rates of renal failure (40% *v* 17%, p=0.02), and fewer histological signs of chronicity (33% *v* 10%, p=0.01) at the time of diagnosis of LN than in the decade from 1980 to 1989. The mean (SD) time from the first appearance of proteinuria until kidney biopsy was significantly shorter in the later decade (15.4 (15.6) *v* 3.9 (4.7) months). Although treatment schedules were not significantly different, the outcome of the disease was significantly better in the patients who were diagnosed with LN between 1990 and 2000 (p=0.045). Whereas 6/15 (40%) patients between 1980 and 1989 had terminal renal failure after a mean time of 94 months, in the group of 1990–2000 no patient developed terminal renal failure (median observation time 24 months). In both groups one patient died from infection. A high chronicity index in histology and the presence of arterial hypertension or renal failure, or both, at the time of diagnosis were significant risk factors for the development of terminal renal failure in the course of the disease.
Conclusions: The outcome of patients with newly diagnosed LN was significantly better between 1990 and 2000 than between 1980 and 1989. Kidney damage and chronic histological changes at time of diagnosis were significantly less common between 1990 and 2000, which is attributable to earlier diagnosis and treatment in the later decade.

The prognosis of systemic lupus erythematosus (SLE) has improved constantly over the past decades.[1–5] However, patients with SLE still carry a heavy burden of morbidity owing to organ damage.[6–10] Kidney disease with impaired renal function has been a major cause of morbidity in the past. At least 50% of patients with SLE exhibit signs of nephritis at any time during their disease and about half of them have diffuse proliferative nephritis (WHO class IV).[3] When renal failure occurs, this is usually in the first decade of follow up.[2] Confirming outcome analyses published between 1990 and 2000, WHO class IV nephritis still leads to end stage renal failure in 10–26% of patients.[1 11–13] Several factors, such as the initial presence of renal insufficiency, arterial hypertension, cytopenia, and chronicity of kidney biopsy findings, were reported to influence the renal prognosis.[13–15] Most of these parameters reflect the extent of kidney disease at the time when treatment is started. However, race, age, smoking behaviour, and frequency of renal flares in the course of disease are thought to influence renal outcome of lupus nephritis as well.[14 16–20]

Our clinical impression was that the rate of renal failure due to lupus nephritis at our centre declined in the past decade. Therefore, we performed an analysis to evaluate the outcome of lupus nephritis in our group of patients. Besides identifying risk factors for renal failure, we aimed at comparing the characteristics at diagnosis, treatment modalities, and outcome of patients with lupus nephritis diagnosed and treated at the University of Heidelberg, Germany in the last two decades of the 20th century. Our goal was to find out whether the prognosis of lupus nephritis has changed during these two decades and, if so, which factors might be responsible.

METHODS

A retrospective analysis of patient characteristics at diagnosis, treatment modalities, and renal outcome was performed. For this, the charts of all patients with biopsy proven lupus nephritis diagnosed at our centre between 1980 and 2000 were reviewed and all relevant data from the time of diagnosis to the last observation was documented. The SLE disease activity index (SLEDAI) was calculated as a measure of the systemic activity of the disease at the time of diagnosis. As suggested by Bombardier (1992),[21] it included scores which weighted the disease activity of SLE in the central nervous system, the vasculature, the musculoskeletal system, and the kidney as well as serosal, dermal, haematological, immunological, and constitutional manifestations of the disease.

The activity index of lupus nephritis in kidney biopsies was defined by the sum of the scores (mild=1, moderate=2, severe=3) for glomerular proliferation, leucocyte exudation, karyorrhexis and fibrinoid necrosis (×2), cellular crescents (×2), hyaline deposits, and interstitial inflammation.[13 22] All laboratory tests, the results of which were included in the data collection, were performed with standard test methods. All patients fulfilled the American College of Rheumatology criteria for SLE.[23] Between 1980 and 1989, 2/15 (13%) patients and between 1990 and 2000, 4/38 (11%) patients were lost to follow up. The data of all other patients were accessible up to

Abbreviations: ACE, angiotensin converting enzyme; SLE, systemic lupus erythematosus; SLEDAI, systemic lupus erythematosus disease activity index

Table 1 Characterisation of patients with lupus nephritis at the time of kidney biopsy. In comparison with the decade from 1980 to 1989, in the decade from 1990 to 2000 there was a lower rate of proteinuria, renal failure (as determined by the number of patients with creatinine values >110 µmol/l) and arterial hypertension at the time of the histological diagnosis of lupus nephritis

	1980–1989 (group I)	1990–2000 (group II)	p Value
Patients (n)	15	41	
Sex (M/F)	13/2	32//9	
Median age	29 (19–67)	35 (18–70)	NS
Arterial hypertension (%)*	6 (40)	11 (27)	NS
Median serum creatinine (µmol/l)	110 (50–430)	70 (30–250)	NS
Creatinine >110 µmol/l at time of presentation (%)	6 (40)	7 (17)	0.02
Median proteinuria (g/l)	46 (24–212)	17 (2–90)	0.008
Proteinuria >3 g/day (%)	9 (60)	14 (34)	0.03
Anaemia (%)†	5 (33)	25 (61)	0.03
Median dsDNA antibodies (U/ml)	102 (8.7–206)	75 (5.9–1439)	NS
Median SLEDAI	13 (11–26)	16 (8–28)	NS
C3c < normal (90–180 mg/l) (%)	9 (60)	23 (56)	NS

*Arterial hypertension was defined as a diastolic blood pressure >90 mm Hg during three consecutive measurements; †anaemia was defined as haemoglobin <120 g/l (women) or <130 g/l (men).

the set date of 1 March 2000. The data of the patients who were lost to follow up were included in the analysis until the last day of observation. Kaplan-Meier analysis[24] and the log rank test were performed to analyse and compare the renal survival between the decades 1980 to 1989 and 1990 to 2000. Terminal renal failure or death was taken as the end point. Cox proportional hazard regression[25] was used to perform univariate analysis of renal survival as the dependent variable and either histological chronicity, time from first detection of proteinuria to kidney biopsy, or renal insufficiency and arterial hypertension as the independent variables. χ^2 Test and Fisher's exact test were used to compare patient characteristics at diagnosis, treatment, and outcome. SPSS and WinSTAT were used as statistical software.

RESULTS

Between 1980 and 1989 (group I) 15 patients and between 1990 and 2000 (group II) 41 patients with biopsy proven lupus nephritis were seen at our centre. Their charts were reviewed, and the patient characteristics at diagnosis (tables 1–3), treatment (table 4), and outcome (table 5 and fig 1) were analysed. The majority of patients were female (87% in group I and 78% in group II). For patient characteristics at diagnosis, there were significant differences in median proteinuria (46 *v* 17 g/l), the rate of presence of proteinuria >3 g/d (60% *v* 34%), and serum creatinine concentrations >100 µmol/l (40% *v* 17%), which in both groups had significantly higher values in the former decade (group I).

Similarly, the rate of arterial hypertension at time of diagnosis, defined as having a diastolic blood pressure >90 mmHg in three consecutive measurements, was higher in group I (40% *v* 27%), but this difference was borderline. In contrast, the rate of anaemia defined as having a haemoglobin value in plasma <120 g/l in women or <130 g/l in men was significantly higher (33% *v* 61%) in group II. No significant difference was found for the median SLEDAI (13 *v* 16), the mean concentration of complement factor C3c (63.1 *v* 60.5 mg/l) or the median value of dsDNA antibodies (102 *v* 75 U/l) at time of diagnosis in both decades (table 1).

The mean (SD) time from the first detection of proteinuria until kidney biopsy was significantly shorter in the later decade (15.4 (15.6) *v* 3.9 (4.7) months) (table 2). A review of the histology findings (table 3) showed that in both groups most of the patients had diffuse proliferative nephritis WHO class IV (60% and 78%, respectively). The rate of high chronicity indexes was significantly increased in group I (33% *v* 10%), with significantly higher incidence of interstitial fibrosis (73% *v* 59%) and glomerulosclerosis (67% *v* 41%) in this group. In contrast, the presence of a high activity index of lupus nephritis in kidney biopsy (13% *v* 24%) and the presence of crescents (33% *v* 49%) were significantly more common in group II. In the biopsies in which crescents were present, the extent of crescents (15 (5)% *v* 36 (25)% of glomeruli) was significantly (p=0.045) higher in group II.

The treatment modalities were analysed (table 4). All patients received corticosteroids either alone or together with other immunosuppressive drugs. The patients received either an initial dose of methylprednisolone 1 mg/kg body weight (intermediate dose) or higher initial doses of 250–500 mg intravenous methylprednisolone a day (corticosteroid boli) in both groups with slow tapering of the corticosteroid dose. The proportion of patients with corticosteroid boli was not significantly different between the groups. A large proportion of patients in both decades received cyclophosphamide treatment (53% *v* 61%), all of them having WHO class IV nephritis.

Table 2 The mean time from the first detection of proteinuria until kidney biopsy was significantly shorter in the decade from 1990 to 2000 than in the decade from 1980 to 1989. The time in months between the first diagnosis of SLE until the referral to our centre and the kidney biopsy showed no significant differences between the two decades. Results are given as mean (SD) [range]

	1980–1989 (group I)	1990–2000 (group II)	p Value
Time from first diagnosis of SLE* until referral to our centre	29.2 (27.9) [range 11–156]	32.0 (41.2) [range 0–132]	NS
Time from first diagnosis of SLE until kidney biopsy	50.3 (52.3) [range 0–60]	39.3 (41.6) [range 1–132]	NS
Time from first detection of proteinuria† until kidney biopsy	15.4 (15.6) [range 5–60]	3.9 (4.7) [range 1–24]	0.00002

*Time when the diagnosis of SLE was first mentioned (not the first appearance of symptoms); †proteinuria >500 mg/day.

Table 3 Histological classification and specific histological characteristics of the patients with biopsy proven lupus nephritis in the two decades. High chronicity in kidney biopsy as well as the presence of interstitial fibrosis and/or glomerulosclerosis were found significantly less often in the decade from 1991 to 2000 than in the previous decade. In contrast, a high activity index and/or the presence of crescents in kidney biopsy was found more often in the decade between 1990 and 2000. Results are shown as No (%)

	1980–1989 (group I)	1990–2000 (group II)	p Value
Patients (n)	15	41	
Histological classification (WHO)	IV=9, II=2, III=1, V=2, VI=1	IV=32, II=7, V=2	NS
high chronicity index	5 (33)	4 (10)	0.01
High activity index	2 (13)	10 (24)	0.03
Crescents	5 (33)	20 (49)	0.04
Interstitial fibrosis	11 (73)	24 (59)	0.03
Tubular atrophy	12 (80)	30 (73)	NS
Glomerulosclerosis	10 (67)	17 (41)	0.002

Table 4 Treatment of patients with lupus nephritis in both decades. Antihypertensive treatment had to be performed significantly more often in the decade from 1980 to 1989 than in the later decade. Beside this no significant differences in the treatment schedules were found between the groups. Results are given as No (%)

	1980–1989 (group I)	1990–2000 (group II)	p Value
Patients (n)	15	41	
Cyclophosphamide	8 (53)	25 (61)	NS
Oral	2	4	
Bolus	6	15	
Both		6	
Corticosteroids	15 (100)	41 (100)	NS
Intermediate dose*	9	24	
Initial bolus†	6	17	
Azathioprine	4 (27)	16 (39)	NS
Cyclosporin A	3 (20)	4 (10)	NS
Hydroxychloroquine	2 (13)	11 (27)	NS
Mycophenolate mofetil	–	1 (2)	
Antihypertensive treatment in general	12 (80)	21 (51)	0.026
ACE inhibitors	3 (20)	11 (27)	NS
Statins	3 (20)	10 (24)	NS

*Intermediate dose = initial dose of 1 mg/kg body weight methylprednisolone/day followed by slow dose tapering; †initial bolus = >250 mg intravenous methylprednisolone/day followed by slow dose tapering.

A minority in both groups received a daily oral regimen (Fauci scheme)[26] with no significant difference in the frequency of this kind of treatment in both decades (15% *v* 24%). The remaining patients received intravenous cyclophosphamide in a bolus schedule (Austin scheme). The Austin scheme was performed as a modified NIH protocol.[27] Monthly pulses of 1 g cyclophosphamide were given intravenously for six months, and then, with the exception of refractory cases, daily oral azathioprine was given to maintain remission and to avoid side effects. If the initial serum creatinine was >180 µmol/l, the cyclophosphamide bolus was reduced to 750 mg/month, if the serum creatinine exceeded 440 µmol/l the cyclophosphamide bolus was 500 mg/month. Other immunosuppressive drugs such as cyclosporin A or mycophenolate mofetil were used less often. Antihypertensive treatment was given less often in group II (51%) than in group I (80%), and patients who required this treatment were more likely to receive angiotensin converting enzyme (ACE) inhibitors in group II (47% of patients with antihypertensive treatment) than in group I (25%). There was a similar frequency in the use of statins (around 20%) in both groups.

Table 5 Outcome of patients with lupus nephritis diagnosed in different decades. Results are given as No (%) unless otherwise stated

	1980–1989 (group I)	1990–2000 (group II)
Patients	15	41
Median (range) time of observation in months	95 (9–225)	24 (1–120)
Patient characteristics at last observation		
Median (range) creatinine (µmol/l)	100 (50–380)	80 (60–1070)
Creatinine >110 µmol/l	8 (53)	10 (24)
Mortality	1 (7)	1 (2)
End stage renal failure	6 (40)	–
Kidney transplantation	3 (20)	–

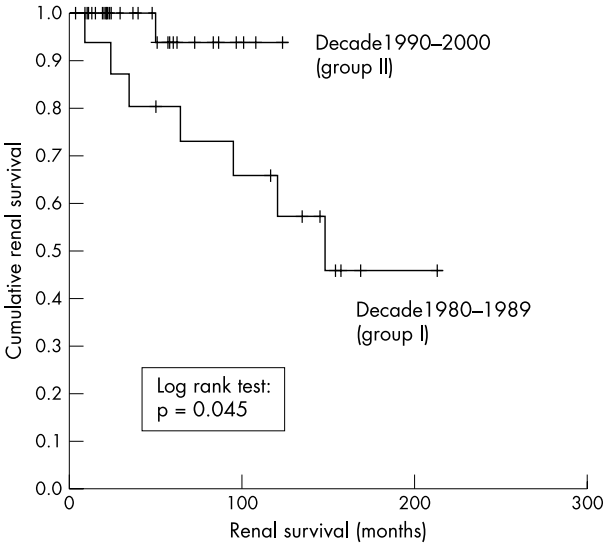

Figure 1 Renal survival curve of patients with lupus nephritis diagnosed in the decade 1990–2000 (group II, n=41) in comparison with 1980–1989 (group I, n=15). Whereas six patients of the earlier decade had terminal renal failure in the follow up, no patient of the later decade had the same event, which is significant (p=0.045). In both groups one patient died from infection.

The outcome of the patients at the set time was analysed (table 5, fig 1). The median observation time in group I was 95 months (range 9–225) and 24 months (1–120) in group II. Two patients died, one in each group. In both of them the cause of death was infectious disease. There was a marked difference in the rate of terminal renal failure at the set time: 40% in group I but no patient in group II had developed terminal renal failure. Serum creatinine concentrations >110 µmol/l at the last observation time were found in 53% of patients in group I and 24% of patients in group II. As observation time was shorter in group II, renal survival analysis using a Kaplan-Meier plot and log rank test for the end point of terminal renal failure was performed (fig 1) and disclosed a significantly better outcome (p=0.045) in group II than in group I.

DISCUSSION

In comparison with the group of patients with lupus nephritis diagnosed in the decade from 1980 to 1989 (group I), in the

group from 1990 to 2000 (group II) there was significantly less proteinuria, renal failure, and fewer histological signs of chronicity at the time of diagnosis. Moreover, the time from the first detection of proteinuria until kidney biopsy was significantly shorter in group II. No differences were found for the prognostic parameters of lupus nephritis age, sex, and race. The rate of arterial hypertension at the time of diagnosis was not significantly different between the groups. However, in the further course of disease group I received antihypertensive treatment significantly more often than group II. Histological signs of activity of kidney disease, such as high activity index and the presence of crescents, were significantly more common in group II.

Therefore, in the earlier decade (group I), renal failure, major proteinuria, and histological signs of chronicity, but not of activity, were significantly more common than in the later decade (group II). Because renal failure and histological chronicity are signs of more advanced kidney disease, an earlier diagnosis of lupus nephritis and an earlier start of treatment in the decade from 1990 to 2000 can be assumed. This conclusion is supported by the finding that the time between the first detection of proteinuria and the kidney biopsy was significantly shorter in group II. This was not the case for the time from the first diagnosis of SLE (irrespective of the kidney involvement) until the reference of the patient to our centre or until the kidney biopsy, which were not significantly different in the two decades. Therefore, better availability of laboratory tests and more knowledge about SLE nephritis, its severity, and its characteristic clinical signs by referring doctors and a more rapid decision towards kidney biopsy in our centre in the last decade might explain this finding. As a consequence, we found significantly less terminal renal failure in group II than in group I. In 41 patients of group II no cases of terminal renal failure were seen during the observation period. In contrast, in group I, 6/15 (40%) patients had terminal renal failure. In both groups one patient died of infection. However, the mean time of observation in the last decade is only 24 months (range 1–120) and it has been reported that when terminal renal failure occurs, this is in the first decade of follow up.[2 28] Therefore, in the group of patients of the later decade terminal renal failure might still occur. However, Kaplan-Meier analysis with application of a log rank test shows that the renal survival curves are significantly different in the two decades. Therefore, it is likely that the occurrence of terminal renal failure will be shown to differ between the two groups when a later analysis is performed.

Univariate analysis of our data showed that histological signs of chronicity and either arterial hypertension or renal insufficiency, or both, were predictive for terminal renal failure. As these are manifestations of more advanced disease, which were found significantly more often in the earlier decade, our conclusion is that in the earlier decade late diagnosis and therefore late start of treatment of lupus nephritis did not prevent terminal renal failure as it may have done in the later decade. It is remarkable that histological signs of activity such as a high activity index and the presence and extent of crescents at the time of kidney biopsy, which are suspected to be bad prognostic signs, were more common in the later decade in which the renal outcome was better. As the histological signs of activity in contrast with those of chronicity are reversible, we conclude that an early start of treatment reduces the negative prognostic value of histological signs of activity. This is in accordance with findings of other groups who question the prognostic value of histological changes in lupus nephritis.[22] There were only small differences in treatment in the groups. Almost the same proportion of patients received treatment with cyclophosphamide in both groups. Whereas 2/8 patients (25%) who received cyclophosphamide in group I had a daily oral dosing regimen (Fauci scheme), in group II only 4/25 patients received daily cyclophosphamide treatment (16%). All other patients who received cyclophosphamide had an intravenous bolus regimen (Austin scheme). All patients received corticosteroids mostly in an initial dose of methylprednisolone 1 mg/kg body weight. The proportion of patients who received higher doses of 250–500 mg intravenous methylprednisolone a day as an initial bolus treatment was similar in both groups (40% *v* 41%). Antihypertensive treatment had to be introduced less often in group II. However, patients who required this treatment were more likely to have received ACE inhibitors in group II than in group I (47% *v* 25%).

Owing to the different observation periods the results are difficult to compare with previous outcome investigations of lupus nephritis from other centres. However, it seems that the rate of terminal renal failure in the last decade might be similar or even lower than the most recently published data from other centres,[12 20 28] which showed a rate of terminal renal failure of 10–25%. In contrast, the outcome of the earlier decade was markedly worse than that reported from other groups. This difference in the prognosis of patients from the same centre between the decades makes it especially worthwhile to analyse parameters that might explain this phenomenon.

Interestingly, in contrast with the difference in the parameters that reflect mainly severity and chronicity of kidney disease in SLE, there was no significant difference between the groups in SLEDAI scores, serum anti-dsDNA antibodies, and complement concentrations at the time of diagnosis. We therefore conclude that parameters of systemic disease activity at the time of kidney biopsy have only limited value for the prediction of renal outcome in lupus nephritis. Like arterial hypertension and renal insufficiency, the presence of anaemia has been reported to be a negative prognostic factor for lupus nephritis. Paradoxically, in our cohort, anaemia at the time of diagnosis was significantly more common in the group of the patients with the better outcome. This might reflect the finding that the patients in the later decade had a more active disease as confirmed by histological findings, and anaemia, therefore, might be a result of this.

In conclusion, our data show improved outcome for patients with lupus nephritis diagnosed in 1990–2000 compared with 1980–1989. This corresponds with previous findings of improving outcome and decreasing mortality in lupus patients.[2 4]

In previous reports the better treatment of severe organ manifestations such as lupus nephritis was taken as one explanation of better outcome in recent years. We were able to show that despite the fact that the outcome is significantly different between the decades, almost the same drugs were used. There were only small differences in the use of oral daily cyclophosphamide and ACE inhibitors, which did not sufficiently explain the difference in the outcome of the patients. However, parameters which reflect severity and chronicity of kidney disease, such as histological changes and renal insufficiency at the time of diagnosis, were significantly different in the two decades and were predictive for the development of terminal renal failure. Moreover, the time from the first detection of proteinuria until kidney biopsy, resulting in the immediate start of immunosuppressive treatment, was significantly shorter in the decade between 1990 and 2000.

The benefit of early treatment with immunosuppressive agents has been recognised for several years.[27] We now conclude that early diagnosis and earlier start of treatment before persistent and irreversible renal damage occurs might be a key factor for the better outcome that others and we observed in lupus nephritis in recent years. Therefore, increasing the knowledge of primary care doctors in recognising this disease, and early referral of lupus patients to specialised centres with experience in the management of severe organ manifestations, might lead to further reduction of severe organ damage in SLE. Our data indicate that patients with currently diagnosed lupus nephritis have, probably as a result of earlier diagnosis, a better outcome than in previous

decades, and this despite the fact that there have been only minor changes in treatment.

In view of these results the question should be asked as to whether patients with lupus nephritis might currently be overtreated and whether better tailoring of the treatment to the clinical presentation, with low dose cyclophosphamide regimens for selected patients as suggested in current editorials[29] and as shown to be effective in current clinical trials,[30] might be a better approach.

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