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

C Fiehn, Y Hajjar, K Mueller, R Waldherr, A D Ho, K Andrassy

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.

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), 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 (x2), cellular crescents (x2), hyaline deposits, and interstitial inflammation. 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. 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.

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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 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 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. \( \chi^2 \) 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 was no significant difference between the two decades. Results are given as mean (SD) [range].

### Table 1 Characterisation of patients with lupus nephritis at the time of kidney biopsy

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<tr>
<td>Patients [n]</td>
<td>15</td>
<td>41</td>
<td></td>
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<tr>
<td>Sex (M/F)</td>
<td>13/2</td>
<td>32/9</td>
<td></td>
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<tr>
<td>Median age</td>
<td>29 (19–67)</td>
<td>35 (18–70)</td>
<td>NS</td>
</tr>
<tr>
<td>Arterial hypertension [%]</td>
<td>11 (27)</td>
<td>11 (27)</td>
<td>NS</td>
</tr>
<tr>
<td>Median serum creatinine (µmol/l)</td>
<td>6 (40)</td>
<td>6 (40)</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine &gt;110 µmol/l at time of presentation [%]</td>
<td>4 (20–40)</td>
<td>7 (17)</td>
<td>0.02</td>
</tr>
<tr>
<td>Median proteinuria (g/l)</td>
<td>46 (24–212)</td>
<td>17 (2–90)</td>
<td>0.008</td>
</tr>
<tr>
<td>Proteinuria &gt;3 g/day [%]</td>
<td>9 (60)</td>
<td>14 (34)</td>
<td>0.03</td>
</tr>
<tr>
<td>Anaemia [%]†</td>
<td>5 (33)</td>
<td>25 (61)</td>
<td>0.03</td>
</tr>
<tr>
<td>Median dsDNA antibodies (U/ml)</td>
<td>102 (8.7–206)</td>
<td>75 (5.9–1439)</td>
<td>NS</td>
</tr>
<tr>
<td>Median SLEDAI</td>
<td>13 (11–26)</td>
<td>16 (8–28)</td>
<td>NS</td>
</tr>
<tr>
<td>C3c &lt; normal (90–180 mg/l) [%]</td>
<td>9 (60)</td>
<td>23 (56)</td>
<td>NS</td>
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*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).

### Table 2 The mean time from the first detection of proteinuria until kidney biopsy was significantly shorter in the later decade (15.4 (15.6) vs 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% vs 10%), with significantly higher incidence of interstitial fibrosis (73% vs 59%) and glomerulosclerosis (67% vs 41%) in this group. In contrast, the presence of a high activity index of lupus nephritis in kidney biopsy (13% vs 24%) and the presence of crescents (33% vs 49%) were significantly more common in group II. In the biopsies in which crescents were present, the extent of crescents (15 (5)% vs 36 (25)% of glomeruli) was significantly higher (p=0.045) in group II.

### 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].

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<tr>
<td>Time from first diagnosis of SLE* until referral to our centre</td>
<td>29.2 (27.9) [range 11–156]</td>
<td>32.0 (41.2) [range 0–132]</td>
<td>NS</td>
</tr>
<tr>
<td>Time from first diagnosis of SLE until kidney biopsy</td>
<td>50.3 (52.3) [range 0–60]</td>
<td>39.3 (41.6) [range 1–132]</td>
<td>NS</td>
</tr>
<tr>
<td>Time from first detection of proteinuria† until kidney biopsy</td>
<td>15.4 (15.6) [range 5–60]</td>
<td>3.9 (4.7) [range 1–24]</td>
<td>0.00002</td>
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*Time when the diagnosis of SLE was first mentioned (not the first appearance of symptoms); †proteinuria >500 mg/day.
A minority in both groups received a daily oral regimen (Fauci scheme) 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. 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%).

**DISCUSSION**

In comparison with the group of patients with lupus nephritis diagnosed in the decade 1980–1989 (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 both 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 observed in the later 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. 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 observed in the later decade has been reported that when terminal renal failure occurs, this is in the first decade of follow up. 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.

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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 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. 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
Improved clinical outcome of lupus nephritis during the past decade

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 and as shown to be effective in current clinical trials, might be a better approach.

REFERENCES

Authors’ affiliations
C Cameron JS, Department of Internal Medicine V, University of Heidelberg, Germany
K Mueller, Department of Internal Medicine II, University of Heidelberg, Germany
R Waldherr, Institute of Pathology, Heidelberg, Germany
KAndrassy, Nephrology Section, Department of Internal Medicine, University of Heidelberg, Germany

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