Nephrol Dial Transplant (2013) 28: 373–379
doi: 10.1093/ndt/gfs428
Advance Access publication 6 December 2012

Improved outcome in anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis: a 30-year follow-up study

Marc Hilhorst[1], Benjamin Wilde[1], Pieter van Paassen[1], Bjorn Winkens[2], Peter van Breda Vriesman[1] and Jan Willem Cohen Tervaert[1], for the Limburg Renal Registry

[1]Department of Internal Medicine/Division of Clinical and Experimental Immunology, Maastricht University Medical Centre (MUMC+), Maastricht, The Netherlands and [2]Department of Methodology and Statistics, Maastricht University, Maastricht, The Netherlands

Correspondence and offprint requests to: Jan Willem Cohen Tervaert; E-mail: jw.cohentervaert@maastrichtuniversity.nl

Abstract

Background. Anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis has a poor prognosis. In the current study, we assessed whether prognosis in these patients improved over the last three decades.

Methods. In a large inception cohort, all consecutive patients with ANCA-associated glomerulonephritis were included between January 1979 and December 2009. Inclusion criteria were the presence of ANCA and the availability of a kidney biopsy. To assess renal and patient survival, patients were divided in three groups through time: 1979–89, 1990–2000 and 2001–09.

Results. A total of 181 patients were included. One-, 5- and 10-year survival was 77, 66 and 49%, respectively. Survival within the time groups was significantly different, yielding a hazard ratio for death of 2.9 for 1990–2000 and 3.9 for 1979–89 compared with 2001–09 ($P < 0.001$). Serum creatinine and active lesions as found in the kidney biopsy significantly decreased through the three decades.

Conclusions. Both patient and renal survival in patients with ANCA-associated renal vasculitis have improved over the last three decades. We postulate that both earlier diagnosis and better therapeutic management of patients are responsible for this effect.

Keywords: ANCA; outcome; renal biopsy; survival; vasculitis

Introduction

Granulomatosis with polyangiitis (GPA; Wegener's) and microscopic polyangiitis are characterized by the presence of vasculitis predominantly affecting small vessels and the presence of anti-neutrophil cytoplasmic antibodies (ANCA) [1–3]. ANCA present in these diseases are directed against myeloperoxidase (MPO) and/or proteinase 3 (PR3).

The introduction of cyclophosphamide and corticosteroids in the 1960s led to a dramatic improvement of the prognosis of these diseases with over 90% of patients achieving remission, while in untreated patients, the 1-year mortality was 80% [4, 5]. Despite advances in treatment during the last decades, relapses frequently occur [6]. Furthermore, long-term mortality as well as morbidity in ANCA-associated vasculitis (AAV) remains high [7–9] and end-stage renal disease is common, occurring in up to 30% of patients [10–16].

Recently, Holle *et al.* [17] showed that the mortality of GPA declined over the last four decades. Since most of the GPA patients in this study did not have renal involvement, we wondered whether the outcome of patients with the more severe form of AAV—i.e. patients with pauci-immune necrotizing crescentic glomerulonephritis—also improved over the last decades. For this purpose, we retrospectively analysed clinical, laboratory and histological data from the Limburg Renal Registry cohort from 1979 to 2009.

Materials and methods

Patients

Consecutive patients from our prospective regional Limburg Renal Registry between 1 January 1979 and 31 December 2009 were included [18]. Inclusion criteria were the availability of a kidney biopsy demonstrating pauci-immune necrotizing crescentic glomerulonephritis at the time of diagnosis and positivity for either MPO- or PR3-ANCA [1]. Exclusion criteria were the presence of co-existent renal diseases such as diabetes mellitus (DM), thin basement nephropathy and/or anti-glomerular basement membrane antibody-associated disease (anti-GBM disease). At the time of biopsy, clinical data and the need for renal replacement therapy (RRT) were recorded. In addition, time between first symptoms and renal biopsy was retrieved from the patient charts. Follow-up was closed in June 2010. Disease activity at the time of renal biopsy was scored using the Birmingham Vasculitis Activity Score (BVAS) [19]. In addition, 24 h urine samples were collected and proteinuria was measured [18]. Relapse of AAV was defined as the recurrence of clinical symptoms and/or the recurrence of erythrocyturia with proteinuria with or without histological confirmation of vasculitis and/or glomerulonephritis in combination with escalation of the dose of immunosuppressive therapy [20]. Renal survival was defined as preserved renal function (i.e. no need for RRT). To assess change of patient and/or renal survival through time, patients were divided into three time groups ranging from 1 January 1979 to 31 December 1989, 1 January 1990 to 31 December 2000 and 1 January 2001 to 31 December 2009.

For induction therapy, patients received steroids with oral cyclophosphamide (2 mg/kg/day) during 3–6 months from 1979 until 2009

[12, 13]. From 2009, patients received steroids with cyclophosphamide intravenously (15 mg/kg/cycle). Patients received three intravenous pulses 2 weeks apart which were followed by pulses 3 weeks apart until remission was achieved. Upon remission, intravenous cyclophosphamide was continued for 3 months. Cyclophosphamide was adjusted for age and renal function when given intravenously [21]. In severe or life-threatening disease, intravenous methylprednisolone (1000 mg/day for 3 days) and/or from 2000 plasma exchange were added [22]. After induction of remission, oral cyclophosphamide was tapered and eventually stopped during follow-up (18–24 months after remission induction). From 2000 on, however, induction therapy was followed by maintenance therapy with azathioprine instead of cyclophosphamide [13].

Methods

Kidney biopsies were processed as previously described [18]. Plasma and serum samples were collected at the time of renal biopsy and stored at −80°C.

Serum was tested for MPO- and PR3-ANCA. Since routine testing for ANCA was introduced in 1989, ANCA was tested retrospectively in serum samples of patients who underwent renal biopsy before 1989. Samples were tested by the indirect immunofluorescence technique and both by a direct and by capture ELISA [23].

Histological scoring

Scoring was performed by our renal pathologist (P.B.V.) blinded from clinical data. We applied the classification scheme developed by the EUVAS for ANCA-associated glomerulonephritis [24]. According to this classification, renal biopsies were classified as 'focal' (≥50% normal glomeruli), 'crescentic' (≥50% crescentic glomeruli) or 'sclerotic' (≥50% sclerotic glomeruli) with the remaining biopsies classified as 'mixed'. Moreover, we classified biopsies using a scheme that we previously adopted [12] based on the classification scheme which was developed by the NIH for lupus nephritis [25]. This scoring system, hereafter called 'histological groups', assesses both glomerular and tubulointerstital damage. Activity scores included fibrinoid necrosis (endothelial necrosis with a capillary leak), leucocyte margination (three or more leucocytes in one glomerular loop), cellular crescents (extracapillary proliferation) and interstitial inflammation (presence of immune cells in the interstitium) adding up to a maximum of 10 points. Chronicity scores included: fibrocellular crescents (extracapillary proliferation with sclerosis), interstitial fibrosis, tubular atrophy, glomerular obsolescence and fibrous crescents (sclerosed extracapillary proliferation) adding up to a maximum of 10 points. Lesions were counted per glomerulus. The number of affected glomeruli was expressed as the percentage of the total number of glomeruli observed in one section. Glomeruli that were not entirely on the slide were not counted. Biopsies were divided in four groups: minor lesions (<3 points on activity and on chronicity), active (>3 points for activity and <3 points on chronicity), chronic (vice versa) and combined lesions (>3 on activity and >3 on chronicity).

Statistical analysis

Continuous variables were presented as mean ± SD or as median and inter-quartile range (IQR). Categorical variables were presented as percentages. Differences in continuous and categorical variables were checked using the independent-samples *t*- or the Mann–Whitney *U*-test and the χ^2 or Fisher's exact test, respectively. Survival rates were estimated with the Kaplan–Meier method and differences in estimated survival curves were assessed using the log-rank test. Endpoints for patient survival were death, loss-to-follow-up or closure of study. Endpoints for renal survival were the start of RRT, patient death, loss-to-follow-up or study closure. Renal survival rate was presented as death-censored and as non-death-censored in separate figures. The effect of time groups (1979–89, 1990–2000 and 2001–09) was analysed by simple and multiple Cox regression, where the effect is adjusted for potential confounders using the 10% rule of Maldonado and Greenland [26]. The proportional hazards assumption was checked using Schoenfeld's residuals [27]. A two-tailed P-value of ≤0.05 was considered statistically significant. Statistical analyses were performed with SPSS 17.0 for Windows.

Results

Patient characteristics

In total, 197 consecutive patients with AAV with renal involvement were eligible for the study. Sixteen patients (8.1%) were excluded for co-existent renal diseases (eight with anti-GBM disease, six with diabetic nephropathy and two with thin basement nephropathy). Thus, 181 patients (age 61.4 ± 14.4; 71.3% male) were included in our study. At the time of renal biopsy, the median serum creatinine level of these patients was 315.0 µmol/L (IQR 347.5) and the median proteinuria level was 1.25 g (IQR 2.15) per 24 h. The mean time between first symptoms and renal biopsy was 87 days (range 2 days to 1.5 years). Twenty-five patients (13.8%) were on dialysis at the time of renal biopsy and 20 patients (11%) had alveolar lung haemorrhage at the time of renal biopsy.

The period of 1979–89 included 34 patients (median follow-up 5.7 years, range 0.1–28.5 years for all patients; for patients alive at the end of study: median follow-up 22.6 years, range 20.3–28.5 years). The period of 1990–2000 included 49 patients (median follow-up 3.9 years, range 0.1–19.4 years for all patients; for patients alive at the end of study: median follow-up 11.5 years, range 10.0–19.4 years). Finally, 98 patients were included in the period of 2001–09 (median follow-up 3.1 years, range 0.4–9.8 years for all patients; for patients alive at the end of study: median follow-up 3.9 years, range 0.4–9.8 years). Baseline characteristics per time group are presented in Table 1.

Patient survival

None of the patients were lost to follow-up. Of the 181 patients included, 79 (43.6%) died after a median follow-up of 39 months (range 1 day to 28 years).

Patient survival was 77.2% at 1 year, 65.8% at 5 years and 49.5% at 10 years (Figure 1). The median survival time as calculated by the Kaplan–Meier estimation was 10.4 years [95% confidence interval (CI) 8.23–12.54]. The 1-year patient survival in patients who presented with a serum creatinine ≥500 µmol/L was 61.9%. Causes of death occurring within 1 year after diagnosis were sepsis (11 patients; 13.9%) or active vasculitis (6 patients; 7.6%), whereas death occurring during long-term follow-up was mainly due to cardiovascular events (18 patients; 22.8%), malignancies (6 patients; 7.6%), kidney failure (i.e. patients refused RRT; 3 patients; 3.8%) or infections (5 patients; 6.3%). Thirty patients (37.9%) died at home (cause unknown; no autopsy was performed). Mortality was significantly associated with age, serum creatinine at the time of diagnosis, ANCA subtype, histological groups and time groups in simple analysis. In the multiple Cox regression, ANCA subtype and histological groups were not significantly associated with mortality, but age, serum creatinine and time groups remained significant (Table 2).

Renal survival

Estimated renal survival rate not censored for death was 66.7% at 1 year, 53.5% at 5 years and 36.9% at 10 years.

Table 1. Baseline characteristics of AAV patients divided over three defined time groups

	1979–89 ($n = 34$)	1990–2000 ($n = 49$)	2001–09 ($n = 98$)
Age[a,c]	55.0 ± 14.7	64.0 ± 14.8	61.0 ± 15.0
Serum creatinine (μmol/L)[b,c]	448 ± 283	456 ± 224	282 ± 202
BVAS[a]	18.0 (range 9–35)	14.0 (range 12–26)	15.0 (range 6–32)
Duration of symptoms prior to renal biopsy (days)	106 (range 7 d to 1 y)	91 (range 2 d to 1 y)	77 (range 7 d to 1 y)
PR3-/MPO-ANCA[a,b]	20/14	31/18	38/60
Patients receiving RRT (%)[a,b]	11.8	32.6	8.2
EUVAS classification	–	–	–
Focal (%)[b,c]	17.6	14.3	38.8
Crescentic (%)[b]	44.1	53.1	36.7
Mixed (%)[b,c]	35.3	32.7	24.5
Sclerotic (%)	0.6	0	0
Lesions	–	–	–
Minor lesions (%)[b,c]	29.4	26.5	40.8
Active lesions (%)[b,c]	20.5	16.3	10.2
Chronic lesions (%)[a,c]	23.5	44.9	45.9
Combined lesions (%)[a,b,c]	26.5	12.2	3.0

Baseline characteristics were defined as findings at the time of renal biopsy. PR3, proteinase 3; MPO, myeloperoxidase; EUVAS, European Vasculitis Study Group; BVAS, Birmingham Vasculitis Activity Score; RRT, renal replacing therapy; CI, confidence interval.
[a]$P < 0.05$ between 1979–89 and 1990–2000.
[b]$P < 0.05$ between 1979–89 and 2001–09.
[c]$P < 0.05$ between 1990–2000 and 2001–09.

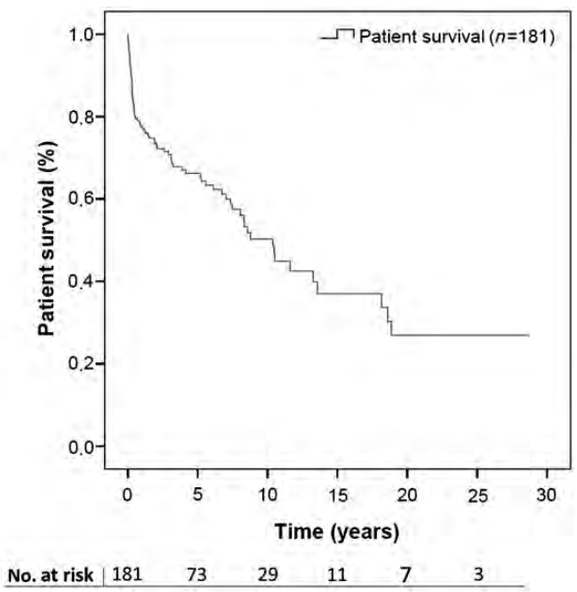

Fig. 1. Patient survival of AAV patients (whole group; $n = 181$).

At the time of renal biopsy, 25 (13.8%) patients were on dialysis. During follow-up, 10 (40%) of these patients recovered. Of the 156 patients who were RRT independent at the time of renal biopsy, 12 (7.8%) became RRT-dependent during follow-up after a median period of 28 months (range 11 months to 16 years). At study closure, 27 (14.9%) patients were RRT-dependent. Serum creatinine, the presence of chronic lesions in the kidney biopsy and time groups were significantly associated with renal survival in the multiple Cox regression analysis (Table 3).

Table 2. Multiple Cox regression analysis for patient survival in AAV

Parameter	Hazard ratio	95% CI	P-value
Time groups	—	—	0.001
2001–09	1 (reference)	—	—
1990–2000	2.957	1.593–5.489	0.001
1979–89	3.918	1.844–8.325	<0.001
Age[a]	1.058	1.033–1.082	<0.001
Serum creatinine[a]	1.001	1.000–1.002	0.035
Lesions[b]	—	—	0.584
Minor lesions	1 (reference)	—	—
Active lesions	1.387	0.656–2.934	0.391
Chronic lesions	1.538	0.834–2.837	0.168
Combined lesions	1.420	0.654–3.085	0.375

CI, confidence interval.
[a]At the time of renal biopsy.
[b]Descriptions about lesions can be found in the text under the Methods and Histological scoring section.

Histology

Applying the EUVAS scoring system, 51 (28.2%) biopsies were classified as 'focal', 77 (42.5%) 'crescentic', 52 (28.7%) 'mixed' and 1 (<0.1%) 'sclerotic'.

The 'focal' group had the best renal survival, whereas the 'crescentic' group had the worst ($P = 0.057$; data not shown). Moreover, patients in the 'focal' group had a significantly better patient survival when compared with the 'crescentic' group in simple Cox regression ($P = 0.020$) but not in multiple analysis ($P = 0.436$).

Scoring the biopsies using the NIH lupus nephritis modified scoring system, 63 (34.8%) biopsies contained minor lesions, 25 (13.8%) contained active lesions, 75 (41.4%) contained chronic lesions and 18 (9.9%) contained combined lesions. Serum creatinine levels were higher in the group of chronic and combined lesions

Table 3. Multiple Cox regression analysis for renal survival in AAV

Parameter	Death-censored			Non-death-censored		
	HR	95% CI	P-value	HR	95% CI	P-value
Time groups	—	—	0.001	—	—	<0.001
2001–09	1 (reference)	—	—	1 (reference)	—	—
1990–2000	4.065	1.948–8.484	<0.001	4.280	2.530–7.241	<0.001
1979–89	1.991	0.755–5.251	0.164	3.206	1.720–5.978	<0.001
Serum creatinine[a]	1.002	1.001–1.003	0.009	1.001	1.000–1.002	0.004
Lesions[b]	—	—	0.091	—	—	0.007
Minor lesions	1 (reference)	—	—	1 (reference)	—	—
Active lesions	2.364	0.848–6.593	0.100	2.142	1.104–4.154	0.024
Chronic lesions	2.860	1.209–6.766	0.017	2.417	1.399–4.176	0.002
Combined lesions	3.178	1.048–9.639	0.041	2.731	1.339–5.573	0.006

CI, confidence interval; HR, hazard ratio.
[a]At the time of renal biopsy.
[b]Descriptions about lesions can be found in the text under the Methods and Histological scoring section.

when compared with the other groups (P = 0.010). Proteinuria, however, was similar in all histological groups (P = 0.421; data not shown). Histological groups were significantly related to renal (Table 3) but not to patient survival (Table 2).

Changes over time

Patient survival was significantly different between the three time periods: 1-year survival was 64.7% for the period of 1979–89, 63.3% for the period of 1990–2000 and 88.5% for 2001–09, whereas 2-year survival was 61.8, 59.2 and 84.8%, respectively (P < 0.001; Figure 2). These differences were confirmed by the multiple Cox regression analysis (Table 2) showing a significant difference between 1979–89 and 2001–09 [hazard ratio (HR) = 3.918, 95% CI 1.844–8.325, P < 0.001], and between 1990–2000 and 2001–09 (HR = 2.957, 95% CI 1.593–5.489, P = 0.001). Fatal sepsis occurred in five patients in 1979–89, nine patients in 1990–2000 and two patients in 2001–09 (P = 0.049 between 1979–2000 and 2001–09). The 1-year patient survival in patients who presented with a serum creatinine ≥500 μmol/L was 61.5% for patients in 1979–89, 42.1% for patients in 1990–2000 and 92.3% for patients in 2001–09 (P = 0.003). Five-year patient survival in these patients was 38.5, 21.1 and 76.9%, respectively (P = 0.003).

Non-death-censored renal survival showed a 1-year survival of 55.9% for 1979–89, 40.8% for 1990–2000 and 82.5% for 2001–09. Two-year survival was 41.2, 36.7 and 79.9%, respectively (P < 0.001; Figure 3). Death-censored renal survival showed a 1-year survival of 83.2% for 1979–89, 61.6% for 1990–2000 and 90.7% for 2001–09 and a 2-year survival of 64.9, 58.5 and 90.7%, respectively (P < 0.001; Figure 4). After correction for serum creatinine and histological groups (Table 3), the multiple Cox regression analysis of the death-censored renal survival showed a non-significant difference between 1979–89 and 2001–09 (HR = 1.991, 95% CI 0.755–5.251, P = 0.164), and a significant difference between 1990–2000 and 2001–09 (HR = 4.065, 95% CI 1.948–8.484, P < 0.001). The multiple Cox regression analysis of non-death-censored renal survival showed a significant difference between 1979–89 and 2001–09 (HR = 2.389, 95% CI 1.280–4.462, P = 0.006) as well as between 1990–2000 and 2001–09 (HR = 2.227, 95% CI 1.301–3.810, P = 0.003; Table 3).

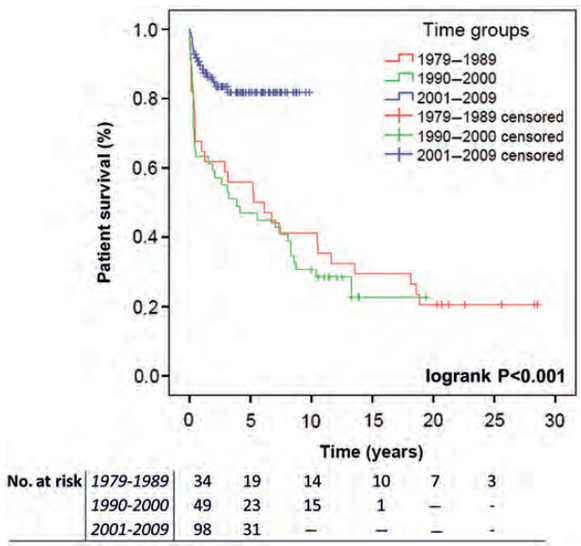

Fig. 2. Patient survival per time period (log-rank P < 0.001). Blue line: patients included between 2001 and 09 (n = 98). Green line: patients included in 1990–2000 (n = 49). Red line: patients included in 1979–89 (n = 34).

Changes of clinical and histological characteristics over time

The duration of symptoms prior to renal biopsy was 106 days for the patients in the time period 1979–89 (range 7 days to 1 year), 91 days for the patients in 1990–2000 (range 2 days to 1 year) and 77 days for the patients in 2001–09 (range 7 days to 1.5 years; P = 0.527 for 1979–89 versus 1990–2000; P = 0.337 for 1990–2000 versus 2001–09 and P = 0.193 for 1979–89 versus 2001–09). At

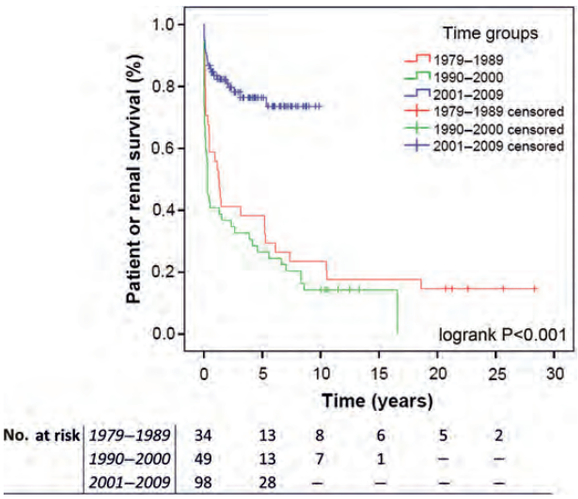

Fig. 3. Patient or renal survival per time period (log-rank P < 0.001). Blue line: patients included between 2001 and 09 ($n = 98$). Green line: patients included in 1990–2000 ($n = 49$). Red line: patients included in 1979–89 ($n = 34$).

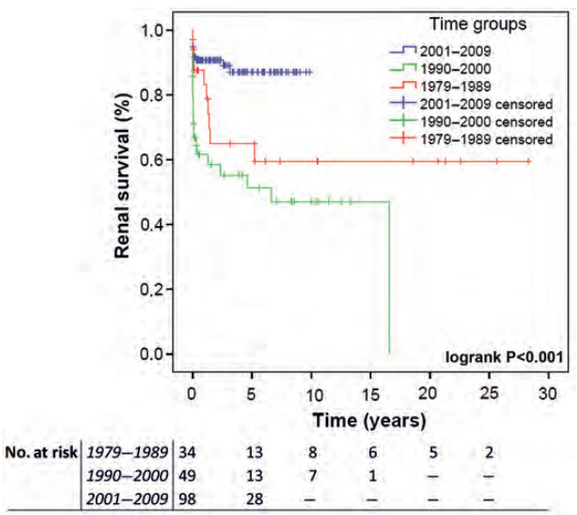

Fig. 4. Renal survival censored for death, per time period (log-rank P < 0.001). Blue line: patients included between 2001 and 09 ($n = 98$). Green line: patients included in 1990–2000 ($n = 49$). Red line: patients included in 1979–89 ($n = 34$).

the time of renal biopsy, 11.8% of the patients received RRT in 1979–89, 33.3% in 1990–2000 and 8.2% in 2001–09. Serum creatinine levels were significantly lower in patients included in 2001–09 when compared with the two other groups (Table 1). Over time, we observed that the number of biopsies in the 'focal' group (EUVAS classification) increased significantly from the 1979–89 group to the most recent time group (P < 0.001; Table 1). Furthermore, according to the NIH lupus nephritis modified scoring system, the activity index decreased, whereas the chronicity index remained stable (activity index P = 0.007, chronicity index P = 0.825; Figure 5) over

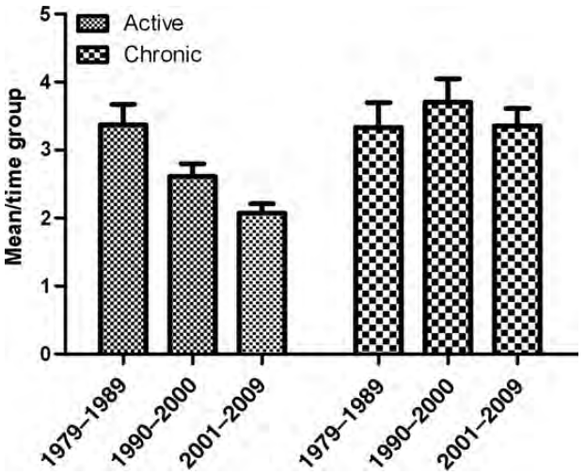

Fig. 5. Activity and chronicity scores during the three decades. The activity index decreased through the years (P = 0.007), while the chronicity index remained stable (P = 0.825).

time. The number of biopsies containing active or combined lesions decreased through the different time groups. Histological groups over the three time groups differed significantly (P = 0.006; data not shown).

Discussion

Over the last three decades, both patient and renal survival have improved significantly in patients with AAV.

Analysing the three different decades of 1979–89, 1990–2000 and 2001–09, we showed that mortality was significantly higher in the period of 1979–89 and 1990–2000 when compared with the last decade. Also, renal survival improved significantly in the last decade.

There are several explanations for this improved outcome:

First, early testing for ANCA in patients with a clinical suspicion of glomerulonephritis may have reduced the diagnostic delay in these patients. Baseline serum creatinine values were lower in the group from 2001–09 compared with the values obtained during the other two decades. Moreover, the number of kidney biopsies containing active lesions decreased and the number of patients with 'focal' and/or 'minor' lesions increased through the years. Both observations may be a consequence of an earlier diagnosis. We postulate that awareness of the ANCA-associated vasculitides and its manifestations increased among all medical specialities in our region during recent years and may be responsible for this effect. Interestingly, major differences in the mean serum creatinine levels and histology were not observed between the periods 1979–89 and 1990–2000, although ANCA testing was introduced in 1989 in our region. We postulate that it took several years before awareness among medical specialists in our region was raised, resulting in lower serum creatinine values and less renal damage in the kidney biopsy only in the period 2001–09. Our finding that the 'focal' group has the best renal survival is in line with the EUVAS

classification by Berden *et al*. [24]. In our study, however, the renal survival of the 'crescentic' group was worse than that of the 'mixed' group which contrasts our findings with those of Berden *et al.* In our study, we found more normal glomeruli in the 'mixed' group than in the 'crescentic' group (43 versus 22%). We think that the higher amount of normal glomeruli in this group compared with the crescentic group may explain the better renal outcome in our 'mixed' group [14, 15].

Secondly, better management and better treatment may have improved patient and/or renal outcome. During the last decades, treatment strategies have changed based on randomized controlled trials resulting in establishing modern treatment paradigms [3]. Importantly, plasma exchange was added to standard therapy in 2000 in our region for cases with severe renal and/or pulmonary vasculitis. A recent meta-analysis showed plasma exchange to be beneficial, diminishing the risk of end-stage renal disease [28]. Indeed, we demonstrated that patients with a serum creatinine value >500 µmol/L had a significantly improved outcome following the introduction of plasma exchange in 2000.

A study from the previous millennium reported no change in prognosis between the time periods of 1975–82 and 1985–95 in patients with ANCA-associated glomerulonephritis [29]. When analysing outcome studies from the last 30 years where patients with AAV with renal involvement were included, an improving trend, however, can be seen [9, 10, 16, 29–36]. In the 1980s, an early study [34] showed a 1-year patient survival of 54% and a late study showed a 1-year survival of 81% [36]. From then on, 1-year patient survival increased in ANCA-associated glomerulonephritis and was reported to be above 85% [9, 10, 16, 35] (Figure 6).

Moreover, recent studies demonstrated improved outcome in patients with non-renal and renal AAV during the last decade when compared with prior decades [17, 37]. In our study, we now demonstrate that this improvement is true for patients with either PR3-ANCA or MPO-ANCA-associated glomerulonephritis. Also, Flossmann *et al.* [9], who studied patients enrolled in EUVAS trials, recently observed improved outcome of patients with AAV. In contrast to the study by Flossmann *et al.*, our study was a study of an inception cohort. We believe this to be of importance since disease presentation and outcome in general may differ between patients who are enrolled in clinical trials compared with those who are followed within an observational cohort [38].

In our study, we observed both an improved patient (Figure 2) and renal survival (Figure 3) over time. Death-censored renal survival was, however, not different between time group 1979–89 and 2001–09 in the multiple Cox regression analysis. Since the HR for 1979–89 was 1.99, non-significance was probably due to a lack of power from the relatively small group in 1979–89 ($n = 34$).

However, the time period 1979–89 was not an independent predictor for death-censored renal survival corrected for serum creatinine and histology. This may indicate that improved outcome is not solely dedicated to improved therapy but also to earlier diagnosis as reflected by lower serum creatinine and fewer renal damage at the time of diagnosis in the most recent time period (Table 1).

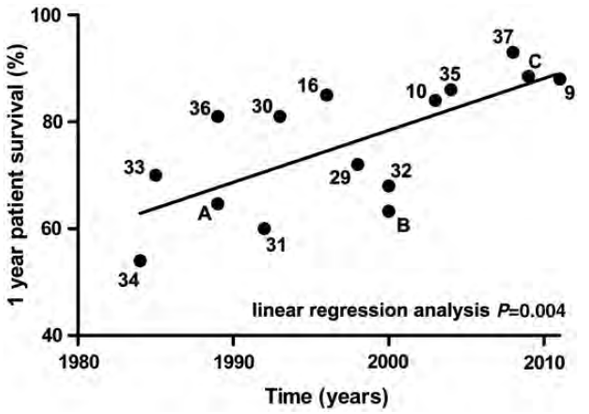

Fig. 6. The 1-year patient survival rates in AAV with renal involvement reported over the last 30 years, including our own data (linear regression analysis P = 0.01). Studies are indicated with their citation number (see references): Serra *et al.* [34] ($n = 53$); Savage *et al.* [33] ($n = 34$); (A) this study period 1979–89 ($n = 34$); Wilkowski *et al.* [36] ($n = 170$); Garrett *et al.* [31] ($n = 30$); Gans *et al.* [30] ($n = 60$); Hogan *et al.* [16] ($n = 170$); McLaughlin *et al.* [29] ($n = 47$); Hedger *et al.* [32] ($n = 128$); (B) this study period 1990–2000 ($n = 49$); Booth *et al.* [10] ($n = 246$); Weidner *et al.* [35] ($n = 80$); Eriksson *et al.* [37] ($n = 95$); (C) this study period 2001–09 ($n = 98$); Flossmann *et al.* [9] ($n = 535$).

In summary, we demonstrated in a large inception cohort that patient and renal survival in ANCA-associated glomerulonephritis improved substantially during the last three decades. This may be due to a decrease in diagnostic delay and improved therapeutic strategies.

Acknowledgements. We gratefully thank J. Damoiseaux, H. van Rie, N. Bijnens and P. Heerings-Rewinkel (Laboratory of Clinical Immunology, Maastricht University Medical Center, Maastricht, The Netherlands) for assistance. We also thank all participating nephrologists of the Limburg Renal Registry: F. de Heer, M.M.E. Krekels, G.H. Verseput (Orbis Medisch Centrum, Sittard); S. Boorsma, W. Grave, J. Wirtz (St Laurentiusziekenhuis, Roermond); W.E. Boer, L.A.M. Frenken, J. Wolters (Atrium Medisch Centrum, Heerlen); and K.M.L. Leunissen, J.P. Kooman, F.M. van der Sande (Dept. of Internal Medicine, Division of Nephrology, Maastricht University Medical Center, Maastricht, The Netherlands). M.H. is supported by a grant from the Dutch Kidney Foundation (KBSO 10.010) and B.W. by a grant from the Deutsche Forschungsgemeinschaft (Wi-3723/1-1).

Conflict of interest statement. None declared.

References

1. Cohen Tervaert J, Goldschmeding R, Elema J *et al*. Autoantibodies against myeloid lysosomal enzymes in crescentic glomerulonephritis. *Kidney Int* 1990; 37: 799–806
2. Falk RJ, Jennette JC. ANCA disease: where is this field heading? *J Am Soc Nephrol* 2010; 21: 745–752
3. Wilde B, Van Paassen P, Witzke O *et al*. New pathophysiological insights and treatment of ANCA-associated vasculitis. *Kidney Int* 2011; 79: 599–612
4. Fauci A, Haynes B, Katz P *et al*. Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. *Ann Intern Med* 1983; 98: 76–85

5. Walton E. Giant-cell granuloma of the respiratory tract (Wegener's granulomatosis). *Br Med J* 1958; 2: 265–270
6. Hogan S, Falk R, Chin H *et al*. Predictors of relapse and treatment resistance in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis. *Ann Intern Med* 2005; 143: 621–631
7. Mukhtyar C, Flossmann O, Hellmich B *et al*. Outcomes from studies of antineutrophil cytoplasm antibody associated vasculitis: a systematic review by the European League against Rheumatism systemic vasculitis task force. *Ann Rheum Dis* 2008; 67: 1004–1010
8. Luqmani RA, Suppiah R, Edwards C *et al*. Mortality in Wegener's granulomatosis: a bimodal pattern. *Rheumatology* 2010; 50: 697–702
9. Flossmann O, Berden A, De Groot K *et al*. Long-term patient survival in ANCA-associated vasculitis. *Ann Rheum Dis* 2011; 70: 488–494
10. Booth AD, Almond MK, Burns A *et al*. Outcome of ANCA-associated renal vasculitis: a 5-year retrospective study. *Am J Kidney Dis* 2003; 41: 776–784
11. Rihova Z, Jancova E, Merta M *et al*. Long-term outcome of patients with antineutrophil cytoplasmic autoantibody-associated vasculitis with renal involvement. *Kidney Blood Press Res* 2005; 28: 144–152
12. Franssen C, Stegeman C, Oost-Kort W *et al*. Determinants of renal outcome in anti-myeloperoxidase-associated necrotizing crescentic glomerulonephritis. *J Am Soc Nephrol* 1998; 9: 1915–1923
13. Slot M, Cohen Tervaert J, Franssen C *et al*. Renal survival and prognostic factors in patients with PR3-ANCA associated vasculitis with renal involvement. *Kidney Int* 2003; 63: 670–677
14. De Lind van Wijngaarden R, Hauer H, Wolterbeek R *et al*. Clinical and histologic determinants of renal outcome in ANCA-associated vasculitis: a prospective analysis of 100 patients with severe renal involvement. *J Am Soc Nephrol* 2006; 17: 2264–2274
15. Vergunst C, van Gurp E, Hagen E *et al*. An index for renal outcome in ANCA-associated glomerulonephritis. *Am J Kidney Dis* 2003; 41: 532–538
16. Hogan S, Nachman P, Wilkman A *et al*. Prognostic markers in patients with antineutrophil cytoplasmic autoantibody-associated microscopic polyangiitis and glomerulonephritis. *J Am Soc Nephrol* 1996; 7: 23–32
17. Holle J, Gross WL, Latza U *et al*. Improved outcome of 445 Wegener's granulomatosis patients in a German vasculitis center over four decades. *Arthritis Rheum* 2011; 63: 257–266
18. van Paassen P, van Breda Vriesman PJ, van Rie H *et al*. Signs and symptoms of thin basement membrane nephropathy: a prospective regional study on primary glomerular disease—the Limburg Renal Registry. *Kidney Int* 2004; 66: 909–913
19. Mukhtyar C, Lee R, Brown D *et al*. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). *Ann Rheum Dis* 2008; 68: 1827–1832
20. Hellmich B, Flossmann O, Gross WL *et al*. EULAR recommendations for conducting clinical studies and/or clinical trials in systemic vasculitis: focus on anti-neutrophil cytoplasm antibody-associated vasculitis. *Ann Rheum Dis* 2007; 66: 605–617
21. De Groot K, Harper L, Jayne DR *et al*. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis. *Ann Intern Med* 2009; 150: 670–680
22. Jayne DR, Gaskin G, Rasmussen N *et al*. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. *J Am Soc Nephrol.* 2007; 18: 2180–2188
23. Damoiseaux JGMC, Slot MC, Vaessen M *et al*. Evaluation of a new fluorescent-enzyme immuno-assay for diagnosis and follow-up of ANCA-associated vasculitis. *J Clin Immunol* 2005; 25: 202–208
24. Berden A, Ferrario F, Hagen EC *et al*. Histopathologic classification of ANCA-associated glomerulonephritis. *J Am Soc Nephro.* 2010; 21: 1628–1636
25. Austin H, Muenz L, Joyce K *et al*. Prognostic factors in lupus nephritis: contribution of renal histologic data. *Am J Med* 1983; 75: 382–391
26. Maldonado G, Greenland S. Simulation study of confounder-selection strategies. *Am J Epidemiol* 1993; 138: 923–936
27. Schoenfeld DA. Partial residuals for the proportional hazards regression model. *Biometrika* 1982; 69: 239–241
28. Walsh M, Catapano F, Szpirt W *et al*. Plasma exchange for renal vasculitis and idiopathic rapidly progressive glomerulonephritis: a meta-analysis. *Am J Kidney Dis* 2011; 57: 566–574
29. McLaughlin K, Jerimiah P, Fox J *et al*. Has the prognosis for patients with pauci-immune necrotizing glomerulonephritis improved? *Nephrol Dial Transplant* 1998*;* 13: 1696–1701
30. Gans R, Kuizinga M, Goldschmeding R *et al*. Clinical features and outcome in patients with glomerulonephritis and antineutrophil cytoplasmic autoantibodies. *Nephron* 1993; 64: 182–188
31. Garrett P, Dewhurst A, Morgan L *et al*. Renal disease associated with circulating antineutrophil cytoplasm activity. *QJ Med* 1992; 85: 731–749
32. Hedger N, Stevens J, Drey N *et al*. Incidence and outcome of pauci-immune rapidly progressive glomerulonephritis in Wessex, UK: a 10-year retrospective study. *Nephrol Dial Transplant* 2000; 15: 1593–1599
33. Savage C, Winearls C, Evans D *et al*. Microscopic polyarteritis: presentation, pathology and prognosis. *QJ Med* 1985; 56: 467–483
34. Serra A, Cameron J, Turner D *et al*. Vasculitis affecting the kidney: presentation, histopathology and long-term outcome. *QJ Med* 1984; 53: 181–207
35. Weidner S, Geuss S, Hafezi-Rachti S *et al*. ANCA-associated vasculitis with renal involvement: an outcome analysis. *Nephrol Dial Transplant* 2004; 19: 1403–1411
36. Wilkowski M, Velosa J, Holley K *et al*. Risk factors in idiopathic renal vasculitis and glomerulonephritis. *Kidney Int* 1989; 36: 1133–1141
37. Eriksson P, Jacobsson L, Lindell A *et al*.. Improved outcome in Wegener's granulomatosis and microscopic polyangiitis? A retrospective analysis of 95 cases in two cohorts. *J Intern Med* 2008; 265: 496–506
38. Pagnoux C, Carette S, Khalidi N *et al*. Are patients with anti-ANCA-AAV entered into clinical trials representative of patients followed in observational cohorts? *Clin Exp Immunol* 2011; 164 (Suppl. 1): 81–82

Received for publication: 4.11.2011; Accepted in revised form: 8.8.2012