ANCA-associated vasculitis with renal involvement: an outcome analysis

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Abstract

Background. The anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides are a group of heterogeneous diseases. This study was undertaken to investigate the outcome of Wegener’s granulomatosis (WG), microscopic polyangiitis (MPA) and renal-limited vasculitis (RLV). Furthermore, we analysed the differences in patients with proteinase 3-ANCA (PR3-ANCA) and those with myeloperoxidase-ANCA (MPO-ANCA), which have not been assessed in a homogeneously treated group of patients with renal involvement.

Methods. In this retrospective analysis, 80 patients with a new diagnosis of WG, MPA or RLV with biopsy-proven renal involvement were followed over a median of 46.7 months (range: 0.8–181.9 months). All patients had induction treatment with cyclophosphamide and oral corticosteroids.

Results. At the end of follow-up, 23% were dependent on dialysis. Renal survival was significantly worse in patients with WG compared with patients with MPA or RLV (P=0.04). A higher rate of end-stage renal disease (ESRD) was noticed in PR3-ANCA- vs MPO-ANCA-positive patients. A total of 21 patients (26%) died. Predictors of patient mortality were development of ESRD, older age and the maximum creatinine in the first month. Mortality was found to be higher in patients with WG and was significantly higher in PR3-ANCA-positive cases (P=0.02). The relative risk of death was 9.32 times higher in PR3-ANCA- vs MPO-ANCA-positive patients.

Conclusions. Our data underscore the pathogenetic potential of ANCA by demonstrating a more aggressive disease state and a poorer outcome in patients with PR3-ANCA.

Keywords: anti-neutrophil cytoplasmic antibody; microscopic polyangiitis; outcome; vasculitis; Wegener’s granulomatosis

Introduction

The anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides, Wegener’s granulomatosis (WG) and microscopic polyangiitis (MPA), are chronic multisystemic autoimmune diseases that follow an unpredictable course even with immunosuppressive treatment. The characteristic features are the presence of ANCA and the necrotizing inflammation of small vessels. However, these disorders exhibit important serological and clinical differences. ANCA are directed against several myeloid enzymes, of which ANCA to proteinase 3 (PR3-ANCA) and myeloperoxidase (MPO-ANCA) are the most common [1]. Clinically, WG and MPA are heterogeneous diseases that may be distinguished by the involvement of different organ systems of variable severity. Furthermore, these disorders are characterized by a relapsing course.

Renal involvement is frequent in ANCA-associated vasculitis and was shown to be one of the negative prognostic factors of mortality [2–4]. Besides full-blown systemic vasculitis with renal involvement, its renal-limited variant is characterized by the absence of vasculitis in any other organ. This renal-limited vasculitis (RLV), previously named idiopathic necrotizing crescentic glomerulonephritis, is now widely accepted to form an entity within the ANCA-associated vasculitides and may be regarded as a ‘forme-fruste’ [5]. The differences in patient survival and renal outcome between RLV, MPA and WG have not been analysed in detail.

Several studies have described clinical features, performed outcome analysis and attempted to determine prognostic markers in ANCA-associated
vasculitis with renal involvement [3,6–11]. However, many of these studies have assessed only small patient numbers or performed analysis for one disease (WG or MPA) only.

In this study, we analysed the outcome in a large cohort of ANCA-associated vasculitis treated with cyclophosphamide and oral corticosteroids for remission induction. All patients had biopsy-proven renal involvement. Attention was especially focused on patient and renal survival in the diagnostic subgroups and the influence of ANCA antigen specificity on these parameters.

Subjects and methods

Patient selection

In a retrospective design, 80 patients with a diagnosis of small-vessel vasculitis, according to the Chapel Hill consensus conference (CHCC) criteria [12], were analysed in this study. Patients were only included when a new diagnosis of WG, MPA or RLV had been made and renal involvement was present. Renal biopsy was performed in all patients, except in one, who was requiring dialysis due to severe renal involvement with active urinary sediment with red blood cell casts. Renal biopsy was not considered in this patient after WG had been histologically confirmed by the presence of granulomatous pulmonary disease. All other patients had histologically proven focal necrotizing glomerulonephritis with few or no immunoglobulin deposits (pauci-immune).

Patient classification

According to the proposal of the CHCC [12], patients were retrospectively divided into the following diagnostic subgroups.

Wegener’s granulomatosis. Patients with systemic vasculitis and presence of granulomatous inflammation in biopsy specimen or presence of clinical signs strongly suggestive for granulomatous disease. This comprised involvement of the upper respiratory tract with nasal inflammation (purulent/bloody nasal discharge), sinusitis or otitis media or lower respiratory tract manifestation with pulmonary nodules or fixed infiltrates.

Microscopic polyangiitis. Patients with systemic vasculitis and absence of granuloma formation in biopsy specimen and absence of clinical signs strongly suggestive for granulomatous disease.

Renal-limited vasculitis. Patients with biopsy-proven pauci-immune necrotizing glomerulonephritis without symptoms of systemic vasculitis.

According to the CHCC, non-invasive evaluations could be used to identify abnormalities that adequately predicted the presence of granulomatous inflammation without having to perform a histological examination. As required by this nomenclature, ANCA antigen specificity was not used as a definition criterion.

Data collection

Start and endpoint. Patients were entered into the study from the time point when renal biopsy was performed and a diagnosis of ANCA-associated vasculitis was established. All data were retrospectively registered at diagnosis and during follow-up by systematically reviewing medical records on patients’ history, laboratory analysis and medication. Glomerular filtration rate (GFR) was calculated using the equation by Cockcroft and Gault [13]. Patients were followed until a given endpoint (end of data collection), end-stage renal disease (ESRD) or death occurred.

ANCA analysis. All patients had been tested for the presence of ANCA by indirect immunofluorescence (iIF) as well as for PR3-ANCA and MPO-ANCA by enzyme-linked immunosorbent assay (ELISA). The iIF tests and ELISA systems used for ANCA detection were manufactured by Euroimmun (Lübeck, Germany).

Organ involvement

Organ manifestations were only registered if symptoms could be ascribed to active vasculitis or objective assessment confirmed the clinical presentation to be attributable to vasculitis. The disease extent index (DEI) was used as a parameter to assess the degree of organ involvement [14].

Treatment

All patients received a homogeneous induction treatment according to local treatment guidelines. None of the patients had received any immunosuppressive medication before diagnosis. All patients received induction treatment with cyclophosphamide (CYC; 2 mg/kg body weight) and oral corticosteroids (OCS; 1 mg/kg body weight). A CYC dose reduction by 25% was performed for age >65 years and for GFR <50 ml/min. A dose reduction by 50% was performed for GFR <10 ml/min. In 50 patients, treatment with OCS was preceded by intravenous pulse methylprednisolone (MEP) (mean: 4.3 mg/kg body weight; range: 2.3–15.1 mg/kg body weight) for 3 consecutive days. Plasmapheresis was additionally used in five patients. In 16 patients, CYC was switched to azathioprine (AZA) after reaching stable remission (median: 6 months; range: 4.2–13 months). Five patients had been included in the European Vasculitis Study Group (EUVAS) CYCAZAREM trial and three patients were studied in MEPEX.

Treatment response

Remission. Remission was defined as the stabilization or improvement of renal function and resolution of extrarenal manifestations of systemic vasculitis. The status of complete remission was supported by normalization of laboratory parameters (erythrocyte sedimentation rate, C-reactive protein and leukocyte count).

Relapse. Relapse was defined as a rise in creatinine concentration occurring with a nephritic sediment or worsening/new extrarenal manifestation involving the typical organ systems. Symptoms were only registered as relapse if they could be ascribed to active vasculitis or objective
assessment confirmed the clinical presentation to be attributable to vasculitis.

**Statistical analysis**

Statistical analysis was performed with SPSS 11.0 for windows (SPSS Inc., Chicago, IL, USA). Medians and ranges are reported for non-normal distributed data and means± SD are reported for normal-distributed data. Differences between means were tested using the Student’s t-test. The Mann–Whitney U-test was applied for non-parametric comparison of metric data. The χ²-test was used for comparison of categorical data. Kaplan–Meier life-table analysis was used to assess patient survival, renal survival and relapse-free survival. Relapse-free survival was only determined in patients living long enough to experience relapse. Pearson’s correlation coefficients were calculated to determine an association between relapse-free survival and the duration of initial therapy. Univariate survival analysis was performed using the log-rank test. Multivariate analysis of patient survival used Cox’s regression model. Variables that did not affect survival significantly were removed by a backwards stepwise procedure according to a likelihood ratio. All tests were two-tailed and P-values of <0.05 were considered significant.

**Results**

**Presentation at time of diagnosis**

In this analysis, 80 patients with a new diagnosis of ANCA-associated vasculitis with renal involvement were studied retrospectively between 1986 and 2001. All patients were European Caucasians from a single centre (Department of Internal Medicine, Division of Nephrology and Hypertension, University of Erlangen-Nürnberg, Germany). The study included 40 women and 40 men. The median age was 63 years, with a range of 30–84 years (Table 1).

**Patient classification and ANCA analysis**

Thirty-two patients were classified as WG and 28 patients as MPA. RLV was present in 20 patients. WG was more common in men (12 women and 20 men; ratio: 1:1.9) and a slight female preponderance was found in MPA (16 women and 12 men; ratio: 1:3:1) (Table 1).

All patients were tested for ANCA by iIF and ELISA. Seventy-six (95%) patients had a positive test result. By ELISA, PR3-ANCA or MPO-ANCA were found in 74 (92.5%) patients. Table 2 shows the frequency of PR3-ANCA and MPO-ANCA in association with diagnostic subgroups.

**Organ involvement**

The majority of patients (96%) presented with constitutional symptoms. The most common finding was musculoskeletal complaints with arthralgias and myalgias in patients with WG, while patients with MPA predominantly complained about constitutional symptoms. The distribution of organ involvement in patients with WG and MPA at time of diagnosis is shown in Table 3. Ear–nose–throat involvement (36%) and pulmonary disease (27%) were the most common organ manifestations. These were most prominent in WG and PR3-ANCA-positive patients. None of the patients with MPA had upper respiratory tract involvement with purulent/bloody nasal discharge, sinusitis or otitis media. Patients with WG and those with PR3-ANCA had significantly higher DEI scores than patients with MPA (8 vs 7; P = 0.012) or MPO-ANCA (8 vs 7; P = 0.017) (Table 3).

**Renal involvement**

The mean serum creatinine at time of diagnosis was 385 ± 238 µmol/l. Patients with WG and PR3-ANCA-positive patients presented with higher creatinine levels than patients with MPA, RLV, MPO-ANCA-positive

| Table 1. Demographic and clinical characteristics of 80 patients with ANCA-associated vasculitis at time of diagnosis |
|-------------------------------|---------------------|-----------------|-----------------|-----------------|-----------------|
| **Variable**                  | **Patients**        | **Female/male** | **Age**         | **Creatinine**  | **GFR**         |
|                               |                     |                 | (years)         | (µmol/l)       | (ml/min)        |
| Total                         | 80                  | 40/40           | 63 (30–84)      | 385 ± 238      | 18 (5–135)      |
| WG                            | 32                  | 12/20           | 57.3 (30–75)    | 434 ± 272      | 17 (5–71)       |
| MPA                           | 28                  | 16/12           | 66.8 (42–54)    | 384 ± 222      | 17 (5–72)       |
| RLV                           | 20                  | 12/8            | 64.7 (35–80)    | 307 ± 187      | 23 (7–135)      |
| PR3-ANCA                      | 43                  | 18/25           | 59.6 (30–80)    | 422 ± 264      | 17 (5–71)       |
| MPO-ANCA                      | 31                  | 19/12           | 67.7 (35–84)    | 353 ± 209      | 18 (5–135)      |
| ANCA-negative                 | 6                   | 3/3             | 49.1 (39–74)    | 281 ± 138      | 24 (18–70)      |

**Table 2. ANCA-ELISA in association with diseases**

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 80)</th>
<th>WG (n = 32)</th>
<th>MPA (n = 28)</th>
<th>RLV (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR3-ANCA</td>
<td>43 (54%)</td>
<td>29 (91%)</td>
<td>7 (25%)</td>
<td>7 (35%)</td>
</tr>
<tr>
<td>MPO-ANCA</td>
<td>31 (39%)</td>
<td>2 (6%)</td>
<td>20 (71%)</td>
<td>9 (45%)</td>
</tr>
<tr>
<td>ANCA-negative</td>
<td>6 (7%)</td>
<td>1 (3%)</td>
<td>1 (4%)</td>
<td>4 (20%)</td>
</tr>
</tbody>
</table>

*aMedian and range are reported for age and GFR. bCreatinine values are mean±SD. GFR was calculated by using the Cockcroft–Gault equation [13].*
patients and ANCA-negative patients (Table 1). However, as serum creatinine is influenced by body weight, age and sex, the GFR was calculated using the equation by Cockcroft and Gault [13]. No essential differences in GFR were found according to diagnosis or ANCA antigen specificity (Table 1). Twenty-two patients (28%) required dialysis at diagnosis or within the first weeks of treatment. Of these, significantly more had WG compared with MPA or RLV (14 vs 6 vs 2; \( P = 0.006 \)).

Follow-up

The median duration of follow-up was 46.7 months with a range of 0.8–181.9 months.

Treatment

At the start of treatment, CYC was given at a mean daily dose of 1.7 mg/kg body weight. The duration of cytotoxic treatment (CYC and AZA) during induction treatment and the following period of stable remission was analysed from the time of diagnosis until the drug was completely withdrawn for the first time (further called initial cytotoxic treatment). Temporary interruptions of immunosuppression (in the case of infection, leukopenia, etc.) were not regarded as discontinuation, if cytotoxic therapy was resumed. Patients who were still on induction treatment at the end of data collection or who had died during active disease were excluded from the analysis of initial cytotoxic treatment (n = 18). In the whole group, the median time of initial cytotoxic treatment was 18 months (range: 0.5–95 months).

OCS were initially given for a median duration of 33 months (range: 1.6–67 months). In 50 patients, treatment with OCS was preceded by pulse MEP. These patients presented with significantly higher creatinine levels (median: 528 vs 380 \( \mu \text{mol/l} \); \( P = 0.02 \)) and lower GFR. Patients having received MEP were evenly distributed between WG and MPA, while only a minority of RLV had been treated with MEP. No difference in renal and patient survival was observed regarding pulse MEP (data not shown).

Renal survival

After 1 month of treatment the creatinine had fallen to a median of 194 \( \mu \text{mol/l} \) with a further reduction to 140 \( \mu \text{mol/l} \) after 1 year. At the end of follow-up, 18 patients (23%) suffered from ESRD. ESRD occurred in a median time of 1.9 months (range: 0–129.6 months). Eight of the 22 patients (36%) requiring dialysis at the time of diagnosis remained at ESRD. Plasmapheresis was additionally used in five patients, which were all PR3-ANCA-positive and had WG. Only one of these patients progressed to ESRD.

Table 3. Distribution of organ involvement in 80 patients with ANCA-associated vasculitis at time of diagnosis according to diagnostic subgroups and ANCA antigen specificity

<table>
<thead>
<tr>
<th>Organ involvement</th>
<th>Total (n = 80)</th>
<th>WG (n = 32)</th>
<th>MPA (n = 28)</th>
<th>PR3-ANCA (n = 43)</th>
<th>MPO-ANCA (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENT</td>
<td>29</td>
<td>29</td>
<td>0</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>22</td>
<td>14</td>
<td>8</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>Renal</td>
<td>80</td>
<td>32</td>
<td>28</td>
<td>43</td>
<td>31</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>11</td>
<td>8</td>
<td>4</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Ocular</td>
<td>12</td>
<td>8</td>
<td>4</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Cardiac</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Neurological</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral nerves</td>
<td>12</td>
<td>3</td>
<td>11</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>CNS</td>
<td>13</td>
<td>6</td>
<td>8</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>DEI(^a)</td>
<td>7 (4–13)</td>
<td>8 (4–13)</td>
<td>7 (3–13)</td>
<td>8 (3–13)</td>
<td>7 (3–13)</td>
</tr>
</tbody>
</table>

\(^a\)Values are medians with ranges in parentheses.

For analysis of renal survival according to initial creatinine, patients were divided into three groups of equal size. Patients presenting with high creatinine levels (\( >582 \mu \text{mol/l} \)) progressed significantly more frequently to ESRD than patients with low serum creatinine (\( \leq 299 \mu \text{mol/l} \)) (\( P < 0.001 \); data not shown). Figure 1A shows the assessment of renal survival according to diagnostic subgroups. Progression to ESRD occurred significantly more often in patients

\( a \)
with WG (n = 11), while only six patients with MPA and one with RLV progressed to ESRD (P = 0.04).

Figure 1B shows the analysis of renal survival according to ANCA antigen specificity: 12 patients with PR3-ANCA and six patients with MPO-ANCA developed ESRD (P = 0.26, not significant).

**Patient survival**

A total of 21 patients (26%) died. Median time of patient survival was 4.1 months (range: 0.8–181.9 months). Overall 1 and 5 year patient survival rates were 86% and 81%, respectively. Most of the deaths were indirectly related to vasculitis [15 patients (71%)] and were mostly treatment-related infectious complications. Two patients died from vasculitis: one from coronaritis (diagnosed post-mortem) and one from severe pulmonary haemorrhage. In four patients the cause of death was unrelated to vasculitis. Two of these patients died from myocardial infarction, one died from skin cancer (unrelated to the duration of immunosuppressive treatment) and one from diverticulitis and septic shock. For statistical analysis of patient survival, these deaths were regarded as censored cases (lost to follow-up) and, therefore, survival analysis strictly involved disease-related and disease-associated deaths only.

No statistical difference was seen according to diagnostic subgroups; however, patients with WG showed a higher tendency to die: nine of 32 patients with WG (28%) died vs five of 28 patients with MPA (18%), while three deaths (15%) were recorded in patients with RLV (P = 0.29). Figure 2A shows the assessment of patient survival according to diagnostic subgroups. By intention-to-treat analysis (not censoring cases, in which the cause of death was
unrelated to vasculitis), mortality rates were identical to the statistical analysis with censored cases: 17 PR3-ANCA- and four MPO-ANCA-positive patients died (P = 0.012) and 11 with WG died vs seven with MPA. There were three deaths in patients with RLV (P = 0.29).

Figure 2B shows the analysis of patient survival according to ANCA antigen specificity. Mortality was significantly higher in PR3-ANCA-positive patients: 15 of 43 PR3-ANCA- and 2 of 31 MPO-ANCA-positive patients died (35% vs 6%; P = 0.02). None of the ANCA-negative patients died. Long-term patient survival was significantly worse for patients with PR3-ANCA compared with MPO-ANCA: respective 1 and 5 year patient survival rates were 79% and 69% for PR3-ANCA- and 93% both for MPO-ANCA-positive patients (P = 0.029).

Mortality was significantly higher in patients requiring dialysis at diagnosis, with 10 of 22 vs 11 of 58 without renal replacement therapy (P = 0.023). At the end of follow-up, 11 of the 18 patients suffering from ESRD had died. The 1 and 5 year patient survival rates were 83% and 61% for patients with ESRD and 87% and 87% for patients with preserved renal function, respectively. Comparison of survival curves showed a significantly worse survival for patients with ESRD (P = 0.029; Figure 3A). By univariate analysis, the relative risk of death was 3.06 times higher in patients with ESRD compared with patients with preserved renal function.

For analysis of patient survival according to age or initial creatinine, patients were divided into three groups of equal size. Long-term patient survival was significantly worse for the oldest patients (P = 0.026;
Table 4. Prognostic factors of patient survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>βa</th>
<th>SD</th>
<th>Relative risk of death</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR3-ANCA vs MPO-ANCA</td>
<td>2.233</td>
<td>0.774</td>
<td>9.32</td>
<td>0.004</td>
</tr>
<tr>
<td>Ageb</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Old (C) vs middle (B)</td>
<td>2.039</td>
<td>0.65</td>
<td>7.68</td>
<td>0.002</td>
</tr>
<tr>
<td>Old (C) vs young (A)</td>
<td>2.13</td>
<td>0.704</td>
<td>8.42</td>
<td>0.003</td>
</tr>
<tr>
<td>Maximum creatinine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle (B) vs low (A)</td>
<td>1.394</td>
<td>0.782</td>
<td>4.031</td>
<td>0.075</td>
</tr>
<tr>
<td>High (C) vs low (A)</td>
<td>1.646</td>
<td>0.799</td>
<td>5.18</td>
<td>0.04</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>0.079</td>
<td>0.028</td>
<td>1.082</td>
<td>0.005</td>
</tr>
<tr>
<td>Maximum creatinine (per µmol/l)</td>
<td>0.003</td>
<td>0.001</td>
<td>1.003</td>
<td>0.012</td>
</tr>
</tbody>
</table>

a β refers to the regression coefficient and corresponds to the natural log of the relative hazard (relative risk).
b The total cohort was divided into three groups of equal size by using the 33rd and 66th percentiles of age [(A) < 56.5 years, (B) 56.5–67.6 years and (C) > 67.6 years].

c The maximum creatinine was divided into three groups of equal size by using the 33rd and 66th percentiles of creatinine and creatinine clearance [(A) < 299 µmol/l, (B) 299–582 µmol/l and (C) > 582 µmol/l; (A) < 10.9 ml/min, (B) 10.9–21.0 ml/min and (C) > 21.0 ml/min].

Figure 3B). No difference was seen for initial creatinine. However, as shown in Figures 3C and 3D, subdivision according to the maximum creatinine or the minimum creatinine clearance in the first month of treatment showed significantly worse patient survival in patients with the highest maximum creatinine or the lowest minimum creatinine clearance (P = 0.025 and 0.024, respectively).

Prognostic factors of patient survival

Cox’s regression model was used for multivariate analysis of selected variables as prognostic factors of patient survival, controlling for diagnostic subgroup, ANCA subspecificity, age, DEI, pulmonary- or upper respiratory tract involvement and the maximum creatinine or minimum creatinine clearance in the first month. Variables that had already shown significantly higher mortality by univariate analysis proved to be significant prognostic factors with Cox’s model thus predicting patient survival at diagnosis (Table 4).

The relative risk of death was 9.32 times higher in PR3-ANCA-positive patients compared with MPO-ANCA. Old patients (> 67.6 years) had 7.68 and 8.42 times the risk of death compared with young patients (< 65.5 years) and those aged 56.5–67.6 years, respectively. Patients with the highest maximum creatinine (> 582 µmol/l) had 5.18 times the risk of death compared with patients with the lowest maximum creatinine (< 299 µmol/l).

Age and the maximum creatinine were further used as metric variables in the Cox’s regression model. The higher the age, the higher the risk of death: a 1.082-fold increase in risk per year of age was noted, corresponding to a doubling in risk of death every 8.8 years. Likewise, for the maximum creatinine, a 1.003-fold increase in risk per µmol/l creatinine was observed. A doubling in risk of death could be calculated from these data in steps of 277 µmol/l creatinine.

Discussion

Systemic ANCA-associated vasculitis follows a fatal course if left untreated and outcome is substantially related to the appropriate immunosuppression. We performed an outcome analysis in a large cohort of 80 patients with ANCA-associated vasculitis treated uniformly with CYC and OCS for induction treatment.

Our data regarding demographic characteristics, organ involvement and ANCA analysis correspond well to the findings of other investigators [8–11]. ANCA-associated vasculitis is a relapsing disease. In the present study, a relapse rate of 33% was noted, with the majority of patients relapsing after 2 years. Other studies have reported similar relapse rates of 11–46% in cohorts of WG and MPA or MPA and RLV [11,15]. There was a trend towards higher relapses in patients with PR3-ANCA compared with MPO-ANCA-positive patients, which did not reach statistical significance (47% vs 35%). The relapse rate in patients with WG was only slightly higher compared with MPA (46 vs 42%, not significant). This differs from the prospective CYCAZAREM study, where patients with WG had a greater chance of relapse than in MPA. The data from CYCAZAREM, however, support the notion of an eventually more aggressive disease state in WG, possibly due to the presence of granulomatous disease and the colonization of diseased respiratory mucosa with Staphylococcus aureus [16].

As immunosuppressive treatment should control disease activity, relapses may be expected to occur when treatment is tapered or has been discontinued. In a study by Aasarød et al. [6], more patients with relapses were not receiving cytotoxic agents, while in an analysis by Westman et al. [11], the majority (69%) had ongoing treatment. Gordon et al. [15] noticed slightly more relapses (57%) under therapy. In general, the discontinuation of cytotoxic drugs has been proposed to promote higher relapse rates [15]. In this study, ~50% were still on immunosuppressive treatment at the time of relapse. In patients without treatment at relapse, relapse-free survival was significantly influenced by the duration of initial cytotoxic treatment. The longer the treatment was administered, the longer overall relapse-free survival was observed in these patients. Whether immunosuppressive treatment may be safely discontinued after a defined period of remission will be answered by REMAIN, one of the trials performed by EUVAS.

Regarding outcome in patients with ANCA-associated vasculitis, the most important questions focus on whether there are differences in mortality and renal survival between the disease entities WG, MPA and RLV and whether there are differences between patients with MPO-ANCA and those with PR3-ANCA.
According to our data, organ involvement and the development of ESRD as well as mortality seem to be influenced by the underlying disease and the ANCA antigen specificity. In this analysis, PR3-ANCA-positive patients had more organs affected at diagnosis than patients with MPO-ANCA, which has been confirmed by other studies [11,17,18]. Progression to ESRD occurred significantly more often in patients with WG (n = 11) compared to patients with MPA (six patients; P = 0.04) and RLV (one patient; P = 0.021). Renal survival was worse in PR3-ANCA-positive patients (not significant). Similarly, patients with WG had a higher mortality than other patients. Furthermore, mortality was significantly higher in PR3-ANCA-positive cases, while none of the ANCA-negative patients died. The relative risk of death was 9.32 times higher in PR3-ANCA-positive patients compared with MPO-ANCA. In contrast, RLV and ANCA negativity were shown to be relatively benign conditions with rather good outcomes concerning death and ESRD. MPA and positivity for MPO-ANCA could be demonstrated to follow a course between WG and RLV or PR3-ANCA and ANCA negativity, respectively. Further prognostic factors associated with significantly higher mortality were older age, ESRD and high maximum creatinine in the first month.

Plasmapheresis was additionally used in five patients, which were all PR3-ANCA-positive and had WG. Only one of these patients progressed to ESRD. These data are in accordance with MEPEX, one of the trials performed by EUVAS, where the major result was the improvement of renal survival by plasmapheresis [19]. No influence of plasmapheresis on renal survival analysis in this study can be determined, as none of the patients with MPO-ANCA or MPA received plasma exchange.

Some studies have demonstrated an influence of PR3-ANCA on disease manifestation or outcome; however, no impact of ANCA subspecificity on mortality has been observed [20]. A higher relapse rate has been seen in PR3-ANCA [17,18] and a higher risk of death has been noted in C-ANCA-positive patients [9]. In an excellent study by Westman et al. [11], no difference regarding mortality was registered according to ANCA subspecificity; however, for the first time, the data presented in their study demonstrated a relationship between PR3-ANCA levels and outcome in ANCA-associated vasculitis. High levels measured by the sensitive capture ELISA at diagnosis were of significant prognostic value of renal survival and a tendency for higher mortality was shown.

We believe that the aggressiveness of WG is due to its high association with PR3-ANCA, and most probably patients with MPA who are positive for PR3-ANCA have a similar disease activity and outcome. In the study by Hogan et al. [9], where patients with WG had been strictly excluded and only patients with necrotizing crescentic glomerulonephritis or MPA were analysed, the relative risk of death was 3.78 times greater in the presence of a C-ANCA pattern that is almost exclusively associated with PR3-ANCA.

Our data underscore the pathogenetic potential of ANCA, where a more aggressive disease state and a poorer outcome can be attributed to the presence of PR3-ANCA. Although these data consist of a retrospective analysis, the strength of this study is that all patients had biopsy-proven renal involvement and induction treatment with CYC and OCS. Outcome analysis of renal and patient survival was not based on the comparison of events between subgroups, but was calculated from Kaplan–Meier life-table analysis. The determination of prognostic factors for patient survival using Cox’s regression model provides important and reliable information for risk stratification. However, ANCA-associated vasculitis is a rare disease. To avoid the statistical difficulties inherent in retrospective studies with small patient numbers, large prospective trials are necessary to allow reliable outcome analysis. An approach could be the long-term follow-up of the multicentre activities of EUVAS, where a large collective is treated uniformly with standardized immunosuppression in consecutive trials.

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References
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