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Predictors of survival and organ damage in Wegener's granulomatosis

W. Koldingsnes and H. Nossent[1]

Department of Rheumatology, Institute of Clinical Medicine, University of Tromsø and [1]Department of Rheumatology, University Hospital in Tromsø, Norway

Abstract

Objective. To determine survival, organ damage and predictors of these outcomes in a population-based, longitudinal cohort study of patients with Wegener's granulomatosis (WG).

Methods. In a retrospective study, 56 WG patients (median age 50 yr) were followed for 56.5 months. Clinical and laboratory data, disease activity, organ involvement and the Vasculitis Damage Index (VDI) were recorded at baseline (start of treatment) and at a research visit after 42.5 months. The Kaplan–Meier method was used to estimate survival and Cox proportional hazards and linear regression models were used to study predictors of outcome.

Results. Duration of symptoms before the start of treatment (baseline) was 6 months (1–102 months) and 21 patients (37.5%) had organ damage (VDI $\geqslant$1) at baseline. Baseline organ damage was associated with delay in the start of treatment and an elevated serum creatinine concentration. Fifty-five patients received prednisolone (Pred) and 53 patients received cyclophosphamide by intravenous pulse (CYCiv) or as a daily oral dose (CYCpo). CYCiv patients received lower cumulative doses of CYC and spent less time on Pred >20 mg/day than CYCpo patients. Thirteen patients died during the study period. Ten-year patient survival was 75%. Baseline predictors of reduced survival were higher age, dialysis-dependence and the presence of organ damage. Chronic, end-stage renal failure developed in 10 patients overall and was associated with reduced renal function at baseline. Severe organ damage (VDI $\geqslant$5) developed in 71% of the patients and new damage occurred mainly during the first 6 months. Increased time (months) on Pred >20 mg/day during follow-up increased the last VDI [$\beta = 0.5$, 95% confidence interval (CI) 0.3 to 0.8], $P < 0.001$), whereas increased time on CYC during the first 6 months reduced the last VDI ($\beta = -0.6$, 95% CI -1.1 to -0.02, $P = 0.04$).

Conclusion. Treatment with CYC and corticosteroid led to a 10-yr survival rate of 75% in WG but did not prevent severe organ damage. The presence of baseline organ damage was a marker of poor outcome. There was an association between damage and treatment given.

KEY WORDS: Wegener's granulomatosis, Vasculitis, Survival, Damage, Outcome.

Wegener's granulomatosis (WG) is characterized by systemic necrotizing vasculitis and granuloma formation and most frequently involves the respiratory tract and the kidney. Often starting as a limited disease with granulomatous inflammation in the upper airways, it proceeds to a systemic vasculitis with multi-organ involvement [1, 2]. Survival in WG increased dramatically after cyclophosphamide (CYC) and corticosteroids (CS) were established as the standard treatment, and 5-yr survival in the 1990s exceeded 60% [2–4]. However, WG still leads to overmortality and most patients develop permanent organ damage [1, 5–7]. Several studies have found greater age and reduced renal function to be predictors of poor outcome [2, 6, 8–10]. Less consistent results have been found for other manifestations [pulmonary, upper airways (ENT), serum albumin concentration, haemoglobin concentration, white blood cell (WBC) count, platelet count and ESR] [2, 6, 8–12]. Most studies have been performed at referral centres and only a few studies have included a multivariable analysis of predictors. In addition, some studies have also included patients with other forms of vasculitis [7, 9], thereby limiting their applicability in clinical practice.

The purpose of the present study was to describe predictors of poor outcome in WG, defined as mortality, end-stage renal disease (ESRD) and total organ damage, in a population-based cohort of patients and, if applicable, to perform multivariable analysis on these predictors. We considered as potential predictors

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Correspondence to: W. Koldingsnes, Department of Rheumatology, Institute of Clinical Medicine, University of Tromsø, N-9037 Tromsø, Norway.

the above-mentioned baseline variables, the treatment variables and the following validated tools: the Birmingham Vasculitis Activity Score (BVAS) [13], the Disease Extent Index (DEI) [14] and the Vasculitis Damage Index (VDI) [15].

Patients and methods

Patients

Patients were recruited from a regional population-based WG register, as described previously [16]. This register contains all WG cases registered since 1984 in the three northernmost counties in Norway. All 56 patients fulfilled two or more of the American College of Rheumatology (ACR) 1990 classification criteria for WG [17]. In addition, 37 patients had biopsy-proven granulomatous inflammation and 17 more patients had positive tests for cytoplasmic antineutrophil antibodies (cANCA) as supporting evidence. The study was approved by the regional ethics committee and all living patients gave informed consent. Baseline data were those collected at the start of immunosuppressive treatment (except for one patient with low disease activity who was included at the start of monotherapy with trimethoprim–sulfamethoxazole). Data from an extensive follow-up visit (research visit) performed between May 1998 and August 1999 were used as measures of damage outcome. For 17 patients (12 non-survivors and five patients unable to attend the research visit), data from the last routine control visit were used. No patient was lost to follow-up. For patient survival and renal survival analyses, the censoring date was the last visit before 15 June 2000.

Data collection

The onset of the first symptom attributable to WG and baseline data [demographic and laboratory findings and organ involvement by BVAS-1 (see Disease activity and damage, below), DEI, VDI] were retrieved from hospital records by the use of a predefined data collection form, which was done by one investigator (WK). All recorded data were based on documentation present in the record. When there was no information on relevant symptoms or findings, the symptoms were considered not to be present unless other information could be obtained from the surviving patient at the research visit, or by telephone interview. The same data were recorded again at the research visit (or the corresponding control visit). Data on damage and treatment variables (initial immunosuppressive regimen, cumulative dose and time on cytotoxic and steroid drugs) were recorded after 6, 12, 18 and 24 months and at the research visit. Four outcome measures were used: death, end-stage renal disease, VDI $\geqslant 5$ and the increase in VDI from baseline until the research visit.

Laboratory data

The laboratory data recorded were haemoglobin concentration, complete blood cell count, ESR, CRP level, serum creatinine level, the result of the urine dipstick test, 24-h urinary protein and urine sediment microscopy. ANCA results were recorded as positive or negative as different methods (indirect immunofluorescence and enzyme immunoassays) were used during the study period.

Disease activity and damage

Organ involvement was defined according to DEI, which records vasculitic activity in 10 organ systems; the maximum number of points is 20 and one point is added for constitutional symptoms with malaise [14]. Disease activity was scored according to BVAS-1, which scores nine organ systems for new or worse vasculitic findings [13]. Each item is weighted and there is a maximum score for each organ system; the maximum total BVAS-1 score is 63. Permanent organ damage was scored by VDI, which gives a cumulative record of damage that must have been present for at least 3 months [15]. Eleven organ-based systems are recorded, with a maximum score of 64. The VDI form also gives the opportunity to record treatment-related damage (nine items of damage attributable to drug toxicity). Renal involvement was defined as the presence of haematuria [urine dipstick result rated at least $++$ or >10 red blood cells (or casts) per high-power field] after excluding infection. Normal renal function was defined as a serum creatinine level of $\leqslant 100$ μmol/l in females and $\leqslant 120$ μmol/l in males.

Complete remission was defined as the absence of active disease, complete resolution of pulmonary infiltrates or evidence of stable scarring, absence of systemic inflammatory disease such as serositis and fever, and stabilization or improvement in renal function without active urinary sediment. In partial remission there was a clear-cut suppression of disease with stabilization of renal function and at least partial resolution of pulmonary infiltrates, and disease in other organs was required to show signs of improvement. Relapse was defined as the re-emergence of clinically detectable vasculitis or the worsening of previous manifestations after a period of at least partial remission. Infection was excluded as the likely cause of symptoms.

Treatment regimens

Ninety-three per cent of the patients were treated at the two main centres in the study region (Tromsø and Bodø), and four patients received initial treatment at other, local hospitals. The decision how and when to start treatment was based on clinical grounds by the attending physicians. Induction therapy for active disease was either CYC given daily orally (CYCpo) at 2 mg/kg body weight (19 patients) or as intravenous pulses (CYCiv) at 15 mg/kg body weight every second week (32 patients), increasing the pulse interval after remission had been achieved, as described earlier [18]. The CYC dose was decreased by 25% when the WBC count was $<3.5 \times 10^9$/l, platelet count $<150 \times 10^9$/l or serum creatinine concentration >150 μmol/l. Oral corticosteroids (CS) were given as daily doses of

prednisolone (Pred) 0.5–1.0 mg/kg body weight to all but one patient, with dose reduction after 2–6 weeks. Intravenous methylprednisolone pulse therapy (500–1000 mg daily for 3 consecutive days) before CYC treatment was given to 32 patients. Trimethoprim–sulfamethoxazole was started in 19 patients and nine patients received adjuvant plasma exchange therapy for life-threatening disease during induction therapy.

During follow-up, patients were seen every 2–4 weeks until remission and thereafter at least every 6 months. Patients were switched to maintenance therapy 6–18 months after remission had been achieved. This consisted of methotrexate 0.3 mg/kg body weight weekly (20 patients), azathioprine 2.0–2.5 mg/kg body weight daily (17 patients) or intravenous gammaglobulin 0.4 g/kg body weight monthly (four patients).

Statistics

Data are presented as median and range unless stated otherwise. The non-parametric Mann–Whitney *U*-test and the Kruskal–Wallis test were used to compare continuous variables between groups, and the χ^2 test and Fisher's exact test to compare categorical data. The Kaplan–Meier method was used to calculate the probability of survival and the Cox proportional hazards regression model to test predictors of patient and renal survival and survival with VDI <5. The log-log plot for each potential risk factor was examined to determine if the proportional hazards assumption was valid.

In univariate analysis, we tested the following baseline features as potential predictors of poor outcome: gender, age, diagnostic delay (time from onset of symptoms to start of treatment), organ involvement, dialysis-dependence, serum creatinine concentration, 24-h urinary protein, haemoglobin concentration, ESR and DEI, BVAS-1 and VDI scores. Because of missing data, CRP and serum albumin were not tested (data missing for 14 and 24 patients respectively). Data were also missing for ESR (two patients) and urinary protein (six patients). The two patients with missing ESR data were deleted from the relevant analyses, but the analyses were re-run after assigning the median value of ESR to the two missing values to see if that changed the result. For the patients with missing 24-h urinary protein data, we assigned the sample median for that group of patients with the same urine dipstick result ($+ = 1.0$ g/24 h, $++ = 2.0$ g/24 h, $+++ = 2.6$ g/24 h) as there were no missing data for the urine dipstick test. One patient who developed ESRD before baseline was excluded from the analyses of prognostic factors for ESRD. In the analyses of prognostic factors for severe organ damage (VDI $\geqslant 5$), the patients who died within 3 months from baseline (four patients) were considered not at risk and were excluded.

When analysing the effect of treatment on organ damage, we used the increase in VDI from baseline until the research visit as an outcome parameter. Multiple linear regression models (regression coefficient $= \beta$) were used, examining residual plots to determine if the assumptions for the linear regression model were valid. All analyses of increases in VDI until the research visit were adjusted for time of follow-up. Treatment parameters examined were the mode of administration of CYC, the cumulative dose of CYC, the cumulative times on CYC, CS and daily Pred >20 mg during the first 6 months and until the research visit. Gender, age, BVAS-1 and DEI and the number of relapses were included as factors of interest. Adjusted R^2 was interpreted as the amount of variation explained by a given model including several variables.

Multivariate analyses were performed on predictor variables with a *P* value of < 0.2 [19] in the univariate analyses. A stepwise forward selection method was used to find the statistically most important model, using a cut-off *P* value of 0.05 for both entry and removal from the model. Possible confounders, such as treatment centre (Tromsø *vs* others) and calendar year of diagnosis (1984–1991 *vs* 1992–1998) were tested in the multivariate models. A two-sided *P* value < 0.05 was considered significant. Statistical analyses were made using the Statview statistical package, version 5.0.1 [SAS Institute, Cary, NC, USA (1998)].

Results

Baseline data

The mean age at baseline of the 56 patients in this cohort was 50.3 (S.D. 18.4) yr. Descriptive baseline data are shown in Table 1. Involvement of at least three organ systems (DEI $\geqslant 6$) was present in 48 patients (86%), while 34 patients (61%) had DEI $\geqslant 8$. Serum creatinine level was >150 μmol/l in 29 patients (52%) and 12 patients required haemodialysis. Non-renal WG was seen in 20% of the patients, but 38% had normal

TABLE 1. Demographic and baseline clinical features in 56 patients with Wegener's granulomatosis

Clinical or laboratory feature	Value
Males, females (ratio)	35, 21 (1.7 : 1)
Age (yr)	50 (10–84)
Time from onset of symptoms to treatment (months)	6 (1–102)
Time from baseline to research visit (months)	42.5 (0.5–173)
Follow-up in survival analysis up to June 2000 (months)	56.5 (0.5–192)
Disease activity (BVAS-1)	23 (4–46)
Disease extent (DEI)	9 (2–21)
Haemoglobin concentration (g/dl)	9.8 (6.4–15.3)
WBC count (10^9/l)	10.6 (4.0–30.1)
Platelet count ($n = 54$) (10^9/l)	415 (204–878)
ESR ($n = 54$) (mm/h)	92 (2–135)
CRP ($n = 42$) (mg/l)	109 (13–295)
Serum creatinine concentration (μmol/l)	168 (56–1356)
Urine protein ($n = 50$) (g/24 h)	1.4 (0–8.7)
Number of ANCA-positive patients (% of 43 patients tested)	37 (86%)

Values are median (range) unless stated otherwise.

serum creatinine levels (seven females and 14 males). Patients with ENT involvement (45 patients) were younger (49 *vs* 63 yr, $P = 0.03$) and patients with serum creatinine concentration >150 μmol/l were older (56 *vs* 48 yr, $P = 0.046$). Two patients (4%) had ENT involvement only.

Permanent organ damage (VDI $\geqslant 1$) was seen in 21 patients (38%) and tended to be more frequent in females than in males (52 *vs* 29%, $P = 0.07$). Patients with organ damage had a longer diagnostic delay (10 *vs* 4 months, $P < 0.001$) and a higher serum creatinine concentration (395 *vs* 135 μmol/l, $P = 0.03$). The extents of baseline organ involvement and damage are shown in Fig. 1.

Treatment data

Table 2 shows cumulative doses and treatment time on CYC and CS for all patients and for 46 patients completing 2 yr of follow-up (six patients died and four had <2 yr of follow-up). The CYC dose received by CYCpo patients was more than twice that received by CYCiv patients and the CYCpo patients spent a longer time on Pred >20 mg daily. The CYCiv patients had higher BVAS-1 scores at baseline (BVAS-1 27 and 23 respectively, $P = 0.02$) but were not different from CYCpo patients in the number of organs involved and other baseline features.

Cumulative treatment for more than 2 yr with CS or CYC was given to 59 and 36% of the patients respectively. Only two patients received a cumulative dose of CYC of more than 100 g and nine patients (16%) used the higher daily dose of Pred (>20 mg) for more than 6 months. Methotrexate was given to 20 patients for a median period of 7.5 months (range 1–23 months) and azathioprine to 17 patients for 12 months (1–115 months). There was no significant difference in azathioprine or methotrexate treatment between patients receiving daily and pulse treatment with CYC.

Mortality

Overall mortality was 23.2% (13 patients died) and the 1-, 5- and 10-yr survival estimates were 93, 79 and 75% respectively (Fig. 2). Eleven patients died while WG was active. Four patients (7.1%) died within 1 month after starting treatment; all had multi-organ disease with a BVAS-1 of 31 and a VDI of 4, values that were higher than those for the remaining non-surviving patients (BVAS-1 = 19, $P = 0.04$; VDI = 0, $P = 0.03$). Seven patients died while they had active disease during a relapse after 57 months (16–140 months). The immediate cause of death was suicide in one of these patients, five patients also had pneumonia and five had congestive heart disease. Two patients in remission died due to myocardial infarction after 42 and 43 months, having been on long-term CS treatment, one was still on 20 mg daily at the time of death, and one had a history of ischaemic heart disease since the exact time of onset of WG.

Reduced survival was seen with increased age, increased serum creatinine concentration and 24-h urinary protein, dialysis-dependence, the absence of ENT involvement and baseline VDI $\geqslant 1$ in univariate Cox regression analysis. When adjustment was made for age, the ENT involvement was no longer significant, but diagnostic delay was important (Table 3). Upon

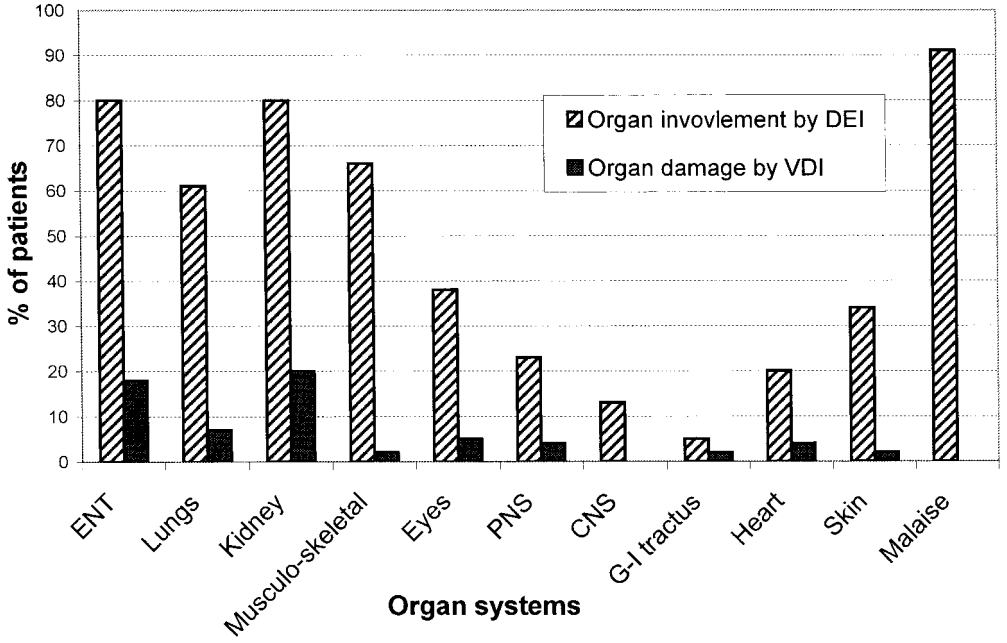

FIG. 1. Organ involvement and organ damage at baseline in 56 patients with Wegener's granulomatosis. ENT, upper airway; PNS, peripheral nervous system; CNS, central nervous system; G-I tractus, gastrointestinal tract.

TABLE 2. Treatment given according to the route of administration of cyclophosphamide (CYC) in patients with WG

	Route of administration of CYC				
	Pulse	Daily oral	Combined daily oral and pulse	All patients	P^a
No of patients treated (%)					
During the first 2 yr	32 (60%)	17 (32%)	4 (8%)		
Until research visit	28 (53%)	13 (25%)	12 (23%)		
2-yr cumulative treatment given to 46 patients completing 2 yr of follow-up[b] [median (range)]					
Dose of CYC (g)	19.175 (2.750–52.500)	45.925 (5.200–132.050)	34.975 (24.375–43.700)	23.663 (0–132.05)	0.003
Time on CYC (months)	20.5 (2.0–24.0)	15.5 (1.5–24.0)	16.5 (11.0–24.0)	15.5 (0.0–24.0)	0.7
Time on prednisolone >20 mg/day (months)	2.25 (0–7.0)	4.5 (2.0–13.0)	3.25 (0.5–4.0)	3.0 (0–13.0)	0.01
Cumulative treatment given until research visit (all treated patients) [median (range)]					
Dose of CYC (g)	12.850 (0.750–81.500)	50.100 (9.000–93.675)	45.900 (17.400–302.400)	28.850 (0.750–302.400)	<0.001
Time on CYC (months)	12.0 (0.5–48.0)	14.0 (4.0–36.0)	34.0 (11.0–79.0)	14.0 (0.5–79.0)	0.03
Time on prednisolone >20 mg/day (months)	2.0 (0–7.0)	5.0 (0.5–18.0)	4.5 (0.5–15.0)	3.0 (0–18.0)	0.001
Time on corticosteroids (months)	18.0 (0.5–117.0)	31.0 (12.0–140.0)	38.5 (22.0–119.0)	24.0 (0.5–140.0)	0.003

[a]Difference between groups according to the route of administration of CYC (Kruskal–Wallis test); [b]median time on corticosteroids was 24 months in all groups.

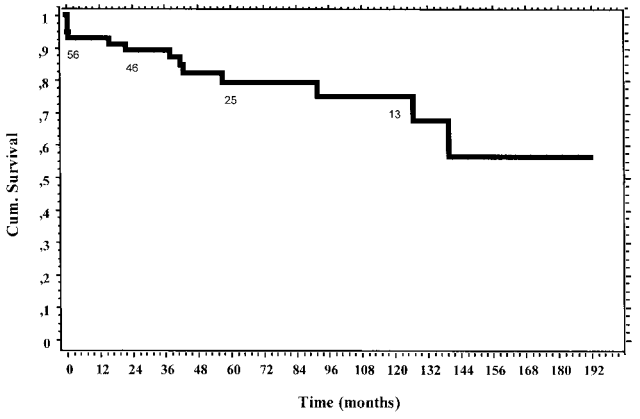

FIG. 2. Survival in WG estimated by the Kaplan–Meier method. Numbers on the curve are numbers of patients still in study.

forward selection, increased age, dialysis-dependence and organ damage at baseline were selected as the most important predictors for reduced survival (Table 3). BVAS-1 and DEI were not predictors of survival.

ESRD

Ten patients (17.9%) developed ESRD, six of whom died, and one patient received a successful renal transplant. Renal survival for 1, 5 and 10 yr was 93, 86 and 77% respectively. Baseline features representing renal function were all associated with a risk of developing ESRD, as the risk of ESRD was increased by increased serum creatinine concentration [increase of 100 μmol/l, hazard ratio (HR) = 1.35, 95% confidence interval (CI) 1.11–1.49, $P = 0.001$] and 24-h urinary protein (increase of 1 g/24 h, HR = 1.50, 95% CI 1.08–2.07, $P = 0.02$), by dialysis-dependence (HR = 4.78, 95% CI 1.27–17.86, $P = 0.02$) and by decreased haemoglobin concentration (decrease of 1 g/dl, HR = 1.64, 95% CI 1.05–2.57, $P = 0.03$). Increased age also tended to increase the risk of ESRD (increase of 10 yr, HR = 1.47, 95% CI 0.95–2.24, $P = 0.08$).

Of the eight patients who were dialysis-dependent at baseline and survived 3 months, four regained renal function permanently (median follow-up of 80 months, range 24–173). Three patients regained renal function temporarily, for a period of 32 months (range 10–91 months), before they developed ESRD, and one patient remained in end-stage renal failure. Patients who regained long-term renal function were younger (39.5 *vs* 64 yr, $P = 0.02$) and had a higher haemoglobin concentration at baseline (10.5 *vs* 7.4 g/dl, $P = 0.04$) than the four patients who developed ESRD, but these two groups of patients did not differ in baseline serum creatinine concentration, VDI or diagnostic delay.

Specific organ damage

All patients developed some type of organ damage (Table 4). Nasal and sinus dysfunction was the most frequent non-renal damage, and these patients were younger (49 *vs* 57 yr, $P = 0.007$) and had a lower serum creatinine concentration at baseline (115 *vs* 348 μmol/l, $P = 0.004$) than patients without ENT problems. In contrast, patients who developed significant dyspnoea were older (64 *vs* 48 yr, $P = 0.024$). Amenorrhoea developed in three out of eight premenopausal women (38%) and four men claimed to be infertile. Three patients (5%) developed haemorrhagic cystitis but no case of bladder cancer was observed. Four patients developed malignancies (cutaneous basal cell carcinoma, cervix cancer *in situ*, carcinoid tumour and Kaposi sarcoma), but malignancy was not the main cause of death in any patient.

Overall organ damage

Development of organ damage, as measured by VDI, is illustrated in Fig. 3. The rate of increase in VDI was six times greater during the first 6 months than during the

TABLE 3. Baseline predictors of reduced survival in WG

	Each variable adjusted for age			Result of multivariable analysis, forward selection		
Potential predictors	HR	95% CI	*P*	HR	95% CI	*P*
Age, increase of 10 yr	2.18	1.37–3.46	0.001	2.18	1.38–3.42	< 0.001
Diagnostic delay, increase of 6 months	1.20	1.01–1.43	0.04			
Absence of ENT involvement	1.81	0.53–6.20	0.35			
Heart involvement	3.82	0.99–14.73	0.05			
Serum creatinine, increase of 100 μmol/l	1.35	1.11–1.65	0.003			
Urinary protein, increase of 1 g/24 h	1.57	1.23–2.01	<0.001			
Dialysis-dependency	9.17	2.57–32.79	<0.001	8.20	2.03–33.11	0.003
VDI $\geqslant$ 1	6.10	1.68–22.17	0.006	5.54	1.28–24.05	0.022

Summary of Cox regression analyses performed on variables with $P < 0.2$ in univariate analyses.

next 18 months, and the 6-month VDI constituted 52% of the last VDI. The early increase in VDI was due mainly to disease-related damage, which constituted 93% of the total damage at 6 months. The last recorded median VDI score was 6 (range 2–16) and was higher in non-surviving patients (9 *vs* 5, $P = 0.005$).

Thirty-seven patients (71% of the patients who survived 3 months) reached VDI $\geqslant 5$ after a median period of 12 months (range 0–120 months). Baseline risk factors for such severe damage identified by univariate analysis were heart involvement and increased serum creatinine concentration and 24-h urinary protein (Table 5), but cardiac involvement was the only important predictor on forward selection. Cardiac involvement was seen in nine patients who survived 3 months and these patients had significantly more of all the other risk factors listed in Table 5, except for organ damage. When we included all the variables listed in Table 5 in a multivariable model and performed backward selection, increased ESR (increase of 10 mm/h, HR = 1.15, 95% CI 1.02–1.29, $P = 0.02$) and VDI $\geqslant 1$ (HR = 2.54, 95% CI 1.23–5.24, $P = 0.01$) were the most important predictors.

BVAS-1 and DEI at baseline were not associated with the increase in VDI during total follow-up ($P = 0.55$ and $P = 0.22$ respectively by linear regression analysis), but predicted early damage by the VDI increase until 6 months (DEI $\beta = 0.14$, 95% CI 0.02–0.25, $P = 0.02$; BVAS-1 $\beta = 0.05$, 95% CI 0.01–0.09, $P = 0.03$).

Organ damage and treatment

Cumulative time on CS and on daily Pred >20 mg and cumulative dose of CYC turned out to be explanatory variables for increasing VDI during follow-up (Table 6). For time on CYC, only the initial treatment period was relevant for further multivariate analysis. The number of relapses (52 in 31 patients) was associated with increasing VDI, while baseline BVAS-1 and DEI were not (Table 6). In further analyses, we adjusted the treatment variables for the number of relapses, except for analyses of the early 6-month treatment, for which relapse was not relevant, but baseline DEI might be an important confounder. The increase in VDI still showed significant associations with increasing time on CS, increasing time on Pred >20 mg/day and increasing dose of CYC. The number of relapses was also an independent predictor of VDI. Adjusting for baseline DEI, we found that increasing time on CYC during the early 6-month period reduced the VDI (Table 6).

TABLE 4. Permanent organ damage in 56 patients with WG during the follow-up period of 42.5 months

Organ damage	No. of patients (%)
Proteinuria (>0.5 g/24 h)	34 (60.7)
Nasal and sinus dysfunction	34 (60.7)
Peripheral neuropathy	24 (42.9)
Arterial hypertension	21 (37.5)
Dyspnoea	20 (35.7)
Hearing loss	18 (32.1)
ESRD	10 (17.9)
Cataract	9 (16.1)
Saddle nose	9 (16.1)
Myocardial infarction	8 (14.3)
Severe cutaneous ulcers	8 (14.3)
Premature gonadal failure	7 (12.5)
Diabetes mellitus	7 (12.5)
Osteoporotic fracture	6 (10.7)
Loss of vision	5 (8.9)
Malignancy	4 (7.1)
Bone marrow toxicity	4 (7.1)
Haemorrhagic cystitis	3 (5.4)
Tracheal stenosis	3 (5.4)
Aseptic bone necrosis	2 (3.6)

These results were confirmed when we made a separate study of the increase in VDI until 2 yr of follow-up in the 46 patients with at least 2 yr of follow-up, to avoid the problem of different durations of follow-up. Time on Pred >20 mg/day and time on CYC during this period were predictors of the 2-yr increase in VDI (months on Pred >20 mg/day, $\beta = 0.29$, 95% CI 0.08–0.50, $P = 0.007$; months on CYC, $\beta = -0.10$, 95% CI -0.17 to -0.03, $P = 0.008$ both adjusted for baseline DEI). Time on CS, dose of CYC and relapses until the 2-yr follow-up were not predictors of the 2-yr increase in VDI, but baseline DEI and BVAS-1 were (DEI, $\beta = 0.20$, 95% CI 0.04–0.36, $P = 0.02$; BVAS-1, $\beta = 0.07$, 95% CI 0.01–0.12, $P = 0.02$).

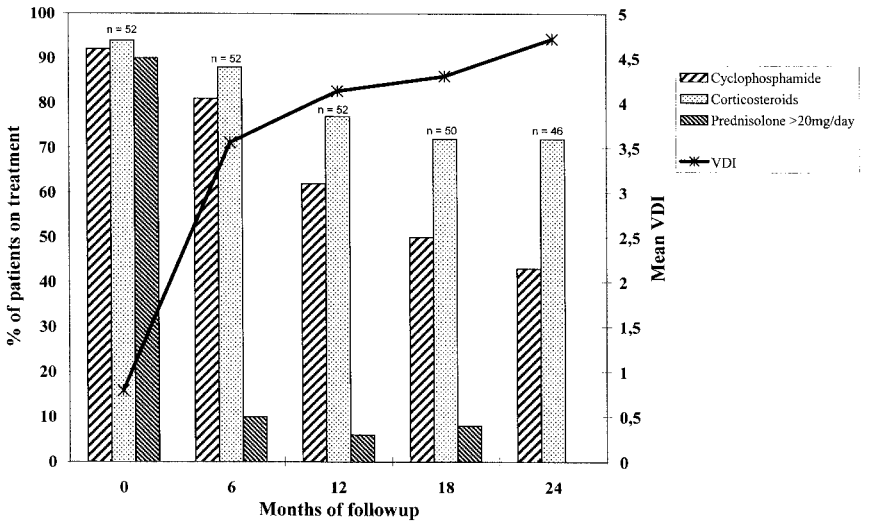

FIG. 3. Organ damage as indicated by VDI and the percentage of patients on different treatments during the first 2 yr of follow-up in patients with WG. Numbers above the bars are numbers of patients studied (four patients with early death were excluded).

TABLE 5. Baseline predictors of severe late organ damage (VDI $\geqslant 5$) in Wegener's granulomatosis

Potential predictors	HR	(95% CI)	P
Heart involvement	2.62	(1.16–5.93)	0.02
Serum creatinine, increase of 100 μmol/l	1.11	(1.00–1.22)	0.03
Urinary protein, increase of 1 g/24 h ($n = 50$)	1.12	(0.99–1.27)	0.08
Haemoglobin, increase of 1 g/dl	0.85	(0.73–1.00)	0.05
ESR, increase of 10 mm/h	1.21	(1.02–1.44)	0.03
VDI $\geqslant 1$	1.92	(0.98–3.78)	0.06

Summary of univariate Cox regression analyses of variables with $P < 0.2$. The analysis was performed in 52 patients who survived 3 months.

Discussion

Outcome assessed by mortality and permanent organ damage is described in this population-based, non-selected group of WG patients. The cohort had no remarkable demographic features and the 10-yr survival rate of 75% agrees with results from Birmingham, UK, and confirms the improved prognosis for WG patients treated with CS and CYC [4, 20]. A recent German study reported a 10-yr survival rate of 88% [2]; this was in a more selected patient population as the study was performed at a referral centre where 36% of the patients were first seen 6 months after the diagnosis. This may explain the lack of early death (within 3 months) in the German study as opposed to 7.1% early mortality in our patients, a rate similar to that in other studies [3, 6, 9, 11]. It is clear, however, that mortality among patients with WG is still about four times greater than the expected mortality in the general population [5, 6].

Identifying predictors of reduced survival may reduce this excess mortality by stratifying treatment according to these prognostic markers. Greater age and dialysis-dependence were predictors of reduced survival, confirming the results of earlier studies [2, 6, 8–10], although we found severe renal failure, assessed by dialysis-dependence, to be a better indicator of poor prognosis than serum creatinine concentration. Baseline organ damage was an important risk factor in the present study. No studies have included this in multivariate survival analysis, although Exley *et al.* [21] have shown that damage occurs early (also shown in Fig. 3) and indicates a poor prognosis.

Baseline BVAS-1 and DEI did not predict survival in this study, as in a recent French study [10]. Two earlier studies have found a threshold of BVAS-1 of 8 in fatal disease, but also concluded that BVAS-1 alone was not a powerful predictor of mortality [7, 13]. In the German study by Reinhold-Keller *et al.* [2], age >50 yr, renal involvement and lung involvement predicted reduced survival, but information on DEI as a prognostic marker was not presented. Matteson *et al.* [5] divided the patients into three organ-specific groups and failed to find an effect of disease extent and severity on survival.

After 4.5 yr, 18% of all our patients had developed ESRD. This rate is in accordance with a recent review [22], which found that 21% of patients with ANCA-associated vasculitis develop ESRD. The 5-yr renal survival rate of 86% is higher than the 75% reported by Aasarød *et al.* [6], but these authors included only WG patients with renal involvement. In agreement with that study, we found serum creatinine concentration to predict ESRD, but in addition proteinuria and haemoglobin concentration were predictors of ESRD. Also, a study of myeloperoxidase-associated necrotizing glomerulonephritis found that proteinuria was a more important predictor of renal outcome than serum creatinine [23]. Initial dialysis-dependence, though a predictor of late ESRD in univariate analysis, does not necessarily indicate irreversibility of renal

TABLE 6. Predictors of increasing organ damage by VDI during follow-up in patients with WG

Potential predictor	Analyses of each variable adjusted for time of follow-up				Analyses of each treatment variable adjusted for time of follow-up and number of relapses[a] or DEI[b]			
	β	(95% CI)	P	Adjusted R^2	β	(95% CI)	P	Adjusted R^2
Age increase, per yr	0.04	−0.01 to −0.09	0.14	0.12				
Male gender	1.05	−0.80 to −2.89	0.26	0.10				
Baseline BVAS-1	0.03	−0.06 to −0.12	0.55	0.08				
Baseline DEI	0.14	−0.09 to −0.38	0.22	0.11				
Number of relapses	1.29	0.44 to 2.14	0.004	0.23				
Pulse CYC *vs* daily oral CYC	−1.71	−3.54 to −0.12	0.07	0.15	−1.87[a]	−3.54 to −0.19[a]	0.03[a]	0.29[a]
Time on corticosteroids (months)	0.07	0.04 to 0.09	<0.001	0.37	0.06[a]	0.03 to 0.09[a]	<0.001[a]	0.43[a]
Time on daily Pred. >20 mg (months)	0.59	0.34 to 0.85	<0.001	0.37	0.52[a]	0.27 to 0.78[a]	<0.001[a]	0.42[a]
Cumulative dose of CYC (g)	0.02	0.002 to 0.04	0.03	0.18	0.02[a]	0.0001 to 0.036[a]	0.049[a]	0.28[a]
Time on CYC (months)	0.03	−0.03 to −0.09	0.28	0.11				
Time on CYC during first 6 months (months)	−0.38	−0.91 to −0.16	0.16	0.12	−0.57[b]	−1.13 to −0.02[b]	0.044[b]	0.16[b]

Summary of linear regression analyses of variable adjusted for follow-up and of treatment variables adjusted for a disease activity-related parameter.

injury. Most of our patients, who were dialysis-dependent at baseline and survived at least 3 months, regained renal function, and 50% remained independent of long-term dialysis. Similar findings were reported in a study of initially dialysis-dependent WG patients [24].

All patients suffered some kind of damage, either disease-related or iatrogenic. The amount and type of cumulative organ damage in our cohort (Table 4) were largely similar to those found in studies by the National Institutes of Health (NIH), with upper airway damage more frequent in younger patients [1, 25]. Severe damage, defined previously as VDI $\geqslant 5$ [26], occurred in more than two-thirds of all patients and was related to cardiac and renal involvement at baseline. However, multivariate analyses identified baseline organ damage and elevated ESR as the most important predictors. ESR has been shown in another study to be a good marker of disease activity in WG [10]. These findings, together with the rapid increase in VDI during the first 6 months, as also shown by others [21], point up the need for early and aggressive treatment to impede disease-related damage.

However, toxicity of CS and CYC also contribute to morbidity in WG patients [1]. The present study is the first to try to quantify the effect of the actual treatment on damage in WG. A similar approach has been used in a study of systemic lupus erythematosus [27] in which cumulative CS dose was significantly associated with osteoporotic fractures, coronary artery disease and cataract. We did not relate cumulative doses to specific types of organ damage, but to overall damage by VDI. We found that a longer period with a daily dose of Pred >20 mg increased the risk of organ damage after 2 yr as well as at the last examination. Although patients developing osteoporotic fractures and cataract had used Pred >20 mg daily for a longer period than patients without these complications, cumulative time on CS treatment did not differ between these groups. This indicates that the risk lies more in the time spent on higher doses than the total time on CS.

The cumulative dose of CYC contributed to late organ damage, as it was a predictor of increase in VDI until the research visit but not until the 2-yr follow-up. The same pattern was seen for pulse *vs* daily oral CYC treatment. Pulse treatment was not a predictor of VDI after 2 yr, but reduced late VDI, an effect that was probably related to the smaller cumulative dose of CYCiv. Furthermore, increasing duration of any mode of CYC treatment during the first 6 months, and even during the first 2 yr, had a protective effect against permanent organ damage. The explanation may be the ability of CYC to suppress initial disease activity quickly, which on its own is a predictor of early damage. Thus, to balance the short-term positive and long-term negative effects of CYC treatment, the optimal therapy would be to give initial CYC treatment for 6–24 months while reducing the long-term cumulative dose of CYC. This may favour the use of pulse CYC therapy.

CYC-induced cystitis occurred in three patients (6% of the CYC-treated patients), in each case while they were receiving daily oral CYC, but none has yet developed bladder cancer. This rate is considerably lower than the 50% reported by Talar-Williams *et al.* [28] and about half that reported in the recent German study [2]. The difference may be due to the route of administration, as most of our patients were given CYC as pulses, resulting in the smaller median cumulative CYC dose of 29 g (*vs* 75 g in both other studies [29]). More than 90% of the patients in the NIH study and the German study received daily oral CYC and 35 and 37% of the patients respectively received a cumulative CYC dose of $\geqslant$100 g (*vs* 4% in our study). Uroprotection with mesna was not used in our cohort until 1996. Thus, the most likely explanation for the low frequency of CYC-induced cystitis and the absence of bladder cancer was the administration-related lower cumulative dose of CYC. However, longer observation of our patients may be needed before definite conclusions can be drawn.

There are several limitations to this study. Its retrospective nature, dependence on baseline information provided by records and the open, non-randomized treatment may have biased our results. However, the patients have been followed closely in a relatively uniform fashion after the initiation of treatment and we had the opportunity to supplement the information as needed. Baseline data are missing only for ESR and urine protein. Deleting data for the two patients with missing ESR information from the analyses may have biased our results. However, the result did not change when we re-ran all the analyses after having assigned the sample median value for ESR (which was reasonable according to the patients' CRP levels) to the two patients with missing data. Urinary protein was analysed alternatively by the urine dipstick results, graded as 0, 1, 2 and 3, with no missing values, and this did not change the results.

BVAS-1, DEI and VDI were calculated retrospectively and may thus have been underestimated, as scoring was based on documentation in the records. However, retrospective scoring of both DEI [30] and VDI [26] has been shown to be valid. BVAS-1 assumes detailed information of symptoms and findings, but the rule of a maximum score in each organ system reduces the extent of this problem. Although BVAS-1 scores in this cohort were relatively high (median 23, range 4–46), we cannot exclude the possibility that BVAS-1 values were underestimated.

The use of multivariate analyses in a relatively small cohort of patients with few events is connected with imprecision and may imply over-fitting of the models. To avoid this problem, we have presented the results of univariate analyses or results adjusted only for the most important confounder—age in patient survival analyses and time of follow-up in linear regression analyses of late organ damage. Any further multivariate analyses included a maximum of three variables on forward selection (analysis of VDI $\geqslant$5 was also tested by backward selection). Yet some of the estimates of the risks given by the HR and the regression coefficient β are imprecise, as shown by the relatively wide confidence intervals. Interpretation of the results should be based more on which of the variables have been selected in the model than on the size of the HR or β, and the results should be confirmed in larger studies.

The lack of randomization makes it impossible to compare the two CYC treatment protocols (daily oral and pulse therapy). We found that the cumulative dose of CYC and time on Pred $>$20 mg/day, both of which are predictors of permanent organ damage, were highest in the CYCpo-treated patients. Here, confounding by indication may have been present, as one would expect the most active disease to be treated most intensively, leaving severe disease activity as the real explanation why those patients develop most severe damage. However, CYCpo-treated patients did not have higher BVAS-1 or DEI scores at baseline than the CYCiv-treated patients. Even if relapses were predictive of late damage and baseline disease activity predictive of early damage, the treatment variables were predictors for both early and late damage independently of the markers of disease activity. Furthermore, the analyses are based on the actual treatment given, not the intended dose based on a certain protocol, and as the patients had been followed closely the data on treatment variables were not difficult to obtain.

We therefore believe that this study indicates some important relationships between treatment and damage despite the relatively low number of patients and the limited follow-up. We also checked if there was confounding by centre of treatment or by change in therapeutic approach over time by including these variables in the regression analyses; this did not change the estimates of the risk factors.

In summary, the presence of organ damage at the start of treatment was an important risk factor for both mortality and late morbidity in this cohort, and this result points up the need for early diagnosis and treatment. Prolonged treatment with moderate to high doses of daily Pred contributed significantly to late morbidity, whereas increasing time on CYC in the first 2 yr had a protective effect on organ damage according to the regression models used in the present cohort. Different CS treatment strategies in WG should be incorporated in prospective studies, but at present reducing the time on even moderately high doses of Pred should be a main concern in trying to reduce damage in WG patients.

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