Clinical and Histologic Determinants of Renal Outcome in ANCA-Associated Vasculitis: A Prospective Analysis of 100 Patients with Severe Renal Involvement

Robert A.F. de Lind van Wijngaarden,* Herbert A. Hauer,† Ron Wolterbeek,‡ David R.W. Jayne,§ Gill Gaskin,‖ Niels Rasmussen,¶ Laure-Hélène Noël,** Franco Ferrario,†† Rüdiger Waldherr,‡‡ E. Christiaan Hagen,§§ Jan A. Bruijn,* and Ingeborg M. Bajema;* for the European Vasculitis Study Group (EUVAS)

*Departments of *Pathology and ‡Medical Statistics, Leiden University Medical Center, †Department of Cardiology, Medical Center Alkmaar, and §§Department of Internal Medicine, Meander Medical Center, Amersfoort, the Netherlands; §Renal Unit, Addenbrooke's Hospital, Cambridge, and ‖Renal Unit, Hammersmith Hospital, London, United Kingdom; ¶Department of Otolaryngology, Rigshospitalet, Copenhagen, Denmark; **INSERM U507, Hôpital Necker, Paris, France; ††Renal Immunopathology Center, Ospedale San Carlo Borromeo, Milan, Italy; and ‡‡Department of Pathology, University of Heidelberg, Heidelberg, Germany*

This study aimed to identify clinical and histologic prognostic indicators of renal outcome in patients with ANCA-associated vasculitis and severe renal involvement (serum creatinine >500 μmol/L). One hundred patients who were enrolled in an international, randomized, clinical trial to compare plasma exchange with intravenous methylprednisolone as an additional initial treatment were analyzed prospectively. Diagnostic renal biopsies were performed upon entry into the study. Thirty-nine histologic and nine clinical parameters were determined as candidate predictors of renal outcome. The end points were renal function at the time of diagnosis (GFR_0) and 12 mo after diagnosis (GFR_{12}), dialysis at entry and 12 mo after diagnosis, and death. Multivariate analyses were performed. Predictive of GFR_0 were age ($r = -0.40$, $P = 0.04$), arteriosclerosis ($r = -0.53$, $P = 0.01$), segmental crescents ($r = 0.35$, $P = 0.07$), and eosinophilic infiltrate ($r = -0.41$, $P = 0.04$). Prognostic indicators for GFR_{12} were age ($r = -0.32$, $P = 0.01$), normal glomeruli ($r = 0.24$, $P = 0.04$), tubular atrophy ($r = -0.28$, $P = 0.02$), intraepithelial infiltrate ($r = -0.26$, $P = 0.03$), and GFR_0 ($r = 0.29$, $P = 0.01$). Fibrous crescents ($r = 0.22$, $P = 0.03$) were predictive of dialysis at entry. Normal glomeruli ($r = -0.30$, $P = 0.01$) and treatment arm ($r = -0.28$, $P = 0.02$) were predictive of dialysis after 12 mo. No parameter predicted death. Both chronic and acute tubulointerstitial lesions predicted GFR_{12} in severe ANCA-associated glomerulonephritis, whereas plasma exchange was a positive predictor of dialysis independence after 12 mo for the entire patient group. Plasma exchange remained a positive predictor when patients who were dialysis dependent at presentation were analyzed separately ($r = -0.36$, $P = 0.01$). Normal glomeruli were a positive predictor of dialysis independence and improved renal function after 12 mo, indicating that the unaffected part of the kidney is vital in determining renal outcome.

J Am Soc Nephrol 17: 2264–2274, 2006. doi: 10.1681/ASN.2005080870

Rapidly progressive deterioration of renal function is a common and usually severe clinical feature of ANCA-associated vasculitis, which may lead to end-stage renal failure or death (1). Histopathology of renal biopsies shows pauci-immune crescentic glomerulonephritis (2) with variable amounts of extracapillary proliferation, fibrinoid necrosis, and glomerulosclerosis (3). The most frequently occurring forms of ANCA-associated vasculitis are microscopic polyangiitis and Wegener's granulomatosis, whereas renal limited vasculitis occurs less frequently (4). Despite the existence of clear definitions (5), the diagnosis for individual patients may be difficult. Patients with ANCA-associated glomerulonephritis are treated similarly regardless of which form is diagnosed. European trials are aimed at developing treatment that corresponds to disease severity (6).

Therapy is associated with severe and potentially lethal adverse effects for a substantial number of patients (7–9); nearly 90% of patients experience persistent morbidity despite adequate treatment (10). Therefore, there is a need for prognostic markers of renal outcome to help to modify therapy for patients who have ANCA-associated vasculitis (11). Several studies that searched for clinical and histologic predictors of renal outcome provided contradictory results (11–19). Meta-analyses are difficult to conduct because there is substantial heterogeneity with regard to study designs, inclusion criteria, scoring methods, treatment strategies, and end points (11–19). We previously studied patients who had ANCA-associated vasculitis and mild

Received August 22, 2005. Accepted May 17, 2006.

Published online ahead of print. Publication date available at www.jasn.org.

Address correspondence to: Dr. Rob de Lind van Wijngaarden, Leiden University Medical Center, Department of Pathology, Postbus 9600, 2300 RC Leiden, The Netherlands. Phone: +31-71-526-6574; Fax: +31-71-524-81-58; E-mail: r.a.f.de_lind_van_wijngaarden@lumc.nl

ISSN: 1046-6673/1708-2264

to moderate renal involvement (serum creatinine <500 μmol/L) and received standardized treatment in an attempt to identify clear clinical and histologic predictors (20). We demonstrated that renal function at diagnosis, in combination with chronic renal lesions identified by histology, is predictive of renal function after 18 mo, and active lesions are associated with renal function recovery. In this study, performed within the framework of the European Vasculitis Study (EUVAS) group (21), we investigated the distribution of acute and chronic lesions in renal biopsies and evaluated clinical and histologic predictors of outcome in patients with severe renal involvement (serum creatinine >500 μmol/L).

Materials and Methods

Patients

Patients were derived from 29 hospitals located in 11 European countries. Patients were enrolled in the Methylprednisolone *versus* Plasma Exchange (MEPEX) trial, which is a randomized trial to evaluate adjunctive therapy for severe glomerulonephritis in ANCA-associated systemic vasculitis (21). Patients who had a serum creatinine of 500 μmol/L or more were included. The local ethics committees approved the study, and all patients gave written informed consent for participation. Inclusion criteria for MEPEX are listed in Table 1. Exclusion criteria of this study are described extensively elsewhere (21). All patients followed a standard treatment regimen. For adjunctive therapy, they were randomly assigned either to receive intravenous methylprednisolone or to undergo plasma exchanges. Standard therapy consisted of oral corticosteroids, which started at 1.0 mg/kg per d and was tapered down within the first 6 mo, and cyclophosphamide 2.5 mg/kg per d, which at 3 mo was replaced by the less toxic azathioprine. Patients who were randomly assigned to receive intravenous methylprednisolone were administered 1000 mg/d for 3 consecutive days, starting directly after diagnosis. The patients in the plasma exchange arm received seven plasma exchanges of 60 ml/kg during the first 14 d after diagnosis. Patients were included in this analysis only when both histologic data, obtained from renal biopsy at the time of study entry, and clinical data were available.

Disease definitions were adopted from the 1992 Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis (5) and a previous European Union study (22). The diseases were distinguished on the basis of criteria that were published previously (21), and determinations were made by local physicians.

Table 1. Inclusion criteria for MEPEX (1, 2, and 3 are required)[a]

1. New diagnosis of WG or MPA or its renal-limited variant, in accordance with the Chapel Hill consensus criteria (7), with active vasculitis, as indicated by the presence of active necrotizing glomerulonephritis on renal biopsy.
2. ANCA positivity for one of the following:
   a. C-ANCA pattern by IIF
   b. in the PR3 ELISA
   c. in the MPO ELISA, with or without P-ANCA ANCA negativity is allowed if the disease is confirmed histologically
3. Biopsy-proven necrotizing and/or crescentic glomerulonephritis, in the absence of another defined glomerulopathy, with severe renal impairment defined by
   a. oliguria (<400 ml/24 h) or
   b. intention to commence dialysis within 48 h of admission
   c. creatinine >500 μmol/L

[a]C-ANCA, cytoplasmic ANCA; IIF, indirect immunofluorescence; MPA, microscopic polyangiitis; MPO, myeloperoxidase; P-ANCA, perinuclear ANCA; PR3, proteinase-3; WG, Wegener's granulomatosis.

ANCA Testing

Indirect immunofluorescence (IIF) and ELISA for ANCA testing were performed locally at all participating centers. The staining pattern in the IIF test was scored as perinuclear (P-ANCA), cytoplasmic (C-ANCA), atypical, or negative. Positive sera for ANCA directed against myeloperoxidase (MPO) or proteinase-3 (PR3) were reported as MPO-ANCA and PR3-ANCA, respectively.

Candidate Predictors of Renal Outcome

Candidate parameters for clinical predictors of renal outcome in this study were renal function at entry (GFR_0), dialysis status at entry, age, gender, quantitatively assessed proteinuria at entry, diagnosis (Wegener's granulomatosis, microscopic polyangiitis, or renal limited vasculitis), ANCA-antigen specificity (PR3-ANCA or MPO-ANCA), IIF pattern (C-ANCA or P-ANCA), and treatment arm (intravenous methylprednisolone or plasma exchange). Candidate parameters for histologic predictors were determined from paraffin sections of renal biopsies that were stained with silver, periodic acid-Schiff, hematoxylin and eosin, and trichrome. Sections were reviewed by two of five participating pathologists (I.M.B., F.F., L.H.N., R.W., or J.A.B.). Both pathologists, blinded to patient data and the other observer's results, scored the biopsies separately and according to a previously standardized protocol (23,24). Briefly, each glomerulus had to be scored separately for the presence of fibrinoid necrosis, crescents (cellular/fibrous and segmental/circumferential), sclerosis (local, segmental, or global), periglomerular infiltrates, granulomatous reactions, and other lesions. The number of glomerular lesions was reported as the percentage of glomeruli in a biopsy. Most interstitial, tubular, and vascular lesions were scored dichotomously, except for interstitial infiltrates, type of cellular infiltrates (neutrophils, mononuclear cells, and eosinophils), interstitial fibrosis, and tubular atrophy, which were scored semiquantitatively. Granulomas were scored quantitatively. In total, 39 histologic parameters were examined. Discrepancies between observers were resolved by conference during central reviews to achieve a consensus for each biopsy.

Clinical Outcome Parameters

Clinical outcome parameters were renal function at diagnosis (GFR_0), renal function at 12 mo (GFR_{12}), dialysis dependence at diagnosis, dialysis dependence at 12 mo, relapse, and death. Renal function was defined as the GFR, which was determined using the equation developed by Cockcroft and Gault (25). Renal function at entry has been shown to be a major predictor of renal outcome for a number of renal diseases (11,26,27). Therefore, we also investigated the correlation between clinical and histologic parameters and GFR_{12} after correction for GFR_0. The latter value was expressed as the corrected GFR_{12} ($CORGFR_{12}$), defined as the difference between the observed GFR_{12} and its linear prediction on the basis of GFR_0. This correction created a corrected value that was statistically independent of the starting value (28).

Statistical Analyses

The software used for statistical analyses was the SPSS 10.0 standard version for Windows (SPSS, Inc., Chicago, IL). Correlation of the quantitative and dichotomous candidate predictors with GFR_0, GFR_{12}, and $CORGFR_{12}$ was determined by using Pearson correlation test. The Spearman rank correlation test was used to correlate categorical variables with GFR_0, GFR_{12}, and $CORGFR_{12}$. Correlations of quantitative candidate predictors with the occurrence of dialysis and death were assessed by the Pearson correlation test. Phi values were used to correlate dichotomous and categorical candidate predictors with the occurrence of dialysis and death at 12 mo. A model for the estimation of GFR_0, GFR_{12}, and $CORGFR_{12}$ was designed using a stepwise linear multiple regression analysis. An estimation model that was based on a binary logistic regression analysis was used for dialysis dependence and death at 12 mo. Each parameter that correlated with $P \leq 0.10$ was entered in the model as a possible predictor of renal outcome. The group was analyzed as a whole, and subgroup analyses were made for patients who were dialysis dependent at entry and those who were not. The values of exponent β were used for the expression of odds ratios. Correlation coefficients were noted as r and predictive values as r^2.

Results

Patients

Patients were enrolled in the MEPEX trial between March 25, 1995, and October 29, 2001. Four of the 151 patients who entered the trial declined further participation, nine were found to have circulating anti–glomerular basement membrane antibodies, and one had already received >500 μg of intravenous methylprednisolone; these patients were excluded. None of the remaining 137 patients was lost to follow-up or withdrawn from the study. Renal biopsies were obtained from 102 patients for reevaluation. Two biopsies were excluded because of the absence of cortical tissue, meaning that 100 biopsies were available for the final analysis. Clinical characteristics of the patients are depicted in Table 2.

The average cumulative dose of cyclophosphamide was 18 g. On average, 4.8 L was exchanged during every plasma exchange; this was performed seven times. A total of 1000 mg of methylprednisolone was administered intravenously three times to patients who were assigned to this treatment arm.

Focusing on the 69 patients who were on dialysis at entry, 51% received plasma exchange; of these, 54% became dialysis independent, 17% were on dialysis, and 29% were dead at 12 mo. Of the 69 patients who were on dialysis at entry, 49% received intravenous methylprednisolone; of these, 32% became dialysis independent, 47% were on dialysis, and 21% were dead at 12 mo. These data show that patients who were on dialysis at entry were equally distributed over the two additional therapy arms and that in both groups, a similar percentage of patients died. However, patients who received plasma exchange had a better prognosis than those who received intravenous methylprednisolone, in terms of dialysis independence.

An overview of patient courses, from study entry to outcome, is shown in Figure 1. Only three patients experienced a relapse. Correlations with patient relapse were not calculated because they were of low statistical value.

Table 2. Clinical characteristics of the whole patient group ($n = 100$)[a]

Characteristic	Value
Age (yr; range)	64.1 (26.8 to 80.7)
Gender (male/female)	63/37
Diagnosis (WG/MPA/RLV)	33/57/10
GFR_0 (ml/min; mean ± SD)	10 ± 4
GFR_{12} (ml/min; mean ± SD)	32 ± 13
Proteinuria (mg/24 h)	30 ± 6
Adjunctive treatment (IVMeP/PE; %)	49/51

[a]IVMeP, intravenous methylprednisolone; PE, plasma exchange; RLV, renal-limited vasculitis.

Histologic Features

The occurrence of the main histologic lesions was analyzed to explore the extent found at the entry period in this group of patients with clinical severe renal impairment. The frequencies of the glomerular and tubulointerstitial lesions are presented in Table 3. The majority of the nonsclerotic glomeruli contained crescents; only very few were unaffected, irrespective of the presence of focal or diffuse glomerulosclerosis. In other words, severe and extensive acute lesions were characteristic of the renal biopsies from this patient group, whereas the extent of chronic changes in the form of global glomerulosclerosis was mild to moderate.

Predictors of Outcome

Correlation coefficients of the variables in relation to the outcome parameters are presented in Table 4. A poor correlation was obtained for the histologic parameters that were excluded from Table 4. Models for the estimation of outcome parameters were designed using binary logistic and stepwise linear multiple regression analyses and are reported in Table 5. These models showed that a combination of parameters predicted the outcome parameter best. The univariate correlation of these predictors with the outcome parameters is shown in

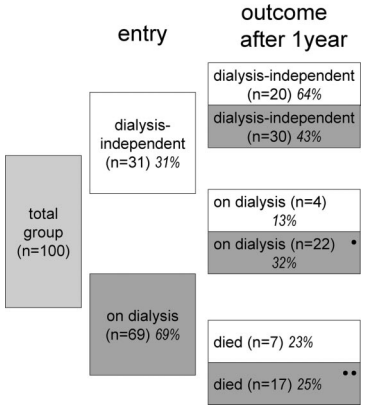

Figure 1. Flow chart of the clinical courses of patients. ▨, Patients who were on dialysis at entry; □, patients who were dialysis independent at entry. Numbers and percentages are listed. Black dots represent patients who experienced a relapse.

Table 3. Average distribution of most characteristic glomerular and tubulointerstitial lesions[a]

Histologic Lesion	%
Normal glomeruli	12.8 ± 15.3
Fibrinoid necrosis	25.5 ± 25.2
Crescents[b]	56.0 ± 28.8
segmental crescents	25.9 ± 27.3
circumferential crescents	74.1 ± 49.5
cellular crescents	90.6 ± 26.1
fibrous crescents	9.4 ± 2.7
Global sclerosis	26.4 ± 25.7
Interstitial edema (0/1)	0.5 ± 0.5
Interstitial infiltrates (0/1/2/3)	1.8 ± 0.7
neutrophils (0/1/2)	0.7 ± 0.5
monocytes (0/1/2)	1.8 ± 0.4
eosinophils (0/1/2)	0.4 ± 0.5
Interstitial fibrosis (0/1/2)	1.2 ± 0.6
Tubular casts (0/1)	0.9 ± 0.3
Tubular necrosis (0/1)	0.8 ± 0.4
Tubular atrophy (0/1/2)	1.1 ± 0.6
Intraepithelial infiltrates (0/1)	0.8 ± 0.4
Small-vessel vasculitis (0/1)	0.1 ± 0.3
Arteriosclerosis (0/1)	0.8 ± 0.4
Arteriolosclerosis (0/1)	0.5 ± 0.5

[a]Glomerular lesions are expressed as a mean percentage of the total number of glomeruli per patient together with the SD. Numbers after tubulointerstitial lesions indicate the categorical scoring system.

[b]All crescents were scored as either segmental or circumferential and as either cellular or fibrous and are expressed as percentage of total number of crescents.

Figures 2 and 4. When the number of variables is high (48 in this study) and the number of cases is relatively low (100 in this study), inclusion of all variables in the regression analysis is not statistically relevant. The number of variables should be lower than one 10th of the number of cases to prevent "over fitting." Therefore, the number of variables that were taken into account was limited to only those that exhibited reasonable correlations with the outcome parameter and with $P < 0.10$. The formulas for the predictive variables with the odds ratios are reported in Table 5.

Predictors of GFR_0 for Patients Not on Dialysis

Patients who were on dialysis at entry ($n = 69$) were excluded from this analysis because their GFR was not measurable. Arteriosclerosis was the best predictor of GFR_0 ($r = -0.53$, $P = 0.01$). Other clinical and histologic parameters that showed relationships to GFR_0 were gender ($r = -0.45$, $P = 0.02$), age ($r = -0.40$, $P = 0.04$), tubular casts ($r = -0.47$, $P = 0.01$), and eosinophilic infiltrates ($r = -0.41$, $P = 0.04$; Table 4). Women had a significantly worse GFR_0 than men. Higher patient age, the presence of tubular casts and arteriosclerosis, and a predominant eosinophilic infiltrate correlated with a worse GFR_0. It seemed from the regression analysis that arteriosclerosis in combination with age, segmental crescents, and eosinophilic infiltrates was predictive for GFR_0 (Table 5). The univariate relationship of these variables with GFR_0 is shown in Figure 2, A through D.

Predictors of GFR_{12} and $CORGFR_{12}$

Age ($r = -0.32$, $P = 0.01$), GFR_0 ($r = 0.29$, $P = 0.01$), dialysis at entry ($r = -0.27$, $P = 0.02$), tubular atrophy ($r = -0.28$, $P = 0.02$), (global) glomerulosclerosis ($r = -0.27$, $P = 0.02$), normal glomeruli ($r = 0.24$, $P = 0.04$), interstitial fibrosis ($r = -0.24$, $P = 0.04$), and intraepithelial infiltrate ($r = -0.26$, $P = 0.03$) showed a relationship with GFR_{12} (Table 4). Although the univariate correlation of some predictive variables with GFR_{12} is weak (Figure 2, E through I), the combination of age, normal glomeruli, tubular atrophy, intraepithelial infiltrate, and GFR_0 showed a reasonable correlation with GFR_{12} ($r^2 = 0.491$, $r = 0.701$) as shown in Figure 3 and Table 5.

An analysis was performed to determine which parameters independent of GFR_0 correlated with GFR_{12} (the so-called $CORGFR_{12}$), which could be regarded as renal function recovery. The same parameters that were predictive of GFR_{12}, except for dialysis at entry and GFR_0 as defined, also were predictive of $CORGFR_{12}$ (Table 5). The univariate correlation of these variables with $CORGFR_{12}$ is shown in Figure 2, J through M.

Predictors of Dialysis Dependence at Entry and at 12 Mo

A prognostic indicator of dialysis dependence at entry was the percentage of fibrous crescents ($r = 0.22$, $P = 0.03$). There was an increased chance for being dialysis dependent with an increased percentage of fibrous crescents, although the predictive value was moderate (Table 5). The percentage of normal glomeruli ($r = -0.30$, $P = 0.01$), dialysis dependence at entry ($r = 0.25$, $P = 0.03$), intraepithelial infiltrates ($r = 0.31$, $P = 0.03$), and treatment arm ($r = -0.28$, $P = 0.02$) showed a relationship with dialysis dependence at 12 mo (Table 5). In the logistic regression analysis, the combination of normal glomeruli and treatment arm was predictive of dialysis at 12 mo. Univariate relationships of these predictors are shown in Figure 4. In clinical terms, the higher the percentage of normal glomeruli, the lower the chance for developing dialysis dependence. Plasma exchange for treatment arm was clinically favorable over intravenous methylprednisolone as adjunctive therapy.

Analyzing the subgroups, only for 69 patients who were dialysis dependent could statistical significance be reached. For this subgroup, the same parameters correlated with dialysis dependence at 12 mo: The percentage of normal glomeruli ($r = -0.31$, $P = 0.03$), treatment arm ($r = -0.36$, $P = 0.01$), and intraepithelial infiltrates ($r = 0.32$, $P = 0.07$). In addition, more glomerulosclerosis ($r = 0.27$, $P = 0.05$) and the presence of arteriosclerosis ($r = 0.32$, $P = 0.03$) correlated with a higher chance for dialysis dependence at 12 mo.

Predictors of Death

Only two parameters correlated with death: ANCA directed against MPO ($r = 0.24$, $P = 0.04$) and the amount of neutrophils in the interstitial infiltrate ($r = 0.37$, $P = 0.01$; Table 4). However, there were no parameters that were predictive of death as determined by regression analysis. Twenty-four patients died within the first year of follow-up. Two deaths clearly were

Table 4. Correlation of clinical and histologic parameters with GFR_0, GFR_{12}, $CORGFR_{12}$, dialysis at entry, dialysis at 12 mo, and death[a]

	GFR_0 of Patients Not on Dialysis		GFR_{12}		$CORGFR_{12}$		Dialysis at Entry[b]		Dialysis at 12 Mo[b]		Death[c]	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Clinical variables												
GFR_0 of patients not on dialysis	—	—	0.255	0.230	0.048	0.824	—	—	0.067	0.754	−0.127	0.520
GFR_0 of all patients	—	—	0.290	0.013[f]	0.000	1.000	−0.918	<0.001[f]	−0.221	0.060	−0.117	0.262
gender[d]	−0.454	0.015[f]	−0.137	0.248	−0.070	0.526	0.066	0.510	−0.092	0.424	0.151	0.130
age	−0.399	0.035[f]	−0.321	0.006[f]	−0.319	0.006[f]	0.017	0.868	0.083	0.476	0.132	0.192
MPA (−/+)	−0.105	0.595	−0.129	0.276	−0.071	0.553	0.117	0.244	0.165	0.149	0.110	0.273
RLV (−/+)	0.250	0.199	0.029	0.808	0.015	0.903	0.019	0.428	−0.038	0.741	0.047	0.640
WG (−/+)	−0.025	0.900	0.116	0.329	0.064	0.592	−0.173	0.083	−0.148	0.196	−0.145	0.146
dialysis at entry[b]	0.135	0.495	−0.274	0.019[f]	−0.002	0.987	—	—	0.251	0.029[f]	0.022	0.826
treatment arm[e]	0.227	0.245	0.125	0.291	0.121	0.309	−0.008	0.935	−0.277	0.016[f]	0.036	0.722
Glomerular lesions												
no abnormalities	−0.094	0.635	0.239	0.042[f]	0.245	0.038[f]	−0.031	0.761	−0.303	0.008[f]	0.102	0.312
fibrinoid necrosis	0.126	0.523	0.152	0.199	0.081	0.498	−0.166	0.100	−0.133	0.253	0.021	0.833
crescents	−0.069	0.729	0.072	0.545	0.049	0.681	−0.043	0.669	−0.025	0.827	−0.043	0.674
fibrous crescents	0.052	0.794	−0.156	0.187	−0.106	0.376	0.220	0.028[f]	0.080	0.492	−0.030	0.763
glomerulosclerosis	0.047	0.813	−0.274	0.019[f]	−0.269	0.022[f]	0.023	0.817	0.207	0.073	−0.014	0.894
global sclerosis	0.044	0.826	−0.282	0.016[f]	−0.273	0.020[f]	0.035	0.732	0.214	0.064	−0.002	0.985
Interstitial lesions												
neutrophilic infiltrate	0.114	0.579	−0.037	0.758	−0.010	0.931	0.288	0.097	0.221	0.299	0.373	0.010[f]
eosinophilic infiltrate	−0.412	0.037[f]	0.169	0.155	0.157	0.190	0.114	0.744	0.126	0.757	0.170	0.431
interstitial fibrosis	−0.007	0.971	−0.244	0.037[f]	−0.233	0.049[f]	0.235	0.239	0.234	0.382	0.155	0.662
tubular atrophy	0.035	0.858	−0.279	0.017[f]	−0.311	0.008[f]	0.241	0.213	0.307	0.128	0.115	0.857
intraepithelial infiltrates	−0.105	0.597	−0.260	0.026[f]	−0.310	0.008[f]	0.116	0.512	0.308	0.027[f]	0.088	0.679
Vascular lesions												
Small-vessel vasculitis	−0.256	0.189	−0.047	0.695	−0.045	0.707	0.028	0.777	−0.007	0.953	−0.048	0.632
arteriosclerosis	−0.531	0.009[f]	−0.131	0.310	−0.142	0.275	−0.201	0.059	0.160	0.196	0.164	0.123

[a]$CORGFR_{12}$, corrected GFR at 12 mo; GFR_0, renal function at time of diagnosis; GFR_{12}, renal function at 12 mo.
[b]Dialysis independence was coded 0, and dialysis dependence was coded 1.
[c]Being alive was coded as 0, and being dead was coded as 1.
[d]Male was coded as 0, and female was coded as 1.
[e]Plasma exchange treatment was coded 0, and intravenous methylprednisolone was coded as 1.
[f]Correlation with $P < 0.05$.

disease related. These deaths were due to pulmonary vasculitis and to vasculitic gastrointestinal bleeding with pulmonary capillaritis and myocardial infarction. Three deaths probably were disease related: These patients died from pulmonary hemorrhage, which was not specified further. Eleven deaths were therapy related. These were due to infections, such as *Pneumocystis carinii pneumoniae* and cytomegalovirus. One patient died of a cerebral abscess; whether this death was due to therapy or disease is unclear. Furthermore, three patients died of vascular causes, such as myocardial infarction and stroke. Finally, four patients died of unknown causes.

Discussion

In this study, clinical and histologic prognostic indicators of outcome for patients with ANCA-associated vasculitis and severe renal involvement (serum creatinine > 500 μmol/L) were determined. This was a prospective study in which patients were treated uniformly, investigating for the first time the subgroup of patients who have ANCA-associated glomerulonephritis and present with acute severe renal dysfunction. It is widely assumed that patients who present with severe renal dysfunction must have an extensive amount of chronic lesions for which treatment would not likely to be successful. This study shows that the majority of patients have extensive acute lesions and that a significant number of patients benefit from treatment, in particular when plasmapheresis is given. The combination of normal glomeruli, acute and chronic tubulointerstitial damage, age, and treatment was predictive of renal outcome at 12 mo. A worse outcome in patients with a low percentage of normal glomeruli, more acute and chronic tubulointerstitial lesions, and intravenous methylprednisolone as adjunctive treatment was observed. A greater extent of acute and chronic glomerular and interstitial lesions predicted a worse renal function and higher chance for dialysis dependence at entry.

Most biopsies at entry showed extensive acute lesions in these patients, who had serum creatinine levels >500 μmol/L, whereas the number of globally sclerosed glomeruli was relatively low. This indicated that the severely disturbed renal function that was observed at entry was not due to a low-level disease that led to extensive chronic damage but rather to an acute onset of disease that was characterized by extensive acute lesions in the form of crescents and fibrinoid necrosis. The acute

Table 5. Formulas for estimated outcomes[a]

Formulas	Label of Values	r^2	Exponent β	Chance
Estimated GFR_0[b] (ml/min) = 23.0 − 4.9 × arteriosclerosis − 0.15 x age + 0.13 × segmental crescents − 3.1 × eosinophilic infiltrate	Arteriosclerosis: −/+ Age: years Segmental crescents: % Eosinophilic infiltrate: −/+/++	0.678		
Estimated GFR_{12} (ml/min) = 79.1 − 0.63 × age + 0.58 × normal glomeruli − 14.4 × tubular atrophy − 14.2 × intraepithelial infiltrate + 0.95 × GFR_0	Age: years Normal glomeruli: % Tubular atrophy: −/+/++ Intraepithelial infiltrate: −/+ GFR_0: ml/min	0.491		
Estimated $CORGFR_{12}$ (ml/min) = 62.1 − 0.63 × age + 0.58 × normal glomeruli − 14.5 × tubular atrophy − 14.1 × intraepithelial infiltrate	See box above	0.443		
Estimated dialysis at entry: $\beta = 0.081$	Fibrous crescents: %	0.212	1.09	OR = Exp ($\beta \times \Delta$fibrous crescents) = $(\text{Exp } \beta)^{\Delta\text{fibrous crescents}}$
Probability dialysis at 12 months: y = −0.64 − 0.070 × normal glomeruli + 1.3 × arm	Normal glomeruli: % Arm: 0 = plasma exchange, 1 = intravenous methylprednisolone	0.309	0.93 3.52	p = Exp (y)/[1 + Exp (y)]

[a]Odds ratios (OR) expressed as exponent β. Values in formulas are β. Predictive values of the models are expressed as r^2.
[b]Estimated GFR_0 applies only to patients who were not on dialysis.

lesions did not correlate with GFR_0 or with dialysis at entry. We also found this in a previous study (29), and we think that this phenomenon may be because although, histologically, acute lesions seem to be similar to each other, they are in fact a heterogeneous group of lesions of which some are in a healing process and others are on their way to irreversible damage. This could explain their lack of predictive value for renal function at time of biopsy.

A relationship existed between GFR_0 and age, gender, arteriosclerosis, tubular casts, and interstitial infiltrates (in particular of eosinophilic granulocytes) for patients who were not on dialysis at entry. Three of these variables, age, tubular casts, and interstitial infiltrates, also showed a relationship with GFR_0 in a previous study of patients with mild to moderate renal involvement (serum creatinine < 500 μmol/L) (20). This indicated that these parameters are important for renal impairment in ANCA-associated glomerulonephritis, both at a high and a low range of renal dysfunction. Age and gender were already known to have a high impact on renal function in ANCA-associated renal disease; worse renal function in elderly patients with acute disease and a relative benefit for men was observed (30–32).

Arteriosclerosis was not associated with age and had prognostic value for determining renal outcome in this analysis. This possibly reflects a component of chronic renal vascular disease (11). It is interesting that the severity of tubular casts and interstitial infiltrates reflected the level of renal dysfunction at entry in this patient group, as well as in our previously described patient group with ANCA-associated glomerulonephritis with moderate renal involvement. The amount of tubular casts may reflect the degree of obstruction (33). The interstitial infiltrate, in part consisting of eosinophilic granulocytes, may be indicative of ongoing chronic interstitial fibrosis and could account for the increased intrarenal collagen synthesis as has been shown for lupus nephritis (34) and renal allograft fibrosis (35).

The percentage of fibrous crescents was the only parameter that was predictive of dialysis at entry. It is tempting to hypothesize that patients who are in need of dialysis at the time of diagnosis have had the disease for some time, which is reflected by the fibrous crescents. However, approximately half of the patients who were on dialysis at entry were no longer on dialysis at 12 mo. This suggests that fibrous crescents should not be a contraindication to start therapy. One parameter that predicted dialysis at 12 mo was the treatment arm. The adjunctive treatment of preference was plasma exchange, which had a favorable effect on dialysis independence after 1 yr. Therefore, plasma exchange seems to be the preferred additional form of therapy for patients who have ANCA-associated glomerulonephritis and present with severe renal failure. The trial report on the MEPEX data revealed that the addition of plasma exchange to oral cyclophosphamide led to an increased chance of renal recovery compared with the addition of intravenous methylprednisolone (unpublished data). This beneficial effect was sustained throughout the 12-mo study period. The mortality rate was comparable between the two treatment groups.

Age, the percentage of normal glomeruli, intraepithelial infiltrates, tubular atrophy, and GFR_0 predicted GFR_{12}. Age has been shown to be important for renal outcome before (11,36). We reported on the importance of normal glomeruli for renal recovery in patients with ANCA-associated glomerulonephritis in 1999 (23) and in 2002 (20). Also in several other studies,

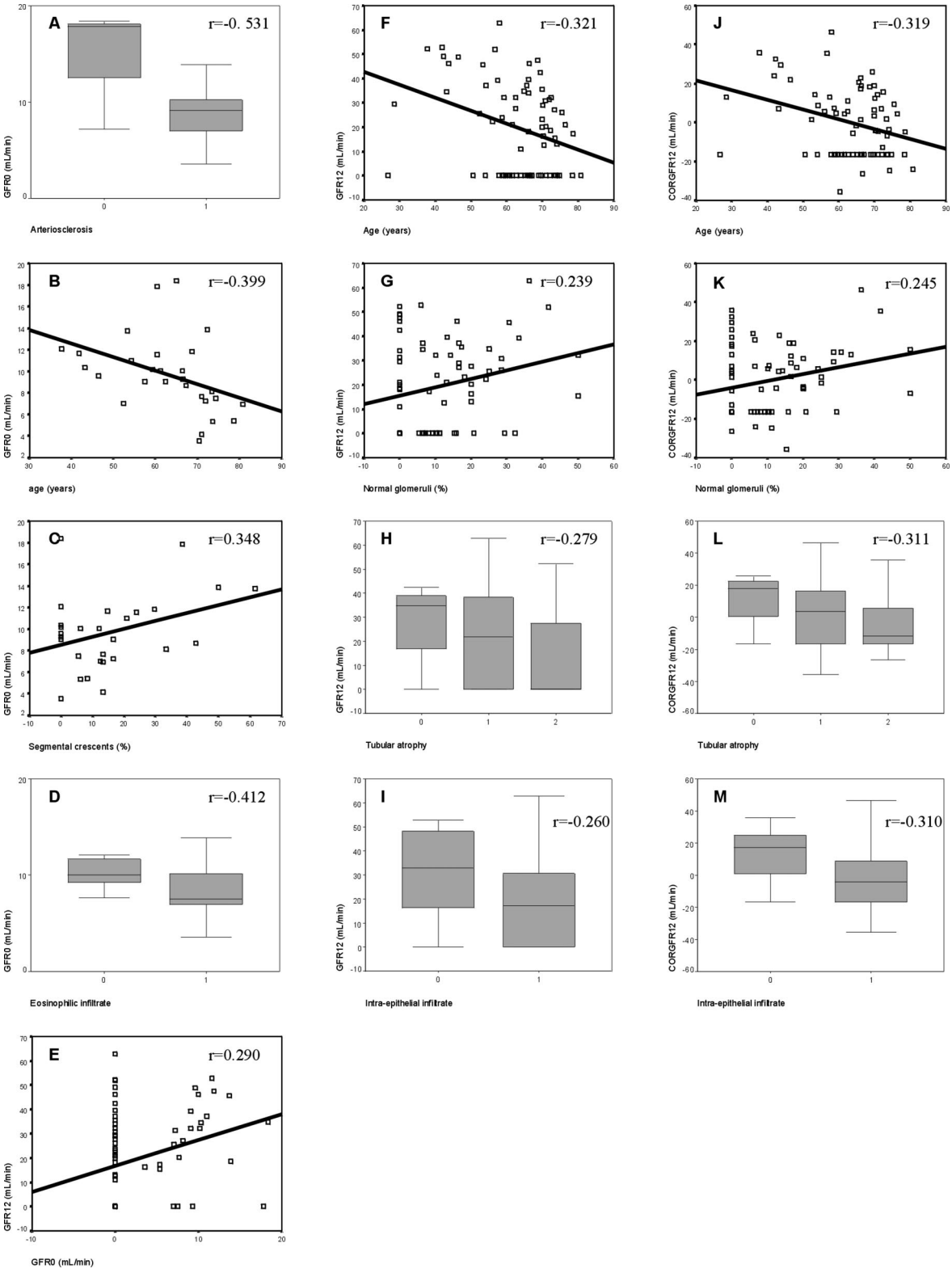

Figure 2. Correlation figures for predictive variables of renal function and renal function recovery. Predictors of renal function at the time of diagnosis (GFR_0) for only patients who were not on dialysis at entry: Arteriosclerosis ($r = -0.531$, $P = 0.009$; A), age ($r = -0.399$, $P = 0.035$; B), segmental crescents ($r = 0.348$, $P = 0.069$; C), and eosinophilic infiltrate ($r = -0.412$, $P = 0.037$; D). Predictors of renal function at 12 mo (GFR_{12}): GFR_0 ($r = 0.290$, $P = 0.013$; E), age ($r = -0.321$, $P = 0.006$; F), percentage of normal glomeruli ($r = 0.239$, $P = 0.042$; G), tubular atrophy ($r = -0.279$, $P = 0.017$; H), and intraepithelial infiltrate ($r = -0.260$, $P = 0.026$; I). Predictors of corrected GFR_{12} ($CORGFR_{12}$): Age ($r = -0.319$, $P = 0.006$; J), percentage of normal glomeruli ($r = 0.245$, $P = 0.038$; K), tubular atrophy ($r = -0.311$, $P = 0.008$; L), and intraepithelial infiltrate ($r = -0.310$, $P = 0.008$; M). All correlations are visualized either as scatter plots (continuous variables) or as box plots (categorical or dichotomous variables).

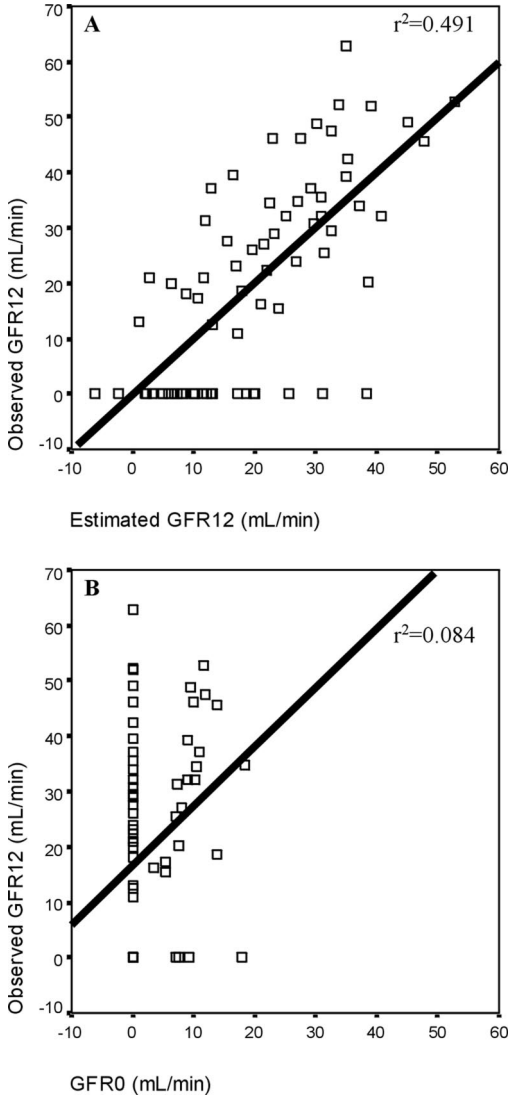

Figure 3. Scatterplot of observed GFR_{12} *versus* estimated GFR_{12} (A). The estimated GFR_{12} was calculated on the basis of the following formula: Estimated GFR_{12} = 79.1 − 0.63 × age (years) + 0.58 × normal glomeruli (%) − 14.4 × tubular atrophy (−/+/++) − 14.2 × intraepithelial infiltrate (−/+) + 0.95 × GFR_0 (ml/min). Scatterplot of measured GFR_{12} *versus* GFR_0 (B).

normal glomeruli were shown to predict renal outcome over time (36–40). In follow-up biopsies of patients with ANCA-associated glomerulonephritis, the percentage of normal glomeruli did not change over time (29). Therefore, apart from reflecting the functioning part of the kidney, normal glomeruli also are a relatively constant parameter, the combination of which may explain their strength as a predictive parameter. Also intraepithelial tubular infiltrates are predictive of GFR_{12}, and their presence may well be related to the development of tubular atrophy, a widely known parameter of chronic renal failure in general and associated with worse renal outcome in ANCA-associated vasculitis (11,18).

No parameters predicted death; however, one of the parameters that correlated with death was the amount of neutrophils in the interstitial infiltrate. It is interesting that leucocytosis was demonstrated previously as a predictor of death in patients with idiopathic renal vasculitis (41), although a causal relationship between leukocyte count and progression of injury could not be established. We think that a possible link could be leucocytosis as one of the first signs of an infection, which, in combination with immunosuppressive treatment, would be a high-risk factor for death. Our study shows that the most important cause of death of patients who died between 3 and 12 mo of follow-up was therapy-related infection. Recent studies also showed that the main cause of death in ANCA-associated glomerulonephritis is treatment-related infectious complication (42,43).

Baseline renal function was found previously to be a predictor of renal outcome in retrospective studies (11,36,44). In addition, our previous study of patients with mild to moderate renal involvement in ANCA-associated vasculitis showed that GFR_0 is important for predicting GFR_{12} (20). $CORGFR_{12}$ was used to determine the influence of the GFR_0-independent variables. This measure for renal function recovery enabled us to study the difference between the measured GFR_{12} and the expected GFR_{12} on the basis of GFR_0. However, the same parameters, except for GFR_0 and dialysis at entry, as expected, predicted GFR_{12} and $CORGFR_{12}$. This means that age, the percentage of normal glomeruli, tubular atrophy, and intraepithelial infiltrates indeed are important predictors of renal function recovery and are independent of renal function at entry.

The reason that some of the parameters that correlated univariately with GFR_{12} were not predictive of GFR_{12}, as resulting from the regression model, could be that some of the parameters correlated with each other. For instance, glomerulosclerosis and interstitial fibrosis were strong correlators with GFR_{12} in the univariate analysis, but because of their positive relationship with tubular atrophy, they did not turn out to be predictors of GFR_{12} in the regression model.

The models that were obtained from regression analysis are useful to the clinician for estimating renal status after 12 mo. In addition, the maximum chance for dialysis could be deducted from one of these models. If patients have the worst phenotype possible in this model—that is, no normal glomeruli in the renal biopsy and intravenous methylprednisolone as adjunctive treatment—then their chance for being on dialysis after 12 mo is 50%. Taking into account the chance of 24% for dying, this means that even in the worst case, there is still a 26% chance for recovery. Despite that the predictive values of the models postulated are limited (r^2 for GFR_{12} = 0.491; r^2 for dialysis at 12 mo = 0.309), these models clearly showed that consideration of several clinical and histologic parameters results in a better prediction of renal outcome after 12 mo than evaluation of GFR_0 (r^2 for GFR_{12} = 0.084; r^2 for dialysis at 12 mo = 0.073) or dialysis dependence at entry (r^2 for GFR_{12} = 0.075; r^2 for dialysis at 12 mo = 0.091) alone.

Predictive parameters in this study were defined for different outcome parameters in patients with ANCA-associated glomerulonephritis and severe renal involvement. All patients who participated in the study presented with severe renal

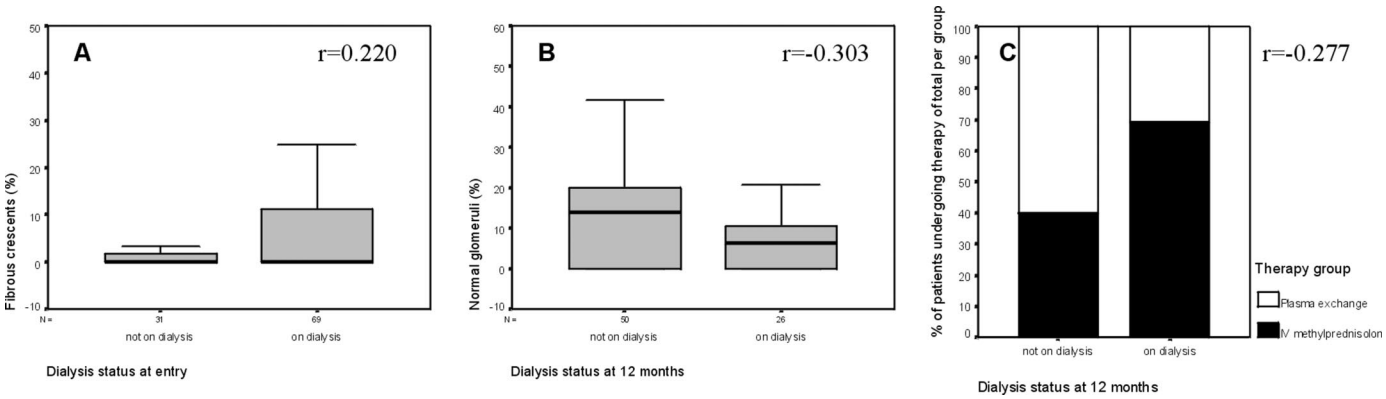

Figure 4. Correlation figures for predictive variables of dialysis status. Predictor of dialysis status at entry: Percentage of fibrous crescents ($r = 0.220$, $P = 0.028$; A). Predictors of dialysis status at 12 mo: Percentage of normal glomeruli ($r = -0.303$, $P = 0.008$; B) and treatment arm ($r = -0.277$, $P = 0.016$; C). All correlations are visualized either as box plots or as bar diagrams.

disease and were treated according to protocol. However, it has to be noted that the results of this study must be interpreted with the understanding that every patient had severe renal disease with a serum creatinine >500 μmol/L and that extrapolation of these results to patients who do not meet this or any of the other inclusion criteria is not advisable. Further studies are required to determine whether these results can be extrapolated to long-term follow-up. Another point of consideration is that the *r* values of the univariate analyses could raise some doubt on the clinical applicability of the findings. A possible explanation for the relatively low *r* values is that the patient cohort is a predefined group of patients with bad renal function at entry, with parameters in a relatively tight range, which is bound to lead to relatively low *r* values. Therefore, it was necessary to analyze the data not only in a univariate manner but also in a multivariate manner, because the combination of parameters predicts much better for outcome than single parameters alone. Another issue concerns that the patients in this study were randomly assigned into two treatment arms, which could have confounded the renal outcome data. However, the treatment arms proved to predict only dialysis dependence at 12 mo, whereas no correlation was found for the other outcome parameters.

Conclusion

This study identified determinants of renal outcome in patients with ANCA-associated vasculitis and severe renal involvement. The prospective design, the homogeneity of the population, the population size, the standardization of patient treatment, and the detailed scoring system provided optimal conditions for this analysis. Our data suggest that in severe ANCA-associated glomerulonephritis, the combination of renal function at diagnosis, the percentage of normal glomeruli, age, and acute and chronic tubulointerstitial lesions predict GFR_{12}. The prediction was much more accurate than that based on GFR at entry alone. The percentage of normal glomeruli at diagnosis combined with adjuvant treatment predicted dialysis dependence at 12 mo. The regression model provides a tool to the clinician for estimating the chances for a favorable outcome for patients.

Acknowledgments

This trial was designed and launched as part of the European Community Systemic Vasculitis Trial project (contracts BMH1-CT93-1078 and CIPD-CT94-0307) and finished as part of the Associated Vasculitis European Randomized Trial project (contracts BMH4-CT97-2328 and IC20-CT97-0019) funded by the European Union.

Parts of this study were presented at the annual meeting of the American Society of Nephrology; October 29 to November 1, 2004; St. Louis, MO (abstract SA-PO183; *J Am Soc Nephrol* 15: 340A, 2004).

We thank the following: N.J.D. Nagelkerke, J. Hermans, and J.C. van Houwelingen, Leiden, Netherlands; P. Landais, Paris, France; J. Thorogood, London, UK (statistical advice); H. Talbot, Edinburgh, UK (software design); F. Compton, London, UK (data management); and L. Jayne, London, UK (trial administration).

Participating clinical physicians: D. Blockmans, Universitair Ziekenhuis, Leuven, Belgium; M. Dhaene, J. Sennesael, Academic Hospital of the Free University, Bruxelles, Belgium; A. Wiik, Statens Serum Institute, Copenhagen, Denmark; A. Ekstrand, C. Grönhagen-Riska, University of Helsinki, Finland; P. Lesavre, Hôpital Necker, Paris, France; P. Bataille, Centre Hospitalier General, Boulogne sur Mer, France; L. Guillevin, Hôpital Avicenne, Bobigny, France; P. Vanhille, Centre Hospitalier, Valenciennes, France; O. Hergesell, K. Andrassy, Heidelberg University Hospital, Germany; E. Reinhold-Keller, Rheumaklinik Bad Bramstedt, Germany; C. Specker, M. Schneider, Heinrich-Heine University, Düsseldorf, Germany; M. Haubitz, Medical School Hannover, Germany; F. van der Woude, Klinikum Mannheim, Germany; H. Rupprecht, S. Weidner, Klinikum Nürnberg, Germany; A. Natusch, Klinikum Buch, Berlin, Germany; M. Abuzakouk, St. James's Hospital, Dublin, Ireland; A. Sinico, Ospedale San Carlo Borromeo, Milan, Italy; G. Poisetti, Ospedale Civile, Piacenzia, Italy; J. Dadoniene, University of Vilnius, Lithuania; C. Verburgh, Leiden University Medical Center, The Netherlands; E. Mirapeix, Hospital Clinic I Provincial, Barcelona, Spain; R. Poveda, Hospital Princeps d'España, Llobregat, Spain; M. Heimburger, Huddinge University Hospital, Sweden; E. Theander, K. Westman, M. Segelmark, University Hospital of Malmø, Sweden; Z. Heigl, I. Lundberg, E. Svenungussen, Karolinska Sjukhuset, Sweden; J. Gibson, Windygates Hospital, Fife, UK; D. Adu, C. Savage, L. Harper, Queen Elizabeth II Hospital, Birmingham, UK; P. Mathieson, C. Tomson,

Southmead Hospital, Bristol, UK; J. Freehally, University Hospital, Leicester, UK; A. Burns, Royal Free Hospital, London, UK; D. Oliveira, St. George's Hospital, London, UK; R. Luqmani, John Radcliffe Hospital, Oxford, UK; M. Rogerson, J. Stevens, Southampton Hospital, UK; A. Williams, Morriston Hospital, Swansea, UK.

Pathologists who provided biopsy material: B. van Damme, University Hospital Leuven, Belgium; M. Depierreux, C. Bourgain, Academic Hospital of the Free University, Bruxelles, Belgium; T. Törnroth, University of Helsinki, Finland; A.C. Feller, University of Luebeck, Germany; E. Gaffney, St. James's Hospital, Dublin, Ireland; R. Tardanico, Ospedale Civili, Brescia, Italy; R. Consalonieri, Ospedale Maggiore CA Granda, Milan, Italy; G. Garibotto, ISUL, Genova, Italy; A.T.M.G. Tiebosch, Academic Hospital, Groningen, The Netherlands; C.D. Kooijman, Eemland Hospital, Amersfoort, The Netherlands; M. Sole Arques, Hospital Clinic I Provincial de Barcelona, Spain; F. Algaba, Puigvert, Barcelona, Spain; M. Carrera, Hospital Princeps d'España, Llobregat, Spain; M. Carreras, Hospital de Bellvitge, Barcelona, Spain; M. Vaquero Perez, Hospital Universitari Germans Trias I Pujol, Badalona, Spain; L. Bernardo, Hospital Dr. Josep Trueta, Girona, Spain; A. Wernersson, Huddinge University Hospital, Sweden; B. Sundelin, Karolinska Hospital, Stockholm, Sweden; M. Simanaitis, B. Veress, University Hospital MAS, Malmø, Sweden; P. Alm, University Hospital of Lund, Sweden; A.J. Howie, University Hospital Birmingham, UK; D. Griffiths, D. Kamel, Southmead Hospital, Bristol, UK; S. Fleming, University Department of Pathology, Edinburgh, UK; P.N. Furness, Leicester Area Histopathology Service, UK; H.T. Cook, Hammersmith Hospital, London, UK; W. Landells, St. Helier Hospital, London, UK; I. Roberts, John Radcliffe Hospital, Oxford, UK; A.P. Griffith, Morriston Hospital, Swansea, UK.

References

1. Pettersson EE, Sundelin B, Heigl Z: Incidence and outcome of pauci-immune necrotizing and crescentic glomerulonephritis in adults. *Clin Nephrol* 43: 141–149, 1995
2. Falk RJ, Jennette JC: ANCA small-vessel vasculitis. *J Am Soc Nephrol* 8: 314–322, 1997
3. Bajema IM, Hagen EC, van der Woude FJ, Bruijn JA: Wegener's granulomatosis: A meta-analysis of 349 literary case reports. *J Lab Clin Med* 129: 17–22, 1997
4. Watts RA, Scott DG: Epidemiology of the vasculitides. *Curr Opin Rheumatol* 15: 11–16, 2003
5. Jennette JC, Falk RJ, Andrassy K, Bacon PA, Churg J, Gross WL, Hagen EC, Hoffman GS, Hunder GG, Kallenberg CG: Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum* 37: 187–192, 1994
6. Jayne D: Update on the European Vasculitis Study Group trials. *Curr Opin Rheumatol* 13: 48–55, 2001
7. Fauci AS, Haynes B, Katz P: The spectrum of vasculitis: Clinical, pathologic, immunologic and therapeutic considerations. *Ann Intern Med* 89: 660–676, 1978
8. Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, Rottem M, Fauci AS: Wegener granulomatosis: An analysis of 158 patients. *Ann Intern Med* 116: 488–498, 1992
9. Savage CO, Harper L, Adu D: Primary systemic vasculitis. *Lancet* 349: 553–558, 1997
10. Gayraud M, Guillevin L, le Toumelin P, Cohen P, Lhote F, Casassus P, Jarrousse B: Long-term followup of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: Analysis of four prospective trials including 278 patients. *Arthritis Rheum* 44: 666–675, 2001
11. Hogan SL, Nachman PH, Wilkman AS, Jennette JC, Falk RJ: Prognostic markers in patients with antineutrophil cytoplasmic autoantibody-associated microscopic polyangiitis and glomerulonephritis. *J Am Soc Nephrol* 7: 23–32, 1996
12. Serra A, Cameron JS, Turner DR, Hartley B, Ogg CS, Neild GH, Williams DG, Taube D, Brown CB, Hicks JA: Vasculitis affecting the kidney: Presentation, histopathology and long-term outcome. *Q J Med* 53: 181–207, 1984
13. Savage CO, Winearls CG, Evans DJ, Rees AJ, Lockwood CM: Microscopic polyarteritis: Presentation, pathology and prognosis. *Q J Med* 56: 467–483, 1985
14. Weiss MA, Crissman JD: Segmental necrotizing glomerulonephritis: Diagnostic, prognostic, and therapeutic significance. *Am J Kidney Dis* 6: 199–211, 1985
15. Furlong TJ, Ibels LS, Eckstein RP: The clinical spectrum of necrotizing glomerulonephritis. *Medicine* 66: 192–201, 1987
16. Croker BP, Lee T, Gunnells JC: Clinical and pathologic features of polyarteritis nodosa and its renal-limited variant: Primary crescentic and necrotizing glomerulonephritis. *Hum Pathol* 18: 38–44, 1987
17. Andrassy K, Erb A, Koderisch J, Waldherr R, Ritz E: Wegener's granulomatosis with renal involvement: Patient survival and correlations between initial renal function, renal histology, therapy and renal outcome. *Clin Nephrol* 35: 139–147, 1991
18. Gans RO, Kuizinga MC, Goldschmeding R, Assmann K, Huysmans FT, Gerlag PG, Donker AJ, Hoorntje SJ: Clinical features and outcome in patients with glomerulonephritis and antineutrophil cytoplasmic autoantibodies. *Nephron* 64: 182–188, 1993
19. Franssen CF, Stegeman CA, Oost-Kort WW, Kallenberg CG, Limburg PC, Tiebosch A, De Jong PE, Tervaert JW: Determinants of renal outcome in anti-myeloperoxidase-associated necrotizing crescentic glomerulonephritis. *J Am Soc Nephrol* 9: 1915–1923, 1998
20. Hauer HA, Bajema IM, van Houwelingen HC, Ferrario F, Noel LH, Waldherr R, Jayne DR, Rasmussen N, Bruijn JA, Hagen EC: Determinants of outcome in ANCA-associated glomerulonephritis: A prospective clinico-histopathological analysis of 96 patients. *Kidney Int* 62: 1732–1742, 2002
21. Jayne DR, Rasmussen N: Treatment of antineutrophil cytoplasm autoantibody-associated systemic vasculitis: Initiatives of the European Community Systemic Vasculitis Clinical Trials Study Group. *Mayo Clin Proc* 72: 737–747, 1997
22. Hagen EC, Daha MR, Hermans J, Andrassy K, Csernok E, Gaskin G, Lesavre P, Ludemann J, Rasmussen N, Sinico RA, Wiik A, van der Woude FJ: Diagnostic value of standardized assays for anti-neutrophil cytoplasmic antibodies in idiopathic systemic vasculitis. EC/BCR Project for ANCA Assay Standardization. *Kidney Int* 53: 743–753, 1998
23. Bajema IM, Hagen EC, Hermans J, Noel LH, Waldherr R, Ferrario F, van der Woude FJ, Bruijn JA: Kidney biopsy as a predictor for renal outcome in ANCA-associated necrotizing glomerulonephritis. *Kidney Int* 56: 1751–1758, 1999
24. Bajema IM, Hagen EC, Hansen BE, Hermans J, Noel LH, Waldherr R, Ferrario F, van der Woude FJ, Bruijn JA: The renal histopathology in systemic vasculitis: An international survey study of inter- and intra-observer agreement. *Nephrol Dial Transplant* 11: 1989–1995, 1996

25. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 16: 31–41, 1976
26. Levey AS, Lan SP, Corwin HL, Kasinath BS, Lachin J, Neilson EG, Hunsicker LG, Lewis EJ: Progression and remission of renal disease in the Lupus Nephritis Collaborative Study. Results of treatment with prednisone and short-term oral cyclophosphamide. *Ann Intern Med* 116: 114–123, 1992
27. Peters DK, Rees AJ, Lockwood CM, Pusey CD: Treatment and prognosis in antibasement membrane antibody-mediated nephritis. *Transplant Proc* 14: 513–521, 1982
28. Senn S, Stevens L, Chaturvedi N: Repeated measures in clinical trials: Simple strategies for analysis using summary measures. *Stat Med* 19: 861–877, 2000
29. Hauer HA, Bajema IM, Hagen EC, Noel LH, Ferrario F, Waldherr R, van Houwelingen HC, Lesavre P, Sinico RA, van der WF, Gaskin G, Verburgh CA, de Heer E, Bruijn JA: Long-term renal injury in ANCA-associated vasculitis: An analysis of 31 patients with follow-up biopsies. *Nephrol Dial Transplant* 17: 587–596, 2002
30. Slot MC, Tervaert JW, Franssen CF, Stegeman CA: Renal survival and prognostic factors in patients with PR3-ANCA associated vasculitis with renal involvement. *Kidney Int* 63: 670–677, 2003
31. Booth AD, Almond MK, Burns A, Ellis P, Gaskin G, Neild GH, Plaisance M, Pusey CD, Jayne DR: Outcome of ANCA-associated renal vasculitis: A 5-year retrospective study. *Am J Kidney Dis* 41: 776–784, 2003
32. Dringenberg C, Apenberg S, Andrassy K: p-ANCA with myeloperoxidase antibodies and c-ANCA with proteinase 3 antibodies define a different vasculitis entity in patients with renal involvement. *Adv Exp Med Biol* 336: 445–447, 1993
33. Bock HA: Pathogenesis of acute renal failure: New aspects. *Nephron* 76: 130–142, 1997
34. Baelde HJ, Eikmans M, Van Vliet AI, Bergijk EC, de Heer E, Bruijn JA: Alternatively spliced isoforms of fibronectin in immune-mediated glomerulosclerosis: The role of TGFbeta and IL-4. *J Pathol* 204: 248–257, 2004
35. Abo-Zenah H, Katsoudas S, Wild G, de Takats D, Shortland J, Brown CB, El Nahas AM: Early human renal allograft fibrosis: Cellular mediators. *Nephron* 91: 112–119, 2002
36. Neumann I, Kain R, Regele H, Soleiman A, Kandutsch S, Meisl FT: Histological and clinical predictors of early and late renal outcome in ANCA-associated vasculitis. *Nephrol Dial Transplant* 20: 96–104, 2005
37. Haroun MK, Stone JH, Nair R, Racusen L, Hellmann DB, Eustace JA: Correlation of percentage of normal glomeruli with renal outcome in Wegener's granulomatosis. *Am J Nephrol* 22: 497–503, 2002
38. Aasarod K, Bostad L, Hammerstrom J, Jorstad S, Iversen BM: Renal histopathology and clinical course in 94 patients with Wegener's granulomatosis. *Nephrol Dial Transplant* 16: 953–960, 2001
39. Kapitsinou PP, Ioannidis JP, Boletis JN, Sotsiou F, Nakopoulou L, Daphnis E, Moutsopoulos HM: Clinicopathologic predictors of death and ESRD in patients with pauci-immune necrotizing glomerulonephritis. *Am J Kidney Dis* 41: 29–37, 2003
40. Vergunst CE, van Gurp E, Hagen EC, van Houwelingen HC, Hauer HA, Noel LH, Waldherr R, Ferrario F, van der Woude FJ, Bruijn JA, Bajema IM: An index for renal outcome in ANCA-associated glomerulonephritis. *Am J Kidney Dis* 41: 532–538, 2003
41. Wilkowski MJ, Velosa JA, Holley KE, Offord KP, Chu CP, Torres VE, McCarthy JT, Donadio JV Jr, Wagoner RD: Risk factors in idiopathic renal vasculitis and glomerulonephritis. *Kidney Int* 36: 1133–1141, 1989
42. Hasegawa M, Watanabe A, Takahashi H, Takahashi K, Kasugai M, Kawamura N, Kushimoto H, Murakami K, Tomita M, Nabeshima K, Oohashi A, Kondou F, Ooshima H, Hiki Y, Sugiyama S: Treatment with cytapheresis for antineutrophil cytoplasmic antibody-associated renal vasculitis and its effect on anti-inflammatory factors. *Ther Apher Dial* 9: 297–302, 2005
43. Weidner S, Geuss S, Hafezi-Rachti S, Wonka A, Rupprecht HD: ANCA-associated vasculitis with renal involvement: An outcome analysis. *Nephrol Dial Transplant* 19: 1403–1411, 2004
44. Okano K, Yumura W, Nitta K, Honda K, Uchida K, Nihei H: Evaluation of prognostic factors for myeloperoxidase anti-neutrophil cytoplasmic antibody- (MPO-ANCA) associated glomerulonephritis. *Clin Nephrol* 55: 275–281, 2001