Baseline Features and Initial Treatment as Predictors of Remission and Relapse in Wegener's Granulomatosis

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ABSTRACT. ***Objective.*** To describe the course of disease activity and determine predictors of remission and relapse in a population based cohort of patients with Wegener's granulomatosis (WG).

Methods. Retrospective cohort study of 56 patients (median age 50 yrs) followed for 42.5 months. Disease activity was assessed by Birmingham Vasculitis Activity Score (BVAS-1) and permanent organ damage by Vasculitis Damage Index (VDI). Induction therapy consisted of prednisolone (Pred) 0.5–1 mg/kg and cyclophosphamide (CYC) daily orally 2 mg/kg (19 patients) or intravenous pulses 15 mg/kg every 2nd week (32 patients). Baseline clinical and laboratory features and cumulative treatment during the first 6 months were recorded. Multiple Cox and logistic regression analyses were used to find risk factors for remission and relapse.

Results. All patients surviving > 1 month achieved either complete (85%) or partial remission (15%). Higher baseline BVAS-1 increased the likelihood of achieving complete remission [BVAS-1 > 23, relative hazard (RH) 2.94, 95% confidence interval (CI) 1.48–5.85]. Relapse occurred in 31 patients (60%) after a median period of 18 months. The risk of relapse was increased in patients having received < 10 g CYC during the first 6 months (RH 2.83, 95% CI 1.33–6.02), in patients having received Pred > 20 mg/day for < 2.75 months (RH 2.41, 95% CI 1.12–5.21), and in patients with initial heart involvement (RH 2.87, 95% CI 1.09–7.58). A higher Pred dose during the first 6 months was associated with severe infections. Therapy resistance (no complete remission) was associated with baseline organ damage (VDI increase by 1, OR 1.53, 95% CI 1.03–2.27).

Conclusion. Initial high disease activity increased and the presence of baseline organ damage reduced the likelihood for complete remission in WG. Relapse was associated with less intensive initial treatment in terms of lower CYC doses and shorter time taking Pred > 20 mg/day. (J Rheumatol 2003;30:80–8)

Key Indexing Terms:
WEGENER'S GRANULOMATOSIS VASCULITIS
TREATMENT REMISSION RELAPSE

The prognosis for patients with Wegener's granulomatosis (WG), a systemic vasculitis that most often involves upper airways and kidneys, has improved considerably over the last decades[1,2]. With combined cyclophosphamide (CYC) and corticosteroid treatment the 10 year survival now reaches 75%[3,4], and initial complete remission occurs in most patients[5,6]. WG has become a chronic disease, where morbidity due to permanent organ damage and disease relapses are major concerns[4,5,7]. Relapse rates vary between 19 and 67% and seem to increase with length of followup[6-9], although one study suggested that the relapse rate declines after the first year[10]. Relapses have been associated with both morbidity and mortality[3,11], hence prediction and early detection of relapses are of great importance.

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Supported by grants from the Norwegian Women's Public Health Association and the Norwegian Rheumatology Society.

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Submitted October 10, 2001; revision accepted June 10, 2002.

Only a few studies have tried to identify predictors for relapse at disease onset. Initial lung involvement[8] and persistently positive antineutrophil cytoplasmic antibodies (ANCA) during followup have been associated with increased relapse rate[8-10,12,13]. Moreover, treatment with pulse CYC has resulted in more relapses than CYC given daily orally[14,15], and patients being on a reduction scale of the immunosuppressive treatment have an increased relapse rate[16,17].

Most studies on relapse rate in WG were performed at referral centers. We describe the course of disease activity in a population based cohort of patients with WG, studying variables at disease onset and the treatment given during the first 6 months as predictors for complete remission and relapse.

MATERIALS AND METHODS

Patients. Patient selection has been described in detail[18]. Briefly, 56 patients were recruited from a regional population based WG register that records all cases of WG since 1984 in the 3 northernmost counties in Norway. WG was defined according to the American College of Rheumatology (ACR) 1990 classification criteria[19]. In addition, 37 patients had biopsy proven granulomatous inflammation and 17 more patients had positive tests for cytoplasmic antineutrophil cytoplasmic antibodies

(cANCA) as supporting evidence. This study comprises all patients included in the register to February 1999. The study was approved by the regional research ethics committee.

Data collection. For each patient, date of first symptom attributable to WG and demographic and laboratory data, organ involvement, and disease activity at baseline (start of treatment) were retrieved from hospital records with the use of a predefined form. All data collection was performed by one author (WK). The same data were recorded at times of relapses as well as at an extensive followup visit ("research visit") performed between May 1998 and August 1999. Time from baseline to first complete or partial remission, time from baseline to every relapse (remission and relapse defined below), and the cumulative time with and without immunosuppressive treatment (defined as no corticosteroids or cytotoxic medication) were recorded. Severe infection necessitating intravenous antibiotics and herpes zoster infections were recorded during the first 6 months of immunosuppressive treatment. Laboratory data recorded were complete blood cell count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) concentration, serum creatinine concentration, the findings of urine dipstick test and urine sediment microscopy, and ANCA testing (positive or negative).

Definitions of disease activity and damage. Disease activity in terms of remission and relapse was defined as described[20]. Complete remission was 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. Partial remission: a clear-cut suppression of disease activity with stabilization of renal function and at least partial resolution of pulmonary infiltrates, and signs of improvement in other organs. Relapse was defined as the reemergence of clinically detectable vasculitis, or worsening of previous manifestations after a period of complete or partial remission of at least one month. Infection had to be excluded as a likely cause of symptoms.

Organ involvement was defined according to the Disease Extent Index (DEI)[21]. Disease activity was scored according to the Birmingham Vasculitis Activity Score (BVAS-1)[22], and permanent organ damage according to the definition of the Vasculitis Damage Index (VDI)[23]. The indexes were scored according to the information in the records. When relevant information on symptoms and findings was missing, these were considered not to be present unless other information could be obtained from the patient when interviewed at the time of the research visit.

Initial treatment regimens. The decision how and when to start treatment was based on clinical grounds by the attending physicians. Induction therapy for active disease consisted of CYC, given either daily orally (CYCpo) 2 mg/kg body weight (19 patients), or as pulses intravenously (CYCiv) 15 mg/kg body weight every second week (32 patients), increasing the pulse interval after remission was achieved, as described[20]. Corticosteroid treatment was given to all but 2 patients, as daily doses of prednisolone (Pred) 0.5–1.0 mg/kg body weight, with dose reduction starting after 2–6 weeks at the discretion of the attending physician. Prior intravenous methylprednisolone pulse therapy (500–1000 mg daily for 3 consecutive days before start of CYC) was given to 25 CYCiv treated patients and to 7 CYCpo treated patients. Plasma exchange was performed during induction therapy in 12 severely ill patients (10 CYCiv and 2 CYCpo treated patients).

Followup. The patients were seen every 2–4 weeks until remission, and thereafter at least every 6 months during total followup. At every visit a clinical examination and full blood cell count, serum creatinine, ESR and/or CRP level, urine dipstick and urine sediment microscopy were performed. Additional blood tests, radiographic examinations, or evaluations by relevant specialists (ENT, eye, neurologist, or others) were done if clinically indicated. Maintenance therapy other than CYC, started 6–18 months after remission, consisted of methotrexate (MTX) 0.3 mg/kg body weight weekly (20 patients), azathioprine (AZA) 2.0–2.5 mg/kg body weight daily (17 patients), or intravenous gammaglobulin 0.4 g/kg body weight monthly (4 patients). Nineteen patients had received trimethoprim-sulfamethoxazole (TMS) at any time. Relapse therapy consisted of transiently increasing the corticosteroid dose (to ≥ 20 mg) in cases with minor symptoms, and a return to induction therapy with CYC and corticosteroid for more severe relapses involving vital organs.

Statistics. Data are presented as median and range. The nonparametric Mann-Whitney U test was used to compare continuous variables between groups, and chi-square or Fisher's exact test when comparing categorical data. We used the Kaplan-Meier method to calculate probability of relapse-free survival and the probability of achieving complete remission. The Cox regression model, testing the assumptions of proportional hazard by log-minus-log plot, was used to test risk factors of relapse and predictors of achieving complete remission. Patients not achieving complete remission and not relapsing were censored at time of death or at the research-visit.

When analyzing the effect of relapses on the increase in damage by VDI, linear regression analyses were used (regression coefficient = ß), checking the assumption for linear regression by residual plots. Logistic regression analyses were used to test risk factors for therapy resistance (defined as early death within 3 months from baseline or never achieving complete remission).

In univariate analyses the following variables at baseline were tested as possible predictors or risk factors: sex, age, diagnostic delay as the time from onset of symptoms to start of treatment; cardiac, lung, upper airway and kidney involvement, hemoglobin, ESR, serum creatinine, and DEI, BVAS-1 and VDI scores. Treatment variables in terms of mode of CYC administration (CYCiv versus CYCpo), the actual 6 month cumulative doses of CYC, and time taking daily Pred > 20 mg during the first 6 months were included in analyses of relapse. Cumulative treatment variables were dichotomized at the median value. All treatment variables were adjusted for baseline disease activity by BVAS-1.

Variables with p value < 0.15[24] in the univariate analyses were adjusted for potential confounders. Age, sex, time period as diagnosis in 1992–98 versus 1984–91, and treatment center as Tromsø versus others (the patients were followed regularly at one center only) were tested for confounding. Only age and treatment center influenced both predictors and outcomes and were adjusted for in the multivariable analyses.

Five patients (4 surviving 3 months) did not receive CYC during the first 6 months, but were treated with Pred alone (3 patients), TMS (one patient), and surgery (one patient). These patients were excluded when analyzing the effect of CYC administration mode; moreover, 2 other patients had missing data on ESR. However, as analyses were rerun at every step, the final models, not containing variables with missing data, included all patients. A 2 sided p value < 0.05 was considered significant. Statistical analyses were made using the Statview statistical package, version 5.0.1 (SAS Institute Inc., Cary, NC, USA; 1998). In analyses of relapse and late organ damage, the patients not surviving 3 months from baseline (4 patients) were excluded.

RESULTS

Baseline clinical and 6 month treatment data. The study population consisting of 56 patients (62.5% male) was followed for a median period of 42.5 months (range 0.5–173). Clinical baseline data are listed in Table 1. Cumulative CYC dose during the first 6 months was 9.93 g (range 0–35.35 g) and the patients stayed 2.75 months taking Pred > 20 mg/day (range 0–6 mo). The median starting dose of Pred was 60 mg/day (range 0–120 mg); 27% of patients had a dose < 40 mg/day and 29% a dose ≥ 100 mg/day. The Pred dose after 6 months was 12.5 mg/day (range 0–50 mg/day); 15% of the patients had no Pred and 10% had a dose > 20 mg/day. Nearly all patients (93%) received initial treatment at one of the 2 main centers in the

Table 1. Baseline features in 56 patients with Wegener's granulomatosis (WG).

Clinical or Laboratory Feature	
Age, median (range), yrs	50 (10–84)
Time from symptom onset till treatment, median (range), mo	6 (1–102)
Disease activity by BVAS–1, median (range)	23 (4–46)
Disease extent by DEI, median (range)	9 (2–21)
Haemoglobin (g/dl), median (range)	9.8 (6.4–15.3)
ESR (mm/hour), median (range)	92 (2–135)
CRP (mg/l), median (range)	109 (13–295)
Serum creatinine (µmol/l), median (range)	168 (56–1356)
Number of patients with specific organ involvement (%)	
Ear, nose and throat	45 (80)
Lung	34 (61)
Kidney	45 (80)
Muscle/joint	37 (66)
Eye	21 (38)
Peripheral nerve system	13 (23)
Central nervous system	7 (13)
Gastrointestinal	3 (5)
Heart	11 (20)
Skin	19 (34)
Malaise	51 (91)
Serum creatinine > 150 µmol/l	29 (52)
ANCA positive patients, n = 46	40 (87)
Organ damage (VDI > 0)	21 (38)

BVAS: Birmingham vasculitis activity score; DEI: disease extent index; ESR: erythrocyte sedimentation rate; ANCA: antineutrophil cytoplasmic antibodies; VDI: vasculitis damage index.

region, Tromsø (33 patients) or Bodø (19 patients). There was no difference between the centers regarding baseline characteristics, except for patients in Tromsø having lower serum creatinine (123 vs 395 µmol/l; p = 0.01) and a higher hemoglobin (10.5 vs 9.0; p = 0.01). Even though 80% of the patients in Tromsø versus 39% in Bodø were given CYCiv, there were no significant differences in 6 month CYC dose or in time taking Pred > 20 mg/day between centers (9.6 g CYC vs 11.4 g CYC, p = 0.43; and 1.5 mo vs 3.0 mo taking Pred > 20 mg/day, p = 0.09, respectively). Also there was no difference in CYC administration mode between patients included 1984–91 versus 1992–98.

The CYCpo treated patients received higher 6 month doses of CYC than CYCiv treated patients (15.75 g vs 9.0 g; p < 0.001) and they continued a longer time taking Pred > 20 mg/day (3 mo vs 1.5 mo; p = 0.02). The CYCiv treated patients had higher baseline BVAS-1 (27 vs 21; p = 0.02), but there were no differences in number or type of organs involved, or in any baseline laboratory measure. Time taking Pred > 20 mg/day during the first 6 months was related to baseline BVAS-1 (BVAS-1 increase by 5 points: ß = 0.32, R^2 = 12%, p = 0.01 by linear regression), but cumulative 6 month CYC dose was not (BVAS-1 increase by 5 points: ß = 0.02, p = 0.98) (Figure 1).

Remission. Four patients (3 men) died within one month

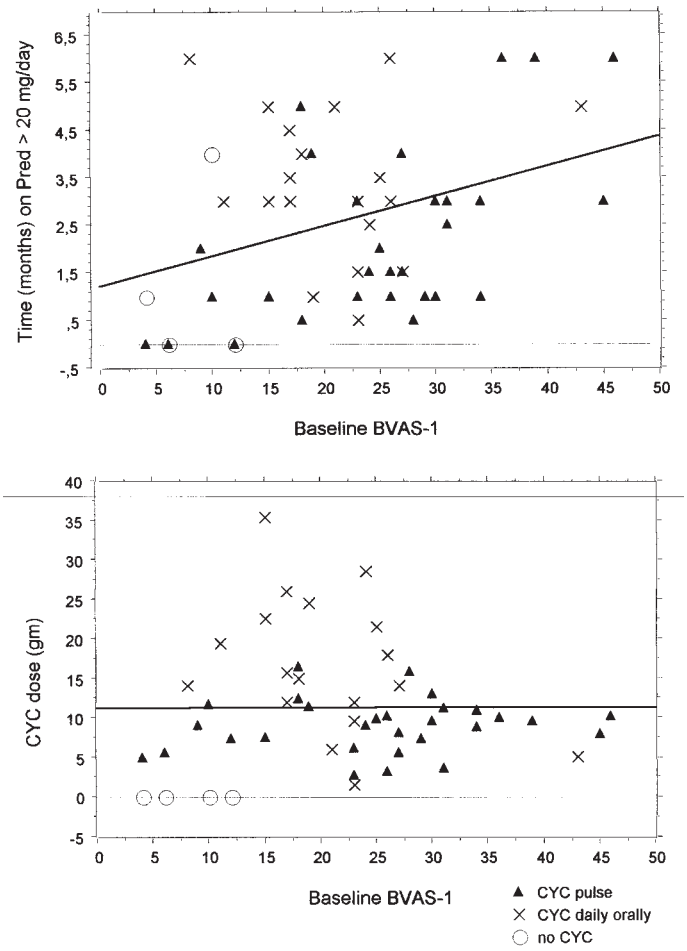

Figure 1. Regression plots of cumulative treatment during the first 6 months versus baseline disease activity by Birmingham Vasculitis Activity Score (BVAS-1) in patients with WG (n = 52).

without achieving remission. In the remaining cohort of 52 patients followed for 45.5 months (range 6–173 mo), 44 patients (85%) entered complete remission. Four of these patients had initially only partial remission, but achieved complete remission after a relapse later in the disease course. Eight patients achieved only partial remission (Figure 2). Time from baseline to first remission was 3 months (range 1–30 mo). Kaplan-Meier estimates for the probability of achieving complete remission (Figure 3) indicate a 75% likelihood of remission within one year of diagnosis, increasing to 84% in the second year of disease. High initial BVAS-1 score was the only baseline variable that increased the likelihood of achieving complete remission in the univariate analysis. After adjusting for potential confounding by age and treatment center, an elevated serum creatinine > 150 µmol/l was also associated with complete remission (RH 2.42, 95% CI 1.20–4.89). By forward selection, BVAS-1 was the only statistically significant predictor of achieving complete remission (BVAS-1 > 23, RH 2.94, 95% CI 1.48–5.85). No initial treatment variable was asso-

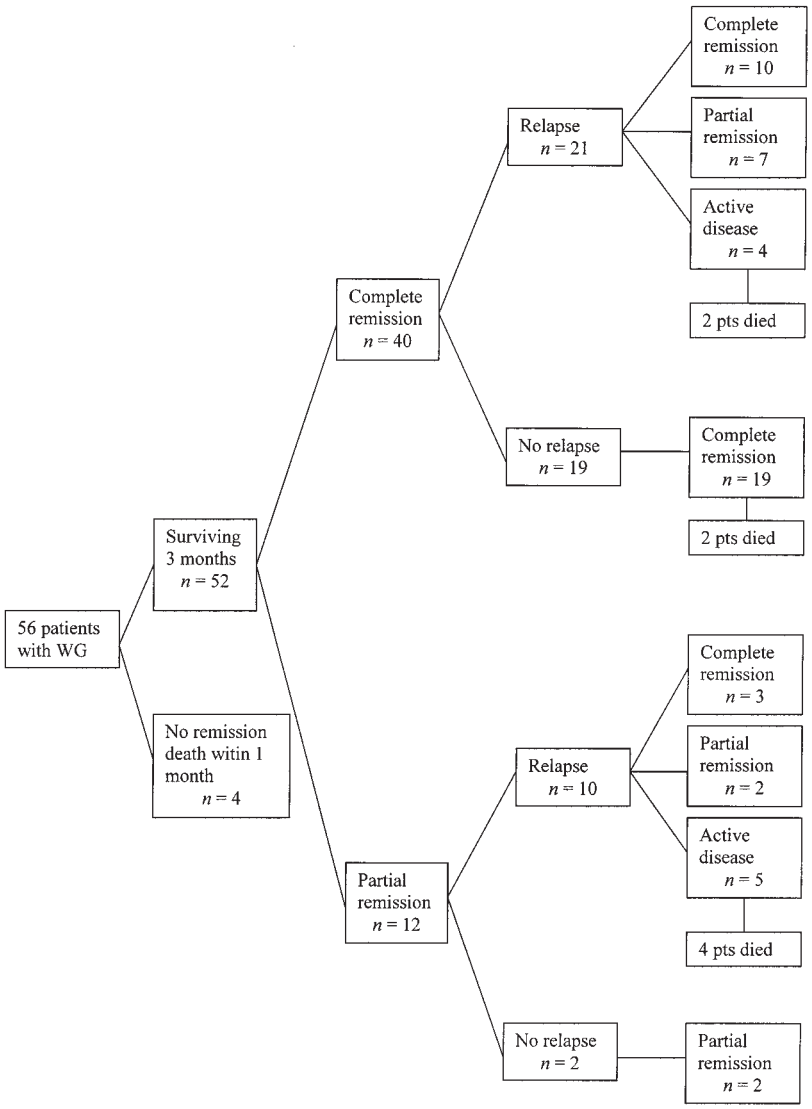

Figure 2. Disease course in 56 patients with WG followed 42.5 months from baseline (onset of therapy) until death or the research visit.

ciated with complete remission. A sustained complete remission was seen in 19 patients, 10 treated with CYCiv and 9 treated with CYCpo.

Therapy resistance. Twelve patients were considered therapy resistant (4 died early and 8 never achieved complete remission). In univariate analyses there was an increased risk of therapy resistance in the patients with cardiac involvement (OR 4.52, 95% CI 1.08–19.00) and with increasing organ damage before onset of therapy. Only baseline organ damage (VDI increase by 1 point: OR 1.53, 95% CI 1.03–2.27) remained a significant risk factor in multivariable analyses.

Relapse, general description. During the followup of 281.8 patient-years, 31 patients (59.6%) experienced a total of 52 relapses (13 patients had more than one relapse), yielding a relapse rate of 0.18 relapses per patient-year. Median time from baseline to first relapse was 18 months (range 4–108 mo). The highest annual risk of relapse (0.28) was seen in the second year, but the annual risk was not statistically different during the next 4 years ($p = 0.13$ by one-sample sign test). This can also be seen as a steady decrease in estimated relapse-free survival during the first 6 years of disease (Figure 4). Moreover, in the 21 patients followed > 5 years, the relapse rate was 71%, while it was 52% in the patients followed ≤ 5 years.

The relapses occurred most often in patients undergoing maintenance treatment or in patients no longer taking any immunosuppressive treatment (54 and 33% of the relapses, respectively). Seven relapses (13%) occurred in patients receiving induction therapy while in partial remission.

BVAS-1 was lower at relapse than at baseline (14 vs 23;

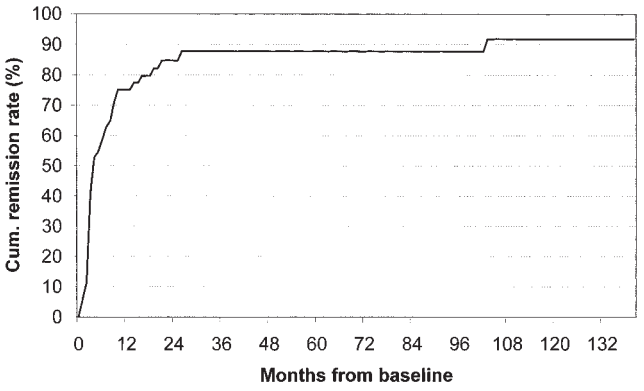

Figure 3. Estimated cumulative complete remission rate in patients with WG by Kaplan-Meier method (n = 56).

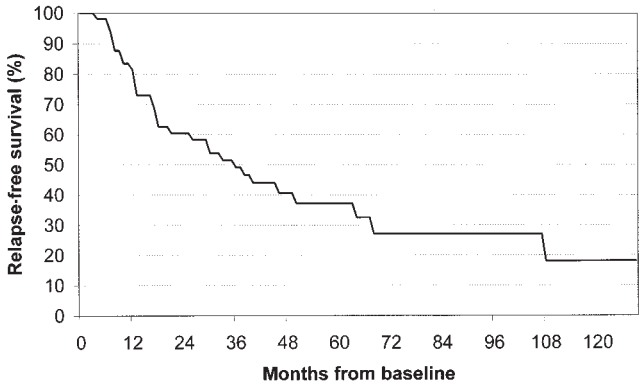

Figure 4. Estimated relapse-free survival rate in patients with WG by Kaplan-Meier method (n = 52).

p < 0.0001), as was DEI (5 vs 9; p < 0.0001), but more than one organ was involved in 79% of the 52 relapses. At first relapse there was significantly less malaise (54 vs 91%; p < 0.001), fewer musculoskeletal symptoms (26 vs 66%; p < 0.001), and less renal involvement (58 vs 80%; p = 0.04) than at baseline. New organ involvement at relapse occurred in 48% of the relapsing patients, mostly lung (7 patients) and peripheral nerve involvement (5 patients).

Risk factors for relapse. Distribution of organ involvement at baseline did not differ significantly between relapsing and nonrelapsing patients, but baseline BVAS-1 tended to be lower in the relapsing patients (21 vs 26; p = 0.05), as did serum creatinine (103 vs 188 µmol/l; p = 0.05). Relapsing patients had also received a significantly lower 6 month cumulative CYC dose (7.95 g vs 11.95 g; p = 0.01). When taking time until relapse into account by Cox regression analyses, baseline lung and cardiac involvement and a diagnostic delay were related to the risk of relapse. Moreover, there was an increased risk of relapse in patients with short time taking Pred > 20 mg/day, and especially in patients with low CYC dose during the first 6 months, even when adjusting for baseline disease activity by BVAS-1 (Table 2). By adjusting for potential confounding by age and treatment center, diagnostic delay and lung involvement were no longer of importance, but the other variables remained risk factors (Table 2). On further analyses of treatment variables, we found no reduced risk of relapse for a CYC dose ≥ 20 g versus 10–20 g, nor was there any reduced risk for Pred > 20 mg/day for ≥ 4 months versus 2–4 months. However, 2–4 months time taking Pred < 20 mg/day incurred lower risk of relapse than 0–2 months (RH 0.41 and 1.0, respectively; p = 0.03).

Relapse tended to be more frequent in patients who were ANCA positive at baseline, as 64% of ANCA positive patients relapsed, versus 17% of ANCA negative patients (p = 0.07). But because ANCA was not tested in all patients at baseline (missing in 10 patients), ANCA could not be included in regression analyses. During followup a total of 53 patients were ANCA tested, and 91% were positive (92% cANCA or proteinase 3 positive, 8% pANCA or myeloperoxidase positive).

Relapse versus survival and organ damage. Six patients died in a relapse and 2 deaths occurred in nonrelapsing patients, in addition to the 4 patients who died during the first month. Relapse did not reduce survival estimates (p = 0.93 by log-rank test of Kaplan-Meier survival estimates). All patients who died had received corticosteroid and 9 had received CYC (5 CYCiv, 4 CYCpo), and 5 patients also had initial plasma exchange. Median followup for the nonsurviving patients was 30 months. Renal involvement at relapse occurred in 21 patients (68%), and 6 of them went on to develop endstage renal disease, while 2 more patients developed renal insufficiency (serum creatinine > 150 µmol/l) after a relapse. Organ damage by VDI at the research visit was significantly higher in relapsing than in nonrelapsing patients (VDI 7 vs 5; p = 0.02). Further, the number of relapses was a predictor for an increase in VDI from baseline until the research visit (ß = 1.29, 95% CI 0.44–2.14, p = 0.004, adjusted R^2 = 23% when adjusting for time of followup).

Early infections. During the first 6 months of immunosuppressive treatment 12 patients (23%) had 16 episodes of severe infections, 8 pneumonia (one *Pneumocystis carinii*), 3 sepsis, 4 skin infections (2 *Herpes zoster*), and one urinary tract infection. Patients with infections had a higher daily Pred dose at 6 months than patients without infections (16.25 mg vs 10.0 mg; p = 0.01), and they tended to have continued longer taking Pred > 20 mg/day (3.5 mo vs 2.25 mo; p = 0.08). This was confirmed by logistic regression analyses showing increased risk of infection in patients having been taking Pred > 20 mg/day for > 3.5 months (OR 4.0, 95% CI 1.02–15.77) or having a 6 month Pred dose > 12.5 mg/day (OR 5.57, 95% CI 1.30–23.98). There was no difference in other treatment variables or in baseline disease activity by BVAS-1 or DEI between patients with and without infections. Only 2 of the infections were associated with leukopenia.

Table 2. Risk factors for relapse in Wegener's granulomatosis. Summary of Cox regression analyses performed on variables with p < 0.15 in univariate analyses.

	Univariate Analyses*			Each Variable Also Adjusted for Potential Confounders**		
	RH	(95% CI)	p	RH	(95% CI)	p
Age, increase by 10 years	0.85	(0.69–1.05)	0.13	0.86	(0.70–1.06)	0.16
Diagnostic delay, by 6 months	1.15	(1.01–1.31)	0.03	1.12	(0.98–1.29)	0.11
Serum-creatinine > 150 µmol/l	0.55	(0.27–1.14)	0.11	0.73	(0.33–1.62)	0.43
Lung involvement	0.47	(0.23–0.97)	0.04	0.60	(0.27–1.31)	0.20
Cardiac involvement	3.37	(1.29–8.77)	0.01	2.87	(1.09–7.58)	0.03
CYC, pulse administration *	2.25	(0.97–5.25)	0.06	1.84	(0.73–4.65)	0.20
Time on Pred > 20 mg/day < 2.75 months *	2.47	(1.17–5.24)	0.02	2.41	(1.12–5.21)	0.03
Cumulative dose of CYC < 10 g *	3.05	(1.44–6.45)	0.004	2.83	(1.33–6.02)	0.007

RH: relative hazard; CI: confidence interval; CYC: cyclophosphamide; Pred: prednisolone. * Treatment variables adjusted for baseline BVAS-1 (Birmingham Vasculitis Activity Score). ** Potential confounders = age and treatment centre (Tromsø versus others).

Time without immunosuppressive treatment. Thirty-four percent of total patient-years of followup were spent without immunosuppressive treatment, as 26 patients (50%) had been able to stop treatment for a cumulative period of 35.5 months (range 4–125 mo). Of the 44 patients alive at time of the research visit, 68% were in complete remission (Figure 2), 25% in partial remission, and 7% had active disease (relapse). Sixteen patients (36%) received no immunosuppressive treatment at the research visit (14 patients in complete remission, 2 in partial remission), having discontinued all immunosuppressive treatment for 31 months (range 4–78 mo).

DISCUSSION

In this population based cohort of patients with WG that received standard therapy, induction of remission was achieved in all patients surviving the first month. The initial remission was complete in 77% of these patients (Figure 2), which is in close agreement with the study by Hoffman, *et al* from the US National Institutes of Health (NIH)[5].

We found increased disease activity by BVAS-1 to be the only independent predictor of complete remission. This might be explained by more intense initial Pred treatment in patients with higher BVAS-1, as BVAS-1 predicted time taking Pred > 20 mg/day. However, adjusting for the initial Pred treatment did not change the result, and patients with higher BVAS-1 did not receive more CYC (Figure 1). Even though initial treatment by CYCiv, methylprednisolone, or plasma exchange were not predictors of complete remission, the patients receiving such therapies had higher BVAS-1, hence these therapies may have influenced the increased remission rate in patients with higher BVAS-1.

The increased likelihood of complete remission in patients with high disease activity versus patients with low grade smouldering disease is in accord with our clinical experience. The phenomenon resembles what is seen in malignant disease where highly active proliferating cells are more sensitive to initial chemotherapy[25,26], and also findings in patients with systemic lupus erythematosus with glomerulonephritis, where patients having highest activity index in renal biopsies were most likely to enter remission[27]. Also, the increased likelihood of achieving complete remission in patients with serum creatinine > 150 µmol/l may be related to an increased overall disease activity, as these patients had significantly higher BVAS-1 and DEI scores.

However, achieving complete remission in WG does not imply that this is a lasting situation. Disease relapse, occurring in nearly two-thirds of our cohort, represents a major problem in WG. Relapses continue to occur throughout followup in both this and other studies[3,7], indicating that reports of relapse rates should always be related to time spent in followup. The overall 60% relapse rate in our cohort and the 70% relapse rate in the subgroup of patients with followup for more than 5 years is comparable to the 64 and 71% recently described in a German study[7], but exceeds the 50% overall relapse rate (49% in patients with followup ≥ 5 years) in a NIH study[5].

The lower relapse rate in the NIH cohort may be related to their treatment protocol with daily oral CYC, resulting in twice the cumulative CYC dose that follows pulse treatment, which was the only administration method in 53% of our patients[4,28]. We found a preventive effect on relapse as long as the 6 month cumulative CYC dose was 10 g or more. These findings may explain some of the inconsistencies in relapse rate in studies using different pulse treatment intervals[14,15,29,30]. A dose of 10 g or more over 6 months implies that, in most patients, pulses have to be given more frequently than every 3rd week. Also, the doses in this study were the actual doses given and not the planned doses, which often have to be reduced due to intercurrent illness or side effects. In addition, the prednisolone dose was important with respect to relapse. We found treating patients with Pred > 20 mg/day for 2 months or more beneficial in reducing relapse risk.

However, a prolonged time, more than 3.5 months, taking Pred > 20 mg/day was associated with an increased

infection rate. An association between high dose Pred therapy and infections is well known from the NIH study by Hoffman, *et al*[5], and is also illustrated by the lower infection rate of 26% in a German study[7] where the Pred dose was 5–10 mg after 3–6 months, and the higher infection rate of 54% in a French study[14] where the Pred dose was > 20 mg/day after one year. Hence the beneficial effect of higher Pred dose on relapse rate must be balanced against the increased risk of infection and other corticosteroid associated side effects.

Both corticosteroid and CYC have been associated with increased organ damage[5]. In this study, damage was only examined in relation to relapses, as relapses will increase late VDI scores. But we previously reported that increasing cumulative time taking Pred > 20 mg/day is associated with increased damage development. Also, increasing longterm cumulative doses of CYC were associated with increased organ damage, but with a preventive effect on late damage for increasing time taking CYC during the first 6 months[4]. Taken together, these studies indicate that the optimal treatment in the present cohort seemed to be intensive initial treatment with both Pred and CYC for at least 6 months, but possibly with upper limits of 2–4 months taking Pred > 20 mg/day and a cumulative CYC dose of 10–20 g.

Most studies have found no relation between baseline organ involvement and relapse[17,31], except for an increased relapse rate in patients with lung involvement[8]. We found that lung involvement reduced the risk of relapse in univariate, but not multivariable analyses. However, cardiac involvement was a risk factor in the current study, although with a wide confidence interval, which reflects the small number of patients. Cardiac involvement was seen in 11 patients at baseline and included ischemic disease, pericarditis, supraventricular arrhythmia, and new cardiac murmur. These patients also had more elevated serum creatinine and higher disease activity by BVAS-1 and DEI, but were given the same treatment as patients without cardiac involvement. The number of separate cardiac conditions was too small to allow further analysis, but our findings indicate that cardiac investigations should become part of both clinical and research settings of patients with WG.

Studies have found that increased relapse rates are related to a persistently positive ANCA test, especially to cANCA/proteinase 3-ANCA[8-10,12,13,17]. The high relapse rate of 60% in our WG cohort, where 92% of patients were cANCA or PR3-ANCA positive, is consistent with these findings. In contrast, the relapse rate was only 29% during a comparable followup in a study of ANCA associated microscopic polyangiitis (MPA) and glomerulonephritis, where only 37% of the patients were cANCA positive[32]. Another striking difference between these 2 studies is the percentage of relapses with new organs involved, 48% in our WG cohort, while it was 23% in the cohort of patients with MPA and glomerulonephritis (20% in MPA, 29% in glomerulonephritis).

The ability to stop immunosuppressive treatment has only been investigated in a few studies. Half the patients in this study were able to stop all immunosuppressive treatment at some time, and 23 patients (41%) discontinued medication for 6 months or longer. This rate is higher than the 17% of the 155 German patients[7], but comparable to a NIH study of 85 WG patients with a treatment period of 46.6 months, where 27% of the patients stayed off treatment for 35.5 months[2]. In the present study, with a treatment period of 41.5 months, 25% of patients in complete remission at followup had stayed off treatment for 33.6 months. Thus, with regard to treatment-free periods, the patients in this cohort, mostly treated with pulse CYC, were not worse off than patients treated with daily oral CYC.

We believe this study, the first to describe actual treatment given, provides indications on how initial treatment can affect outcome, even though the study is observational and retrospective. The choice between pulse and daily oral CYC was left to the treating physician's judgement and thus reflects clinical practice, where different factors influence treatment strategies. In our analyses we corrected for this as far as possible by adjusting for confounding by treatment center and age. We also checked for confounding by sex and a possible change in treatment over time by comparing patients with treatment started in 1984–91 versus 1992–98, but this did not influence the result.

A cumulative treatment found to predict disease relapse might merely be a reflection of disease activity, where the most severe disease was treated most intensely. But, as illustrated in Figure 1, cumulative CYC dose was not related to baseline disease activity, even though time taking Pred > 20 mg/day was. Moreover, the only baseline difference between pulse and oral CYC as the most intensive treatment was a higher BVAS-1 score in the pulse treated patients, not in patients taking oral CYC. Further, all treatment variables were adjusted for baseline disease activity by BVAS-1 in analyses of predictors and risk factors. Because of our consistent adjustment for confounding variables, we believe our conclusions on drug efficacy are sufficiently conclusive despite the limitations of our open study.

Nonetheless, the estimates of the risk factors and predictors should be interpreted with caution, as illustrated for some of the variables by the relatively large confidence intervals, which are related to the sample size and the relatively low numbers of events. Hence interpretation of the results should focus more on which variables are identified to be predictors than on the size of the respective estimate.

The completeness and reliability of data are always an issue in retrospective studies. We tested only variables that were available in all patients, with 2 exceptions, ESR and the mode of CYC administration (5 patients did not receive CYC during the first 6 months). None of these variables

were of significance in the final models, and hence deleting the patients with missing data did not affect the conclusions. Moreover, all data collection was by one observer (WK) using a predefined form, and as the patients had been seen frequently during the first 6 months, treatment variables were not difficult to record. While the use of VDI and DEI in retrospective studies has been shown to be valid[33,34], BVAS-1 requires more detailed information and may be more difficult to use retrospectively. Signs and symptoms were considered not to be present if not mentioned in the record or if not remembered by the patient when interviewed. The maximum score for each organ system may to some degree reduce the problem with completeness of the BVAS-1 score, but we cannot rule out that the scores were underestimated, even though the baseline BVAS-1 was relatively high in this cohort.

Finally, the status of our patients at the research visit is encouraging. Half the patients had been able to stop all immunosuppressive treatment for considerable periods of time and 68% were in complete remission after 45.5 months of followup. This study stresses the importance of early diagnosis before organ damage has developed to avoid treatment resistance. The relapse rate in WG is high, but may possibly be reduced by more intensive treatment during the first 6 months.

ACKNOWLEDGMENT

We thank Dr. A. Prøven, Department of Rheumatology, and Dr. E. Bjørbaek, Department of Internal Medicine, for providing clinical information about patients at Nordland Hospital, Bodø. We thank Dr. Bjørn Straume and Tom Wilsgaard, University of Tromsø, for statistical advice. We also thank staff at the Department of Clinical Research, University Hospital, Northern Norway, for help in performing examinations at research visits.

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