Predictors of Damage and Survival in Patients with Wegener's Granulomatosis: Analysis of 50 Patients

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ABSTRACT. ***Objective.*** To evaluate damage features and impact on survival by Vasculitis Damage Index (VDI) in a cohort of Turkish patients with Wegener's granulomatosis (WG).

Methods. We enrolled 50 (25 female) patients with WG according to ACR criteria. Birmingham Vasculitis Activity Score (BVAS) and VDI were used to analyze disease activity and damage.

Results. Patients had kidney (82%), upper airway (72%), lung (70%), and nervous system (15%) involvement. Median age at diagnosis was 45 years, time to diagnosis was 3.5 months, and total followup time was 35.5 months. All but one patient was positive for antineutrophil cytoplasmic antibodies (ANCA). Mean final dose and duration of corticosteroid and cyclophosphamide was 15 ± 14 g, 39 ± 33 months and 36 ± 34 g, 21 ± 2 months, respectively. Mean early (e) BVAS were 20.2 ± 7.1 (4–38) (median 21). Mean e-BVAS and e-VDI scores at presentation and final (f)-VDI scores at last visit were 20.2 ± 7.1 (4–38), 3.1 ± 1.7 (median 3) (0–7) and 4.4 ± 2.6 (0–12), consecutively. Disease related damage was prominent in kidneys (50%) and upper airways (27%). Amenorrhea (90%), cataract (28%), and diabetes (24%) were the most frequent treatment related damages. Rapidly progressive glomerulonephritis at presentation (42%) progressed to endstage renal failure in 20%. Relapses occurred in 25% with mean BVAS of 6.5 ± 2.3 (4–11). Survival rate was 77% at 37 months. Deaths occurred early (90% in the first year). f-VDI was high in patients who relapsed (6 ± 3 vs 3.8 ± 2.1, p = 0.03). Logistic regression analysis demonstrated that age at time of diagnosis and e-VDI were lower in survivors with OR = 0.9 (p = 0.06, 95% CI: 0.78–1) and OR = 0.5 (p = 0.04, 95%CI: 0.25–0.98), respectively. In this cohort, e-VDI score of 5 or more was related to death with 98% sensitivity and 56% specificity (p = 0.004) (CI: 0.66–0.95).

Conclusion. Disease related damage outweighed treatment related damage in our cohort of predominantly generalized disease activity. Early damage and older age were found to be predictors of final damage and death. (J Rheumatol First Release Dec 15 2009; doi:10.3899/jrheum.090387)

Key Indexing Terms:
WEGENER'S GRANULOMATOSIS VASCULITIS VASCULITIS DAMAGE INDEX

Wegener's granulomatosis (WG) is a multisystem disorder characterized by upper and lower airway and kidney involvement due to systemic necrotizing vasculitis and/or granulomatous inflammation[1].

Since better survival has now been achieved thanks to immunosuppressives, outcome measures of disease activity, damage, and functional status have become important topics for the systemic vasculitides, including WG[2]. Damage as a core component of outcome has been described as irreversible tissue or organ loss or dysfunction related to the disease or treatment. The Vasculitis Damage Index (VDI) is the first proposed damage tool for systemic vasculitides including WG[3]. The VDI has been used in different cohorts to describe damage characteristics, predictors, and relationship with survival[4-6].

We describe damage characteristics and the association of damage, relapses, and survival, in a single center WG cohort.

MATERIALS AND METHODS

We included into the study 50 patients with WG who satisfied American College of Rheumatology (ACR) criteria[7] and were followed up between 1993 and 2006. Our WG cohort consists of patients diagnosed and followed up in the Rheumatology Division of Istanbul Medical Faculty, a tertiary referral center. Final damage at last followup visit was scored prospectively in all patients who survived. All but 2 patients had systemic involvement.

Cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA)/anti-PR3 was positive in 71% of the patients. ELISA confirmation could not be performed in 11 patients (22%) with positive c-ANCA. Three patients had perinuclear (p)-ANCA and one had p-ANCA/anti-myeloperoxidase positivity. One patient had no ANCA positivity, but presented with necrotizing crescentic glomerulonephritis, sinus involvement, and cavitated lung nodules. All patients who presented with systemic findings and rapidly progressive glomerulonephritis had taken consecutive pulse corticosteroid (CS) treatment (1 g/day for 3 days). High dose CS treatment (1 mg/kg/day) was applied during the remission induction and then tapered after remission was achieved. Patients were treated with intravenous (iv) cyclophosphamide (CYC) (500–1000 mg/3–4 weekly according to body surface,

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leukocyte count, and creatininemia), or oral CYC (2 mg/kg/day) for remission induction. Oral CYC (1 mg/kg/day) or azathioprine (2 mg/kg/day) was used for maintenance therapy depending on the severity of WG. Uroprotection with mesna was not used routinely. Final dose and duration of CS and CYC were calculated for each patient. Early disease activity and damage were scored from the hospital and outpatient clinic charts, retrospectively. Final damage at last followup visit was scored prospectively in all patients who survived. Early disease activity at presentation was calculated with the new version of BVAS (BVAS 2003) in accordance with the scoring glossary[8] (e-BVAS), retrospectively. Number of relapses and mean BVAS scores of relapses were also calculated for each patient. Relapses were defined with the newly developed clinical finding of WG according to BVAS definition. The 10 items of the VDI were evaluated by the same rheumatologist (SK) using each patient's clinical and laboratory findings at the third month of followup and at the last visit according to the VDI scoring glossary. Early VDI (e-VDI) scores at third month of disease were calculated for all WG patients including nonsurvivors followed up less than 3 months whose disease duration was more than 3 months and who had received immunosuppressive treatment. Final damage scores (f-VDI) at last followup visit were calculated for 40 patients who survived and continued followup. Severe infection data from the hospital charts were noted.

Correlation of e-BVAS and VDI scores was analyzed by Pearson correlation test. Demographic and treatment characteristics, e-BVAS, e-VDI, and f-VDI scores were compared for patients who relapsed or not by Mann-Whitney U test. We compared demographic and treatment characteristics, BVAS, and only e-VDI scores in WG patients who died or survived using the Mann-Whitney U test. Severe damage was defined with e-VDI score predicting mortality for the WG cohort by receiver operating characteristic (ROC) curve analysis. Survival function was evaluated by Kaplan-Meier method. In multivariate analyses, we estimated the prevalence odds ratio (OR) with 95% confidence interval (CI) for the association between survival and demographic, treatment characteristics and BVAS, and early VDI scores using logistic regression.

RESULTS

Demographic findings of 50 WG patients (25 female, 25 male) were as follows: mean age at diagnosis was 44.1 ± 13.2 years (16–74) (median 45), time elapsed from the first symptom to diagnosis was 6.4 ± 8.5 months (1–48) (median 3.5), total duration of followup was 44.9 ± 34.9 months (2–122) (median 35.5). Eighty-two percent of patients had involvement of the kidney, 72% the upper airways, 70% the lungs, 11% the peripheral nervous system, and 4% the central nervous system. Frequency of organ and drug related damage items is shown in Table 1. Gonadal failure could not be examined systematically because of patient unwillingness in males. Osteoporosis (7.5%) was evaluated in only 31 patients. All patients had taken calcium and vitamin D prophylaxis. Malignancy was not observed in any patient. Twenty-one (42%) patients were admitted with acute renal failure and required hemodialysis, of whom 5 (24%) fully recovered and maintained normal creatininemia. Two patients (10%) recovered with high creatininemia and sustained the same levels. End stage renal failure developed in 10 (20%) patients (one underwent cadaveric renal transplantation at the 3rd year of hemodialysis and 4 patients died), of whom 4 died during the acute stage. CYC was used as 3–4 weekly iv pulse therapy in 28% for 12–20 months, daily oral therapy in 20% for 3–79 months, and oral followed by iv therapy in 52% for 54 months. Mean final dose and duration of CS and CYC were as follows: mean final dose of CS (g) 15 ± 14 (3–99) (median 12), mean total duration of CS (mo) 39 ± 33 (1–124) (median 32), mean final dose of CYC (g) 36 ± 34 (0.3–173) (median 29), mean total duration of CYC (months) 21 ± 21 (1–112) (median 19). Mean e-BVAS scores were 20.2 ± 7.1 (4–38) (median 21). Mean e-VDI and f-VDI scores of patients were 3.1 ± 1.7 (median 3) (0–7) and 4.4 ± 2.6 (median 4) (0–12), consecutively. F-VDI was 1 in 4%, 2 in 12%, 3 in 18%, 4 in 10%, 5 in 10%, 6 in 6%, 7 in 6%, 8 in 6%, 9 in 4% and 12 in 2%. Four patients who died in the hospitalization period during the active disease developed sepsis and multiorgan failure under intensive immunosuppressive treatment. One patient on low dose CS developed cytomegalovirus chorioretinitis during the chronic hemodialysis period. One with generalized disease suffered from pulmonary tuberculosis during the remission induction period: both patients were successfully treated with antiviral and antituberculosis treatment concomittant with mild to moderate dose of CS and 3 cycles of high dose iv immunoglobulin.

Table 1. Disease and treatment related damage items of VDI in 50 patients with WG.

	Frequency of Damage Items, %
Early menopause*, n = 10	90
Pulmonary fibrosis	35
Cataract	28
Chronic nasal discharge/crusting	27
Diabetes	24
Hearing loss	20
Endstage renal disease	20
High creatininemia	15
Proteinuria	15
Avascular necrosis	13
Saddle nose	10
Dyspnea	10
Mononeuritis multiplex	10
Hemorrhagic cystitis	10
Osteoporosis, (n = 31)	8
Subglottic stenosis	5
Chronic asthma	5
Polyneuropathy	5
Cerebrovascular event	3
Proptosis	3
Scleral necrosis	3

* Premenopausal women, mean age 34 yrs.

Relapses occurred in 10 (25%) patients (7 with 1 relapse, 2 with 2, and 1 with 3 relapses). Relapses were less severe than early disease activity [mean BVAS score for all relapses was 6.5 ± 2.3 (4–11)]. Early and final VDI scores were found to be positively correlated with e-BVAS ($p = 0.01$, $r = 0.37$ and $p = 0.04$, $r = 0.33$, respectively) (Figure 1–2). Comparison of demographic and treatment characteristics, BVAS, and VDI scores in patients according to relapses demonstrated that f-VDI was the only finding that was sig-

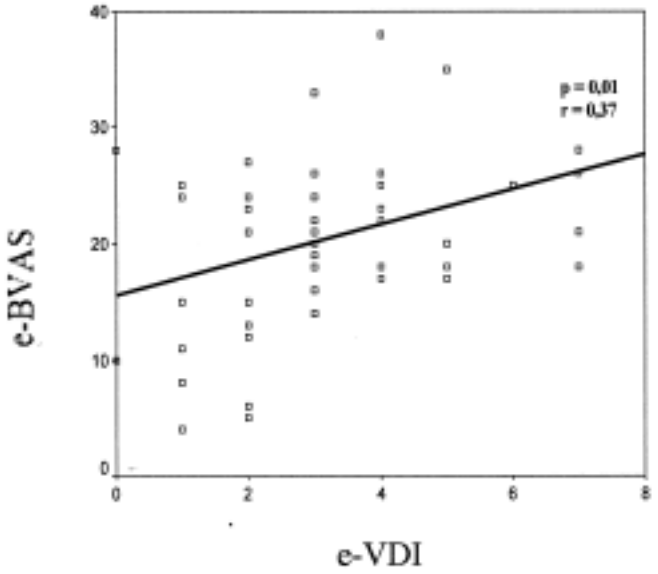

Figure 1. Correlation of early Birmingham Vasculitis Activity Score (e-BVAS) and Vasculitis Damage Index (e-VDI) scores.

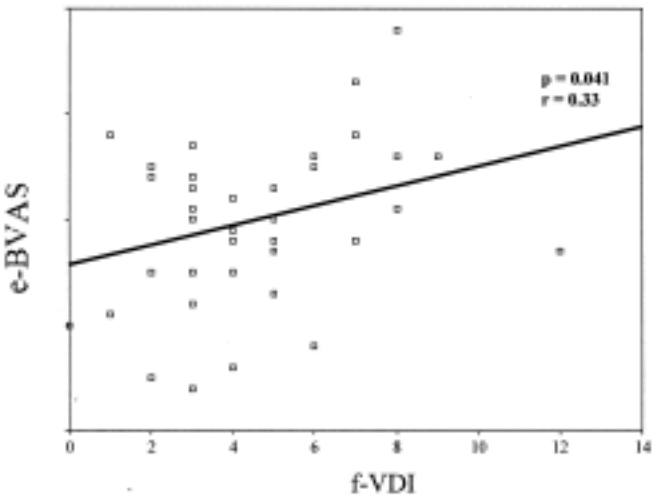

Figure 2. Correlation of early Birmingham Vasculitis Activity Score (e-BVAS) and final Vasculitis Damage Index (f-VDI) scores.

nificantly high in patients who relapsed (6 ± 3 vs 3.8 ± 2.1, p = 0.03) (Figure 3).

Ten (20%) WG patients died during the acute or chronic phase of renal failure. Four patients (40%) died from active disease and sepsis with multiorgan failure during the hemodialysis period. One patient (10%) with cerebral involvement died from cerebrovascular hemorrhage due to cerebral vasculitis at a very early stage of disease. We were informed through telephone inquiry that 4 patients who were lost to followup at the stage of chronic hemodialysis had died in the first year of this period. One patient who recovered with high creatininemia died suddenly at 2 years' followup. The survival rate was 77% at 37 months. Older age of disease onset, shorter followup time, and higher

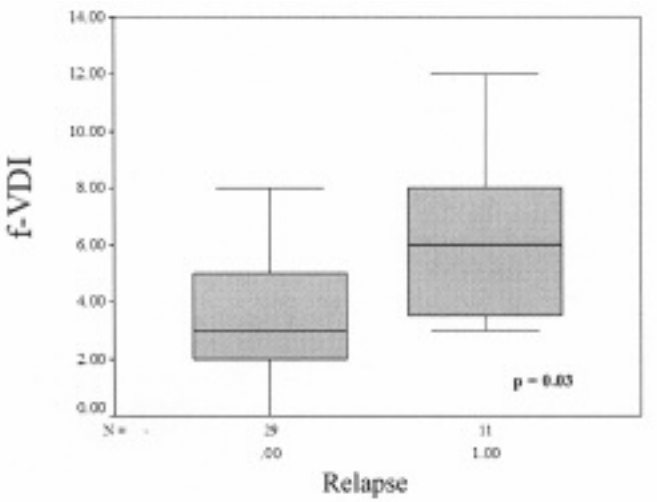

Figure 3. Final Vasculitis Damage Index (f-VDI) scores in accordance with relapse.

e-VDI scores were found in patients who died (Table 2). The doses and duration of immunosuppressives were significantly higher in survivors, as expected.

e-VDI score of ≥ 5 was related to death with 98% sensitivity and 56% specificity (p = 0.004) (95%CI 0.66–0.95) by ROC curve analysis (Figure 4) . Logistic regression analysis demonstrated that age at time of diagnosis and e-VDI were lower in survivors with OR = 0.9 (p = 0.06, 95%CI 0.78–1) and OR = 0.5 (p = 0.04, 95%CI 0.25–0.98), respectively.

DISCUSSION

In the era of immunosuppressive treatment, damage has been a major concern with regard to patient outcome in the systemic vasculitides. WG has considerable potential for damage in different tissues and organs that could result in loss of vital organ functions. Early disease activity, relapses, and immunosuppressives are the major determinants of damage. Since 1997 the VDI has been the only validated tool for damage in systemic vasculitides[3]. Exley, *et al* stressed the importance of severe damage in the early stages

Table 2. Comparison of demographic and treatment characteristics, BVAS, and early VDI scores in patients with WG who survived (Group A) or died (Group B). Values are mean ± SD (median).

	Group A	Group B	p
Age of disease onset, yrs	41.2 ± 12.3 (42.5)	56 ± 9.8 (55)	0.002
Time to diagnosis, mo	6.9 ± 9.2 (4)	4.8 ± 4.5 (3)	NS
Followup time, mo	53 ± 34.1 (50)	12.5 ± 11.1 (9)	< 0.001
Early BVAS	19.9 ± 7.4 (21)	21.8 ± 5.9 (21)	NS
Early VDI	2.6 ± 1.4 (2)	4.8 ± 1.8 (4.5)	0.002
Corticosteroid			
Total dose	17 ± 15.3 (13)	7.4 ± 4.6 (6)	0.002
Total duration	46.4 ± 31.3 (31)	4.7 ± 5.7 (2)	< 0.001
Cyclophosphamide			
Total dose	43.7 ± 33.2 (42)	4.3 ± 8 (2)	< 0.001
Total duration	25.6 ± 21.2 (22)	3.5 ± 5.1 (2)	< 0.0001

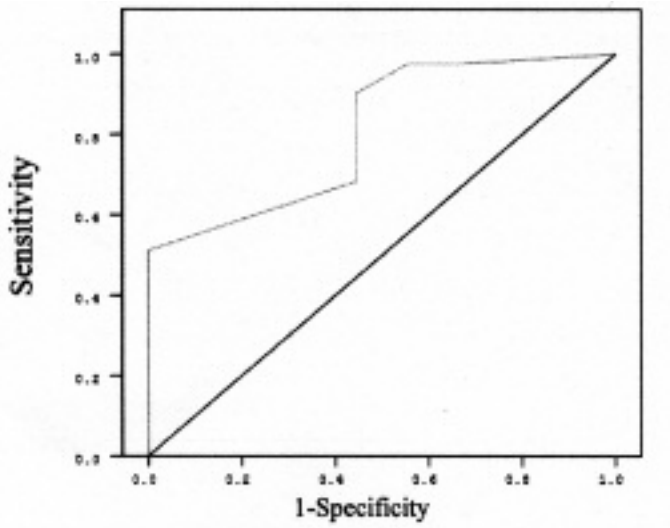

Figure 4. ROC curve analysis of early Vasculitis Damage Index (VDI) according to survival.

of vasculitis using the VDI scoring system[9]. In our present study, we investigated the association of damage with early disease activity, relapse, and survival. Our cohort mainly consisted of patients with severe renal involvement, which can be considered a generalized vasculitic form of WG according to the EULAR definition[10]. Early disease activity has been found to be correlated with both early and final damage scores.

Relapses less severe than the early disease activity were observed in one-fourth of WG patients receiving immunosuppressive treatment during the median followup time of 35 months. No severe renal relapse was observed during followup. Relapse rates differed according to whether the subgroups predominantly presented with granulomatous and/or generalized vasculitic course. Fauci, *et al* reported a 50% relapse rate in a US National Institutes of Health (NIH) cohort during 21 years of followup. This cohort includes WG patients with mainly upper airway involvement (90%). Renal involvement was reported as 18% at presentation and 77% at the second year of followup[11]. In the CYCAZAREM study, patients treated with CYC during the maintenance period had 18% flare rate at the first year of followup[12]. The frequency and severity of relapses might be prevented with longer treatment with CYC (median 19 mo) in our cohort. In different studies, 25% relapse rates were reported in WG patients with renal involvement treated with CYC[13-16]. Final damage was found to be higher in our patients who relapsed. The association between damage and relapses has been emphasized by others[4,9]. A severe damage score on VDI predicting mortality was found to be 5, which is consistent with other reports[4,9]. Older age and significantly higher early damage scores were demonstrated in WG patients who died in comparison to survivors. The shorter duration of time to diagnosis in nonsurvivors, although insignificant, was attributed to more explosive disease presentation.

We compared our patients with different WG cohorts being evaluated for damage using the same tool. Serial VDI scoring to assess increased damage was used in both Norway and US cohorts prospectively[4,6]. Baseline characteristics including early disease activity and damage and frequencies of major organ involvement of our cohort were mostly comparable to the Norway cohort[6]. Kidney damage was the most frequent (50%) organ damage in our series. Endstage renal failure as the major determinant of kidney damage developed in 18%, 7%, and 20% of Norway, WGET[6], and our cohorts, respectively. Kidney involvement resulting in endstage renal failure was reported in 24% of 37 WG patients during the mean followup time of 6 years in a French cohort[17]. Prognosis of our patients presenting with dialysis requirement was quite similar to that in other cohorts[4,18].

Immunosuppressive treatment was tailored according to the individual needs in this cohort. The treatment of our cohort was mainly based on the NIH treatment protocol for vasculitis. Generalized disease activity at presentation according to the EULAR definition was observed in one-half of our cohort. These patients were treated with CS and CYC for at least one year in accordance with the literature[10,16,19-21]. Treatment related damage in WG patients was reported to be 42% in the NIH cohort[13], similar to rates in the Norway and in our cohorts, but not in the WGET cohort (15%). We observed amenorrhea in almost all (90%) premenopausal women with median age 34 years. Boumpas, *et al* reported 100% amenorrhea for women older than 31 years after ≥ 15 CYC pulses in a SLE cohort[22]. We found 10% of hemorrhagic cystitis in patients with symptomatic nonglomerular hematuria who underwent cystoscopy. There were different reported rates (12–29%) in the literature[13,23].

We did not observe malignancy in any of our patients during followup. Absence of malignancy could be explained by the relatively short time of followup. The risks of CYC induced acute myeloid leukemia and bladder cancer were found to be high for cumulative CYC doses of > 36 g after 7 years of followup (SIR 9.5, 95% CI 2.6–24) in a recent analysis[24]. In our cohort only one patient who was exposed to self-administered CYC for 5 years developed myelodysplastic syndrome. CS related damage such as cataract, diabetes, and avascular necrosis was evident in our cohort but could not be compared with others[4,6] regarding dose and duration relationships. CS related side effects have been known to be dependent on dose and duration of CS, protective medications, and individual susceptibilities, and could be the reason for distinct results. We explained our findings as the occurrence of various treatment related damage such as diabetes, hypertension, and amenorrhea, in the relatively early stages of disease treated with the high doses of immunosuppressives.

The rate of survival was 80% for mean followup period of 45 months. Survival rates reported from different series were 45%–88% in WG[13,17,23,25-28]. Time elapsed from the first symptom to diagnosis seems to be longer in survivors although

not significant. This might be caused by more indolent disease course in survivors in comparison to nonsurvivors, who had more explosive disease presentation. Early death characterized by higher damage in comparison to survivors was the most striking feature of our cohort. Gottenberg, *et al* found a 38% mortality rate in patients with WG-related renal disease[17]. In our patients with WG, acute renal failure was observed in nearly half the patients, which was related to baseline renal damage and correlated with mortality. Renal involvement resulted in death or endstage renal failure in half the patients in accordance with literature[11,13,16,18].

We describe a WG cohort having a significant subgroup with generalized disease presentation. There are only a few reports[3,4,6] of damage analysis in WG using the VDI. Our report confirms the importance of early damage as a predictor of final damage and survival using a validated damage tool in a group of Turkish patients with WG. Life threatening, disease related early damage was found to be mainly treatment related, reemphasizing the need for effective treatment in the early stages of disease. We found relatively low relapse rates with mild disease activity that might be attributed to longer duration of CYC maintenance therapy. However, we noted the impact of preventing relapses in order to preclude final damage, even though the relapses were less severe than early disease activity. Early menopause in premenopausal women was the most striking adverse event related to CYC. Early aggressive treatment to avoid or reverse loss of organ function in WG patients with severe organ involvement and optimizing maintenance therapy for preventing relapses were important steps for management.

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Correction

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