Impaired Health-related Quality of Life in Patients Treated for Wegener's Granulomatosis

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ABSTRACT. ***Objective.*** To investigate whether patients with Wegener's granulomatosis (WG) experience reduced health-related quality of life (HRQOL) after accomplishment of remission, and to study the influence of WG-associated organ damage on HRQOL.

Methods. Sixty-eight patients with inactive WG and 680 randomly selected, age- and sex-matched controls of the Danish background population completed the Medical Outcomes Study Short-Form 36 (SF-36) survey for evaluation of HRQOL. Irreversible organ damage attributable to WG and/or its treatment was assessed using the Vasculitis Damage Index (VDI).

Results. The median disease duration was 7.5 (range 1–26) years in the WG group, and the median total VDI score was 2.0 (range 0–7). Compared to controls, WG patients reported impaired HRQOL reflected by significantly lower SF-36 physical component summary scores (PCS) and mental component summary scores (MCS) ($p < 0.001$) and by significantly lower scores in 7 out of 8 SF-36 subscales ($p \leq 0.001$). In the WG group, no statistically significant correlations were found between the different SF-36 scores and the total VDI score, number of organ systems affected by damage, disease duration, or number of WG relapses. Patients with organ failure or other major forms of damage did not report significantly lower HRQOL than less severely affected patients.

Conclusion. WG patients experience significantly reduced HRQOL even in phases with no apparent vasculitis disease activity. Our data indicate that the level of HRQOL does not correlate well with the extent of vasculitis-associated organ damage in WG. (First Release August 1 2010; J Rheumatol 2010;37:2081–5; doi:10.3899/jrheum.100167)

Key Indexing Terms:
WEGENER'S GRANULOMATOSIS VASCULITIS VASCULITIS DAMAGE INDEX
SHORT-FORM 36 SURVEY HEALTH RELATED QUALITY OF LIFE

Wegener's granulomatosis (WG) is a systemic inflammatory disease of unknown etiology characterized by granulomatous inflammation of the respiratory tract, necrotizing vasculitis, glomerulonephritis, and the presence of antineutrophil cytoplasmic autoantibodies (ANCA)[1,2]. The introduction of cyclophosphamide-based treatment regimens improved the prognosis of patients with WG dramatically[1,3,4]. Nevertheless, even with modern therapy, the disease remains associated with significant morbidity. In large WG studies, permanent organ damage attributable to WG or its treatment affected the majority of patients during short- and longterm followup[1,5]. The cumulative burden of such inflammation- and treatment-induced irreversible tissue damage can be analyzed using the Vasculitis Damage Index (VDI) or related scoring systems, which quantify different forms of vasculitis-associated damage[6,7,8]. These scoring systems, however, do not provide information on the consequences of WG as perceived by patients living with the disease. To our knowledge, the influence of WG on patient-reported health-related quality of life (HRQOL) has been systematically investigated in only a few published studies. Further, data on the relationship between patient-perceived health status and the extent of WG-associated organ damage are few. Studies based on patients with varied degrees of vasculitis disease activity have demonstrated a negative effect of WG on HRQOL[9,10,11,12]. Comparable observations were made in studies involving WG patients as well as patients with other ANCA-associated vasculitides[13,14,15]. Seo and coworkers used the Medical Outcomes Study Short-Form 36 (SF-36) survey[16,17,18] to evaluate HRQOL in 180 WG patients and found a statistically significant, inverse correlation between the SF-36 PCS and the VDI score in their cohort[5]. In contrast, Koutantji, *et al* did not detect statistically significant correlations between SF-36 scores and a modified VDI score among 51 patients with ANCA-associated vasculitides, including 31 WG patients[19].

We used the SF-36 survey to examine the self-reported health status of 68 Danish WG patients with inactive vasculitis. The SF-36 scores of the patients were compared to SF-36 scores of 680 randomly selected, age- and

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Accepted for publication May 31, 2010.

sex-matched controls of the Danish background population. Moreover, we analyzed the influence of vasculitis-associated organ damage on HRQOL in the WG group.

MATERIALS AND METHODS

Study subjects. The Department of Rheumatology at the Copenhagen University Hospital, Rigshospitalet, provides treatment for patients with systemic vasculitides in Eastern Denmark. Patients with inactive WG followed at the department were invited to participate in the study. Patients receiving treatment with cyclophosphamide, chlorambucil, and/or doses of prednisolone > 10 mg/day were not considered eligible for the study. Out of 75 invited WG patients, 68 (91%) accepted the invitation and completed the SF-36 questionnaire. No patient displayed clinical or laboratory signs of active vasculitis at the time of SF-36 survey, corresponding to a Birmingham Vasculitis Activity score (BVAS)[20,21] of zero. All patients met the American College of Rheumatology 1990 criteria for the classification of WG[22].

Irreversible organ damage attributable to WG and/or its treatment was evaluated at the time of the study, and the level of damage was scored using the VDI data collection form[6,7]. Further, we calculated a weighted damage score, in which items of damage of the VDI were scored according to grade of severity, and summed. In this scoring system, we adapted the median damage severity ratings described by Seo, *et al*, who asked a group of experts to score different forms of organ damage related to WG and microscopic polyangiitis on a severity scale from 0 to 10, with 10 representing the most severe form of damage[23].

For each WG patient, 10 age- and sex-matched control subjects were randomly selected among participants in a Danish national health survey conducted in 2005[24]. The participants had been recruited at random from the general population of Denmark by means of the Danish Central Population Register, which holds key information on all citizens of the country. The survey was the fourth of its kind conducted during the period 1987–2005. The purpose of the 4 surveys was to evaluate the health status and analyze factors influencing health and morbidity among adult citizens of Denmark[24].

Assessment of HRQOL. HRQOL was evaluated using a validated Danish version of the SF-36 questionnaire[25,26]. The SF-36 questionnaire contains 36 items that assess HRQOL in 8 health dimensions: physical functioning (PF); role physical (RP); bodily pain (BP); general health (GH); vitality (VT); social functioning (SF); role emotional (RE); and mental health (MH). In each dimension, item scores were coded and summed according to standard protocols[16,17]. Scores in the 8 SF-36 subscales range from 0 to 100, zero indicating the worst and 100 indicating the best patient-reported health status. Two summary scores, the PCS and the MCS, were derived from the 8 subscale scores as described by Ware, *et al*[18]. These summary scores were standardized based on US norms so that a score of 50 is the mean score of the US 1998 general population and higher scores indicate better HRQOL.

Statistical analyses. The Mann-Whitney rank-sum test was used for comparison of continuous data. Spearman's rank correlation test was used in correlation studies. In all analyses, $p < 0.05$ defined statistical significance. Analyses were performed using SPSS version 9.0 for Windows (SPSS, Chicago, IL, USA).

RESULTS

Basic descriptive data for patients are summarized in Table 1. Fifty-four patients had received oral therapy with cyclophosphamide (1–2 mg/kg/day) for induction of remission, 2 had been given intravenous cyclophosphamide (0.75 g/m^2 monthly), 6 cyclophosphamide-intolerant patients had received oral chlorambucil (2–4 mg/day), and 3 patients had been treated with oral azathioprine (1.5–2.0 mg/kg/day). All these patients also received high-dose corticosteroid therapy during the induction phase. The remaining 3 patients had received corticosteroid monotherapy as the initial treatment for WG. At the time of the SF-36 survey, 28 patients were receiving immunosuppressive maintenance therapy as outlined in Table 1, while 40 patients were followed without any immunosuppressive medication.

Table 1. Descriptive data recorded at time of Medical Outcome Study Short-Form 36 survey for 68 Danish patients with inactive Wegener's granulomatosis (WG).

Characteristic	
No. patients	68
Sex, no. (%)	
Male	36 (53)
Female	32 (47)
Median age, yrs (range)	58 (17–78)
Median time since WG diagnosis, yrs (range)	7.5 (1–26)
Immunosuppressive medication, % of patients	
Methotrexate +/– prednisolone therapy (≤ 10 mg/day)	25.0
Low-dose prednisolone monotherapy (≤ 10 mg/day)	8.8
Other drugs* +/– prednisolone therapy (≤ 10 mg/day)	7.4
No immunosuppressive medication	58.8
Median no. WG relapses (range)	1.0 (0–3)
Median Vasculitis Damage Index score (range)	2.0 (0–7)
Damage by organ system, % of patients	
Musculoskeletal	5.9
Skin/mucous membranes	1.5
Ocular	13.2
Ear, nose, throat	36.8
Pulmonary	17.6
Cardiovascular	27.9
Peripheral vascular disease	14.7
Gastrointestinal	0.0
Renal	23.5
Neuropsychiatric	44.1
Other	10.3
Median no. organ systems with damage** (range)	2.0 (0–5)

* Azathioprine (4 patients), mycophenolate mofetil (1 patient).
** Assessed by the Vasculitis Damage Index.

Compared to controls, the WG patients reported impaired HRQOL reflected by significantly reduced SF-36 PCS and MCS and by significantly lower scores in 7 out of 8 SF-36 subscales (Table 2). Patients < 58 years of age (the median patient age in the cohort) reported somewhat better HRQOL than patients ≥ 58 years of age compared to controls. Thus, while patients ≥ 58 years presented with significantly lower PCS and MCS than controls ($p \leq 0.001$ in both comparisons), younger patients did not display significantly reduced MCS compared with matched controls [mean PCS 47.1 (SD 10.0) vs 53.9 (SD 7.6), respectively; $p < 0.001$; mean MCS 52.5 (SD 8.5) vs 54.3 (SD 8.3); $p = 0.1$].

Within the WG group, no statistically significant differences in SF-36 summary scores were found between men and women. Patients who were taking immunosuppressive maintenance therapy had significantly lower PCS than patients who were off immunosuppressive medication at the

Table 2. Medical Outcome Study Short-Form 36 survey scores for 68 Danish patients with inactive Wegener's granulomatosis (WG) and 680 randomly selected age- and sex-matched controls of the Danish background population.

SF-36 Health Dimension	WG, Mean (SD)	Controls, Mean (SD)	p*
Physical function	72.5 (25.9)	88.0 (18.1)	< 0.001
Role physical	57.7 (45.3)	82.8 (32.2)	< 0.001
Bodily pain	72.4 (28.5)	79.6 (22.8)	0.09
General health	50.9 (22.3)	75.5 (19.9)	< 0.001
Vitality	61.9 (22.7)	72.8 (19.8)	< 0.001
Social functioning	80.9 (23.3)	93.0 (15.9)	< 0.001
Role emotional	73.0 (35.3)	87.2 (28.0)	< 0.001
Mental health	78.4 (17.9)	85.3 (14.6)	0.001
Physical component summary score	44.9 (10.5)	52.0 (8.6)	< 0.001
Mental component summary score	51.5 (9.3)	55.1 (8.2)	< 0.001

* SF-36 scores for patients and controls were compared using Mann-Whitney rank-sum test.

time of SF-36 survey [mean PCS 42.1 (SD 9.7) vs 46.6 (SD 10.5); p = 0.04]. These subgroups of patients did not differ significantly from each other with respect to age, male/female ratio, years since WG diagnosis, total VDI score, or number of WG relapses.

Correlation tests revealed no statistically significant associations between SF-36 summary or subscale scores and the number of WG relapses, years since WG diagnosis, the total VDI score, the weighted damage score, or the number of organ systems with damage as assessed by the VDI. Statistically significant, weak inverse correlations were found between 2 SF-36 subscale scores and the VDI item score for pulmonary damage (PF: $r_s = –0.292$; p = 0.02. BP: $r_s = –0.298$; p = 0.01). We did not detect statistically significant correlations between SF-36 scores and other organ-specific VDI item scores. No significant differences in SF-36 scores were observed between patients with major forms of damage, arbitrarily defined as items of damage of the VDI assigned a median severity rating of 7–10 by Seo, *et al*[23] (n = 32), and other patients (n = 36). Further, patients with a VDI score of zero (n = 8) did not differ significantly from patients with a VDI score ≥ 1 (n = 60) with respect to SF-36 summary or subscale scores.

DISCUSSION

Intense cytotoxic and immunosuppressive therapy has transformed WG from a rapidly lethal disorder to a chronic disease, during which prolonged periods of remission can be obtained[4,27]. However, due to recurrent disease flares, grumbling disease, and side-effects related to treatment, WG remains associated with a substantial burden of physical morbidity[1,5,28,29,30,31,32,33,34,35,36,37]. Hoffman and coworkers were the first to demonstrate that WG patients also suffer from impaired self-perceived health status[9]. This finding was subsequently confirmed in European investigations[10,11], which like the study by Hoffman, *et al* were based on WG patients with varied degrees of vasculitis disease activity. In our study, we included only WG patients who were in remission at the time of quality of life assessment. Our observations add to existing knowledge of HRQOL in WG by showing that patients with the disorder experience compromised self-perceived health status even in phases with no apparent disease activity. Thus, our data substantiate findings by Jayne, *et al*, who observed SF-36 scores below UK norms during clinical remission in a large cohort of patients with ANCA-associated vasculitides (WG or microscopic polyangiitis)[14].

In our cohort, patients ≥ 58 years of age presented with lower SF-36 PCS and MCS than age- and sex-matched controls. In contrast, younger patients did not display significantly reduced MCS compared to controls. These observations suggest that the negative influence of WG on HRQOL may be particularly pronounced in elderly patients. Moreover, we observed significantly lower SF-36 PCS for patients who received immunosuppressive maintenance therapy than for patients who were followed without immunosuppressive medication. Since none of the study subjects had active WG at the time of survey, this finding seems to indicate that receiving immunosuppressive therapy per se may influence HRQOL negatively among patients with WG.

Intriguingly, we did not detect significant correlations between SF-36 summary or subscale scores and the total VDI score in our cohort. Statistically significant, inverse correlations were found between the VDI item score for pulmonary damage and the PF and BP SF-36 subscale scores. However, the observed correlations are weak, and the possibility of chance findings related to multiple testing cannot be ruled out. Of note, our analyses did not reveal significant differences in SF-36 scores between patients presenting with major forms of damage and less severely affected patients. Further, patients without permanent organ damage as assessed by the VDI did not present with better SF-36 scores than other patients. It is interesting that comparable observations were made in a study from the UK[19]. Thus, Koutantji and coworkers did not detect statistically significant correlations between SF-36 scores and the number of damaged organ systems as assessed by the VDI in a cohort of patients with different ANCA-associated vasculitides. Together, these observations suggest that the level of patient-perceived quality of life does not correlate well with either the extent or the severity of vasculitis-associated organ damage in WG. It might therefore be speculated that the compromised HRQOL experienced by WG patients relates primarily to other consequences of living with the disease; e.g., development of fatigue and other constitutional symptoms, reduced exercise capacity, social and occupational disability, and fear of recurrent disease flares[9,10,11,15,19]. Future HRQOL investigations should

attempt to elucidate the physical, social, and psychological factors that affect the self-perceived health status of patients treated for WG.

Our study confirms that WG is associated with impaired HRQOL even in phases with no apparent vasculitis disease activity. We observed highly significant differences in SF-36 summary and subscale scores between WG patients with inactive vasculitis and age- and sex-matched controls of the general population. The negative impact of WG on HRQOL should be recognized as an important aspect of the disease in daily clinical practice.

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