The Longitudinal Course of Fatigue in Antineutrophil Cytoplasmic Antibody–associated Vasculitis

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ABSTRACT. ***Objective.*** Fatigue is common and burdensome in antineutrophil cytoplasmic antibody–associated vasculitis (AAV). This study aimed to understand how fatigue changes over time following treatment initiation and to determine whether individuals with the poorest prognosis can be robustly identified.

Methods. One hundred forty-nine patients with AAV and new-onset disease recruited to 2 clinical trials (RITUXVAS and MYCYC) were followed for 18 months. Fatigue was measured at baseline and 6-month intervals using the vitality domain of the Medical Outcomes Study Short Form-36 quality of life questionnaire and compared to a cohort of 470 controls. Group-based trajectory modeling (GBTM) determined trajectories of the symptom to which baseline characteristics and ongoing fatigue scores were compared.

Results. Fatigue levels at diagnosis were worse in patients than controls [median (interquartile range; IQR) 30 (10–48) vs 70 (55–80); $p < 0.001$], with 46% of patients reporting severe fatigue. Fatigue improved after 6 months of treatment but remained worse than in controls ($p < 0.001$). GBTM revealed varied trajectories of fatigue: low fatigue stable (n = 23), moderate baseline fatigue improvers (n = 29), high baseline fatigue improvers (n = 61), and stable baseline high fatigue (n = 37). Participants who followed stable high fatigue trajectories had lower vasculitis activity compared to improvers, but no other demographic or clinical variables differed.

Conclusion. This study longitudinally measured fatigue levels in patients with AAV. Although most patients improved following treatment, an important subgroup of patients reported persistently high levels of fatigue that did not change. Few clinical or laboratory markers distinguished these patients, suggesting alternative interventions specific for fatigue are required. [clinicaltrialsregister.eu, RITUXVAS EudraCT number: 2005-003610-15; MYCYC EudraCT number: 2006-001663-33] (First Release February 1 2020; J Rheumatol 2020;47:572–9; doi:10.3899/jrheum.190113)

Key Indexing Terms:
ANCA-ASSOCIATED VASCULITIS FATIGUE QUALITY OF LIFE

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This work was supported by Vifor Pharma (previously Aspreva Pharmaceuticals), which provided a research grant to cover the trial and mycophenolate mofetil costs for MYCYC and F. Hoffmann–La Roche, which provided the rituximab and a research grant that contributed to trial costs for RITUXVAS. The funding sources had no role in the design and conduct of the study, collection, management, analysis and interpretation of the data, preparation, review, or approval of the manuscript, or the decision to submit the manuscript for publication. The study was conducted within the Birmingham National Institute for Health Research (NIHR)/Wellcome Trust Clinical Research Facility (Birmingham, UK). The views expressed are those of the authors and not necessarily those of the UK National Health Service, the NIHR, or the Department of Health.

LH, DRJ, and RJ have received research grants and speaker fees from F. Hoffmann-La Roche. LH, RJ, DRJ, MDM have been involved in studies in which rituximab was given free of charge by Roche and MMF was given free of charge by Vifor Pharma.

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Accepted for publication June 20, 2019.

Earlier recognition and the successful introduction of immunosuppressive regimens to treat antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV) have transformed the outcomes of these life-threatening diseases[1]. Mortality rates have been reduced to 20% at 5 years; however, relapses and chronic damage are now dominant patient outcomes[2]. Reduced quality of life (QOL) remains common despite disease remission and successful control of the inflammatory process[3]. Previous studies have identified fatigue as the most significant determinant of poor QOL for patients with AAV, with more than 90% of patients reporting fatigue to be the most important limiting factor[4,5,6].

Fatigue in AAV has also been linked to reduced social participation, social withdrawal, and unemployment[7,8]. However, little is known about the longitudinal characteristics of this important symptom because all previously published studies investigating patients with AAV and fatigue have been cross-sectional in design.

Our previous cross-sectional studies in AAV have suggested fatigue is multifactorial in origin[9,10]. Sleep disturbance, pain, and inflammation, as measured by C-reactive protein (CRP), were all associated with fatigue, although the association with inflammation was the weakest[10]. In a further study of AAV patients in remission, fatigue was associated with heightened perception of exertion, depression, anxiety, and sleep disturbance, suggesting that fatigue is of a central origin rather than originating from problems with muscles or the cardiovascular system[9]. Considering the multifactorial characteristics of fatigue, it seems unlikely that the change over time of this complex symptom will be homogeneous; examining average change over time may hide variability in fatigue response to treatment. No previous studies have investigated change in fatigue longitudinally in patients with AAV. This is supported by previous findings in patients with rheumatoid arthritis (RA) that suggest the experience of fatigue over time is not uniform; there are subgroups of patients in whom it improves, while for others it remains a persistent problem despite treatment[11,12]. It is unknown whether this is also true for patients with AAV.

The aim of this study was to describe the longitudinal experience of fatigue, following treatment initiation, in an inception cohort of patients with generalized AAV recruited to 2 clinical trials. It sought to determine how fatigue responds to treatment at a group level, and whether important subgroups of patients could be identified among whom fatigue response differs. Finally, it aimed to characterize those who experienced the poorest fatigue prognosis.

MATERIALS AND METHODS

Patient population. Newly diagnosed patients with generalized AAV recruited to 2 European Vasculitis Study Group clinical trials (RITUXVAS and MYCYC) between 2006 and 2011 were included in this study. Briefly, RITUXVAS compared rituximab (RTX) plus 2 doses of cyclophosphamide (CYC) for inducing remission with conventionally dosed pulse CYC, followed by azathioprine (AZA) for maintenance therapy[13]. MYCYC compared mycophenolate mofetil (MMF) with pulsed CYC for 3–6 months until remission and then transferred to AZA for maintenance therapy[14]. All patients received prednisolone, initially 1 mg/kg body weight per day, tapered to 12.5 mg per day at the end of Month 3, and to 5 mg per day by 18 months.

For this study, patients were recruited who had completed at least 2 Medical Outcomes Study Short Form-36 (SF-36) health-related QOL questionnaires, including baseline: 33 RITUXVAS patients and 117 MYCYC patients.

General population controls were identified from a UK commercial online sampling frame (www.192.com), a representative source shown to have > 80% population coverage[15], and mailed an SF-36 questionnaire. The sample was originally selected to be age- and sex-matched to a large UK AAV cohort[6].

Data collection. MYCYC followed patients for 18 months, while RITUXVAS followed patients for 24 months. For consistency, we used the 18-month timepoint as the end date for this study. The following data were collected at 6-month intervals during the trials and used in this study: patient characteristics such as age, sex, clinical diagnosis (granulomatosis with polyangiitis vs microscopic polyangiitis), ANCA serology, disease activity measured using the Birmingham Vasculitis Activity Score 2003 (BVASv3), assessment of damage using the Vasculitis Damage Index (VDI), dialysis dependency, and time to clinical remission (as defined in the original trial protocols as the complete absence of clinical disease activity using the BVAS item list on 2 separate occasions and supported by a normal CRP concentration); laboratory data including serum creatinine concentration, CRP; treatment, defined by the induction regime (pulse CYC, MMF, or RTX); and the SF-36.

The primary outcome for this study was change in fatigue as defined by the vitality domain of the SF-36. SF-36 contains 36 items that assess health-related QOL in 8 health dimensions: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. The SF-36 has performed well in previous AAV studies[16] and has been endorsed as a core AAV outcome measure by Outcome Measures in Rheumatology (OMERACT)[17]. The SF-36 fatigue domain scores 4 items and is negatively scored with a range 0–100 so that lower scores indicate more fatigue. It has been shown to be a valid measure of fatigue[18,19].

Ethics. The study was conducted in compliance with the Helsinki Declaration. The 2 trials were sponsored by Cambridge University Hospitals (UK) National Health Service Foundation Trust. Vifor Pharma (previously Aspreva Pharmaceuticals) provided a research grant to cover the trial and MMF costs for MYCYC, and F. Hoffmann–La Roche provided the RTX and a research grant that contributed to trial costs for RITUXVAS. The trials received ethical approval from the ethics committee of each participating center and were conducted according to the European Union Clinical Trials Directive (Directive 2001 EU/20/EC; EudraCT numbers: 2006-001663-33 and 2005-003610-15) and the Oxfordshire Research Ethics Committee B (reference number 06/Q1605/120). Regulatory approval was obtained from the national regulatory authorities in each country. Written informed consent was obtained from each participant. The control data collection study was approved for conduct by the University of Aberdeen College of Life Sciences Ethics Review Board (ref: CERB/2010/1/493).

Statistics. Quantitative data are described as mean and SD for normally distributed variables, and median with interquartile range (IQR) for non-normally distributed variables.

Differences in quantitative data were tested with Student t test (with Welch's correction for unequal variances if appropriate) or the Mann-Whitney U test, depending on data distribution. Differences in fatigue scores at each followup were tested using the Kruskal-Wallis 1-way ANOVA test for non-normally distributed data.

All statistical analyses were 2-tailed. A p value < 0.05 was considered statistically significant for all analyses. Clinically meaningful differences in fatigue were examined in reference to previously applied minimum clinically important difference (MCID) estimates[20,21,22]. The MCID for fatigue was > 10 units on the 0–100 SF-36 vitality subscale.

Latent trajectories of fatigue change were identified using group-based trajectory modeling (GBTM). GBTM is used to cluster individuals who show similar progressions of scores over time and can inform between-group comparisons of differences in outcome. We therefore applied GBTM to determine whether clusters of participants followed similar fatigue trajectories during followup.

Specifically, GBTM for censored normal data was used, as the SF-36 vitality subscale is a continuous scale, with a minimum value of 0 (maximum fatigue) and a maximum value of 100 (minimum fatigue). Initially, the existence of 4 plausible cubic trajectories was proposed. Trajectories were then added or removed in consultation with the model-fit statistics, and clinical interpretation of the model, until the best-fitting model was identified. The best-fitting number of trajectories is determined as the model with the lowest Bayesian Information Criterion (BIC), provided there is

sufficient support for the complexity of a model. A model with additional trajectories was accepted if the log-Bayes factor was > 6 [$2\log_e(B_{10} \geq 6)$]. Model fit was then further improved by specification of the correct order polynomial (e.g., liner, cubic, quadratic) for each trajectory.

Characteristics of each GBTM group were defined using the data collected. Differences in fatigue scores at each followup within the GBTM group and differences between the GBTM groups were analyzed using Friedman's test for repeated measures. Time to remission was analyzed using Kaplan-Meier survival analysis and the log-rank test. Differences in categorical data were analyzed using Pearson chi-square test. Correlations were assessed using Pearson correlation. Analysis of correlations between fatigue and disease severity, inflammation, and creatinine were prespecified before data collection.

The GBTM analysis was conducted using Stata 14.0 (StataCorp); all other analyses were performed using SPSS Statistics Version 22 (IBM Corp.).

RESULTS

Patient characteristics. One hundred fifty patients with newly diagnosed AAV, of whom 117 of 140 patients were from the MYCYC trial and 33 of 44 patients were from the RITUXVAS trial, and 470 general population controls were included in the study. Controls were older than patients but there was no difference in the sex ratio (Table 1). Patients had high levels of disease activity at baseline. There were no differences in the 2 trials when comparing the patients' ages, diagnoses, disease activity scores at entry, CRP concentrations, or fatigue scores. Because of protocol differences related to the inclusion criteria, patients recruited to the RITUXVAS trial had worse renal function than those recruited to MYCYC trial [creatinine RITUXVAS 310 μmol (114-443) vs MYCYC 109 μmol/l (75-177); $p < 0.001$].

Fatigue change. Patients reported substantial levels of fatigue at diagnosis, which were worse than those of controls (Table 1). The median fatigue score for patients was 4 times greater than the MCID (18–20) compared to controls [median 30 (IQR 10–48) vs 70 (IQR 55–80)].

Table 1. Patient characteristics at baseline.

Characteristics	Controls, n = 470	Patients, n = 150	p
Age, yrs, mean ± SD	61.5 ± 13.6	57.9 ± 17.5	0.002
Sex, M/F	223/247	76/74	0.512
Trial, MYCYC/RITUXVAS		117/33	
Diagnosis, MPA/GPA		58/92	
ANCA, MPO/PR3/negative/unknown		54/90/3/2	
VDI at diagnosis		0 (0–0)	
Disease activity (BVASv3 score) at diagnosis		19 (13–24)	
Creatinine at diagnosis, µmol/l		124 (80–231)	
C-reactive protein, mg/l		22 (7–72)	
Fatigue	70 (55–80)	30 (10–48)	< 0.001

Values are median (IQR) unless otherwise specified. CYC: cyclophosphamide; MYCYC: mycophenolate vs CYC for induction therapy trial; RITUXVAS: rituximab vs CYC for induction trial; MPA: microscopic polyangiitis; GPA: granulomatosis with polyangiitis; ANCA: antineutrophil cytoplasm antibody; MPO: myeloperoxidase; PR3: proteinase 3; VDI: Vasculitis Damage Index; BVASv3: Birmingham Vasculitis Activity Score (version 2003); IQR: interquartile range.

The median fatigue level improved over the first 6 months with treatment (Figure 1) but then remained stable with no differences between fatigue scores at 6, 12, and 18 months. One hundred five patients (70%) reported a clinically significant improvement in fatigue between baseline and 6 months following the start of treatment. The median change of improvers was 45 (IQR 30–60), 4.5 times the MCID. However, despite improvement from baseline, the median fatigue score for the patient population remained worse at all timepoints compared with healthy controls (Figure 1). Despite the median change analysis suggesting improvement in fatigue scores, this concealed important differences in the longitudinal pattern of fatigue; 25% of patients had deterioration, and 12% of patients had no change in fatigue scores at 6 months compared to baseline. Reductions in fatigue did not correlate with reductions in CRP ($r = -0.01$; $p = 0.93$), change in disease activity ($r = 0.13$; $p = 0.17$), change in creatinine ($r = 0.01$; $p = 0.65$), or treatment allocation ($p = 0.68$).

Trajectory analysis. One hundred ten patients completed all 4 SF-36 questionnaires and 14 completed only 2 SF-36 questionnaires; 12 lacked 6-month data, 23 lacked 12-month data, and 25 lacked 18-month data. GBTM identified 4 distinct groups of patients based on changes (or stability) of their fatigue scores during followup (BIC all datapoints: –2369.1, BIC per participant: –2356.3; Figure 2). Model fit was further improved by refining the specification of the order polynomial for each trajectory (BIC all datapoints: –2348.3, BIC per participant: –2340.7). The 4 groups identified:

- Stable low fatigue — patients with low fatigue at trial entry who remained non-fatigued
- Stable high fatigue — patients with high fatigue at trial entry who remained fatigued
- High baseline fatigue improvers — patients with high fatigue at trial entry who improved over time
- Moderate baseline fatigue improvers — patients with moderate fatigue at trial entry who improved over time.

The fatigue scores over time were compared within each GBTM group (Table 2). The stable low fatigue group (15%) reported median fatigue scores that were comparable to controls at baseline [median 70 (IQR 60–75) vs controls, median 70 (IQR 55–80); $p = 0.77$] and did not change over 18 months. In contrast, the stable high fatigue group reported high median levels of fatigue at baseline [median 30 (IQR 15–45)], which did not improve over time. The stable high fatigue group were more fatigued than the 3 other patient groups and controls at 18 months [stable high fatigue, median 30 (IQR 15–40); high baseline fatigue improvers, median 55 (IQR 45–70); moderate baseline fatigue improvers, median 80 (IQR 70–85); stable low fatigue, median 65 (IQR 50–70); controls, median 70 (IQR 55-80); $p < 0.001$]. In the 6 months

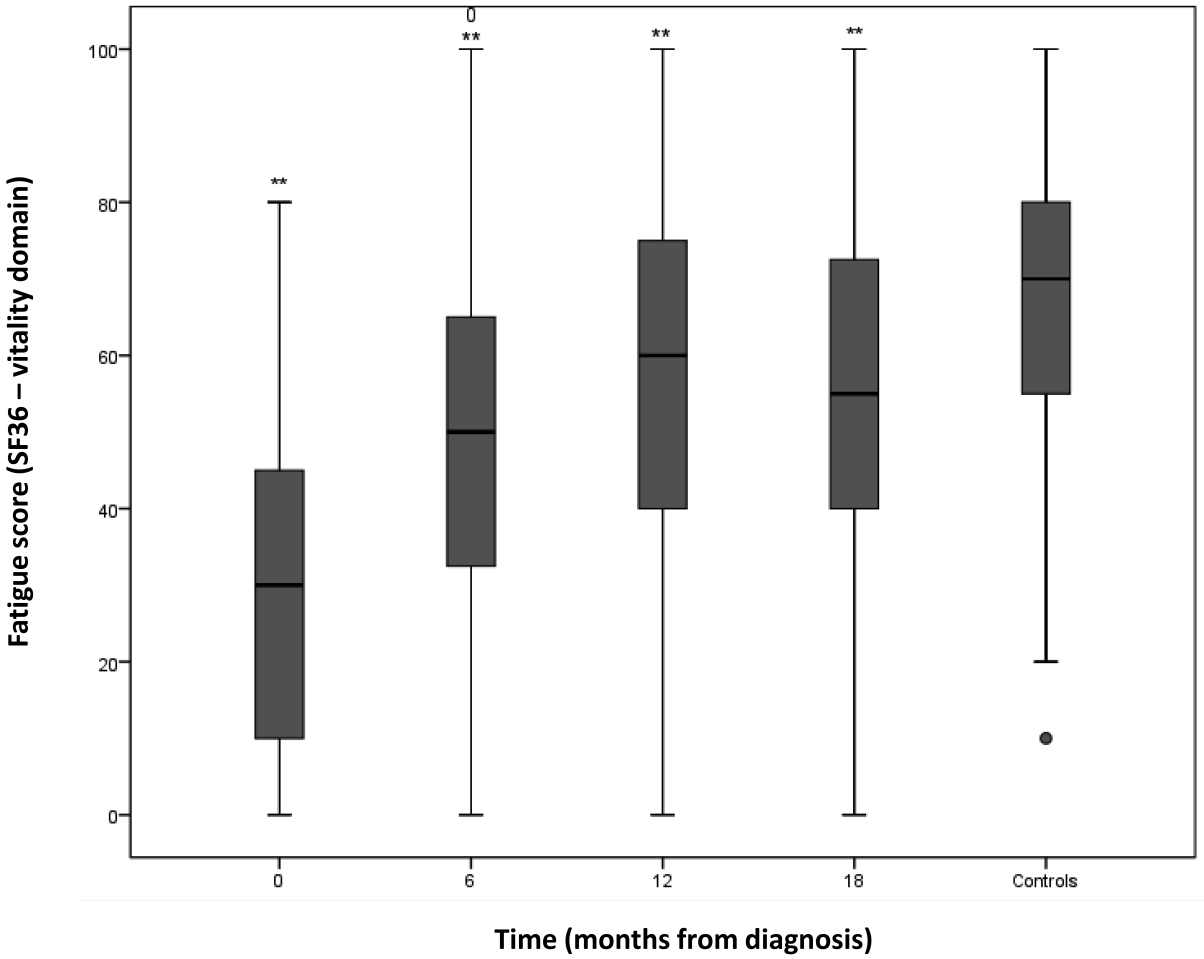

Figure 1. Data presented as box plots noting median, IQR, and outliers of fatigue scores at each timepoint for all patients and healthy controls. The fatigue score is reverse scored, with 0 indicating maximum fatigue and 100 indicating minimum fatigue. ** $p < 0.001$ timepoint compared with control. 0: $p < 0.001$ fatigue score at time 0 compared with 6 months. Black dot indicates outlier value > 1.5 times the IQR from the median. IQR: interquartile range; SF-36: Medical Outcomes Study Short Form-36.

following treatment initiation, the moderate baseline fatigue improver group achieved a median reduction in fatigue of 4 times the MCID [baseline median 40 (IQR 30–49) vs 6-month median 80 (IQR 70–80)]. The high baseline fatigue improver group achieved a less rapid but continued fatigue improvement until Month 12 (Table 2). However, at 18 months this group continued to have worse fatigue levels than controls [median 55 (IQR 45–70) vs median 70 (IQR 55–80); $p < 0.001$].

Group characterization sought to identify robust baseline markers that differentiated those who would remain fatigued (stable high fatigue) from those who improved over time. This would allow early identification of those most in need of fatigue-specific interventions. Therefore, patients in the stable high fatigue group were compared with the 2 groups of patients whose fatigue improved. Stable low fatigue patients were excluded as their fatigue levels were not different from controls at baseline. There were no differences in demographic variables between the 3 groups compared. Disease activity was lower in the stable high fatigue group compared to the 2 groups whose fatigue improved (Table 3). Additionally, there were no differences in the other SF-36 domains at baseline that differentiated the stable high fatigue patients from the patients who improved (data not shown).

Stable high fatigue patients had lower BVASv3 scores at diagnosis compared to improvers. Because there were no other demographic differences at diagnosis, we investigated whether there was any difference in time to remission or disease relapse over the first 6 months, because that was the period of fatigue improvement. Seven patients failed to achieve remission in the 3 fatigued groups; there were no differences in the time to remission (log-rank = 2; $p = 0.57$) or relapse rates during followup (Table 3). At 6 months there were no differences between the 3 trajectory groups in renal function, damage (VDI), or inflammation levels (CRP).

DISCUSSION

In this cohort of patients with incident AAV recruited to 2

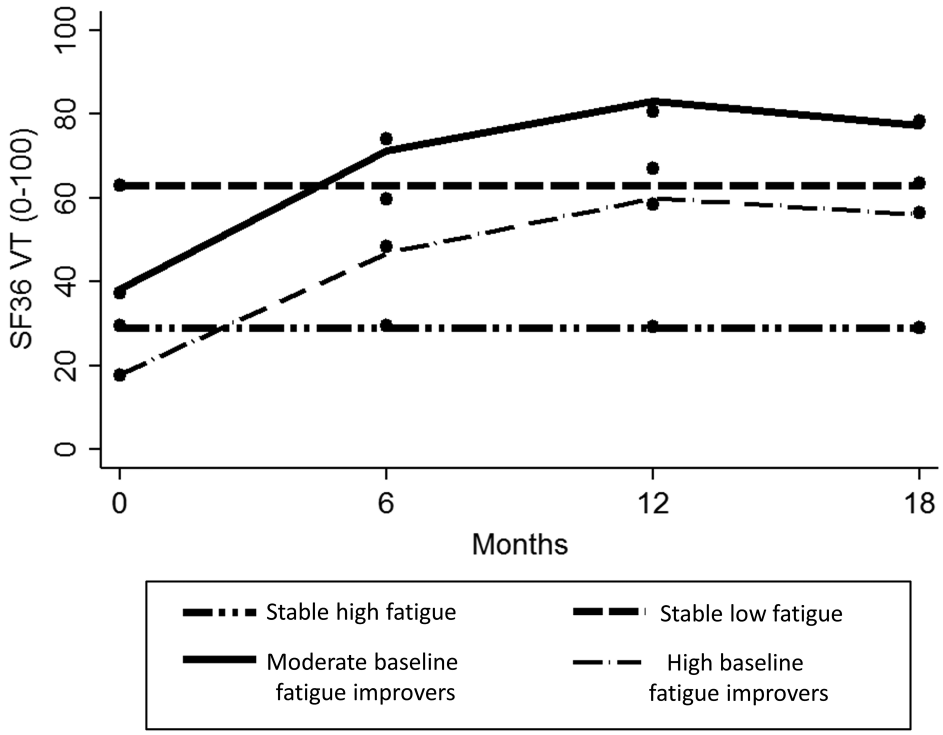

Figure 2. Trajectory analysis identified 4 distinct groups of patients based on changes (or stability) of their fatigue. SF36 VT: Medical Outcomes Study Short Form-36 vitality subscale.

Table 2. Fatigue score of each GBTM group associated with time.

Time, mos	Stable High Fatigue, n = 37	High Baseline Fatigue Improvers, n = 61	Moderate Baseline Fatigue Improvers, n = 29	Stable Low Fatigue, n = 23	Controls
0	30 (15–45)	15 (5–25)	40 (30–49)	70 (60–75)	70 (55–80)
6	25 (15–40)	45 (40–55)	80 (70–80)	60 (50–65)	
12	28 (20–40)	58 (50–66)	80 (75–90)	70 (50–80)	
18	30 (15–40)	55 (45–70)	80 (70–85)	65 (50–70)	
P values	0.81	< 0.001	< 0.001	0.11	

P values are derived from Friedman's test for repeated measures for change in fatigue score over time within the GBTM group. Values are median (IQR) unless otherwise specified. GBTM: group-based trajectory modeling; IQR: interquartile range.

clinical trials, fatigue levels were worse than the control population. The extent and features of the fatigue experienced by the patients in our study is comparable to that reported in our previous study[6] and in other rheumatological diseases. We have shown that, on average, fatigue responds well to treatment among patients with AAV. However, using GBTM we identified important differences in an individual's symptom change and identified a group of patients whose fatigue did not improve. In doing so, this study assessed the longitudinal response of fatigue in patients with AAV using trajectory analysis. We propose that such analytic approaches are crucial for patient-reported outcomes such as fatigue, which are subjective and have a multifactorial etiology. This study provides patient-level detail of the course of fatigue in AAV and information on the prognosis of fatigue, sorely needed by patients, identifying those who may require additional treatment focused on fatigue rather than disease activity.

Patients in the stable high fatigue group had lower levels of vasculitis activity at diagnosis (BVASv3 score) compared to those whose fatigue improved over the first 6 months from diagnosis. Although the differences were statistically significant, there was considerable overlap in disease activity and fatigue between patient groups such that these factors did not predict, at an individual level, whose fatigue would fail to improve. It is unclear why those patients with high stable fatigue had lower disease activity compared to those patients who improved. There were no other disease characteristics

Table 3. Group characteristics.

Group Characteristics	Stable High Fatigue	High Baseline Fatigue Improvers	Moderate Baseline Fatigue Improvers	Stable Low Fatigue	p
N	37	61	29	23	
Sex, M/F	18/19	31/30	14/15	13/10	0.966
Male, %	49	51	48	56	
Diagnosis, GPA/MPA	20/17	43/18	16/12	13/10	0.179
GPA, %	54	70	55	56	
Trial, MYCYC/RITUXVAS	28/9	50/11	22/6	17/6	0.69
MYCYC, %	75	81	76	74	
Treatment, MMF/CYC/RTX	14/18/5	27/25/9	7/16/6	10/9/4	0.46
Age, yrs, mean ± SD	62.0 ± 18	55.3 ± 17	55.8 ± 18	61.8 ± 15	0.201
BVAS at entry	14 (12–21)	21 (15–25)	20 (14–25)	18 (12–21)	0.014
BVAS at 6 mos	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0.15
VDI at 6 mos	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–2)	0.56
CRP at baseline, mg/l	16 (4–88)	22 (8–61)	28 (8–90)	28 (6–78)	0.977
CRP at 6 mos, mg/l	3 (1–7)	3.5 (1–7.6)	2.7 (1–4.2)	5 (2–18)	0.162
Creatinine at baseline, µmol/l	115 (67–353)	119 (83–209)	150 (92–209)	116 (78–223)	0.889
Creatinine at 6 mos, µmol/l	105 (70–205)	98 (78–116)	106 (95–126)	105 (87–185)	0.451
Patients achieving remission, n (%)	35 (95)	56 (92)	27 (93)	22 (96)	0.708
Patients who relapsed, n (%)	15 (41)	15 (25)	6 (21)	5 (22)	0.213

Values are median (IQR) unless otherwise specified. CYC: cyclophosphamide; RTX: rituximab; MYCYC: mycophenolate vs CYC for induction therapy trial; RITUXVAS: RTX vs CYC for induction trial; MMF: mycophenolate mofetil; MPA: microscopic polyangiitis; GPA: granulomatosis with polyangiitis; BVAS: Birmingham Vasculitis Activity Score (version 2003); VDI: Vasculitis Damage Index; CRP: C-reactive protein; IQR: interquartile range.

that associated with persistent fatigue, specifically no association with renal function or inflammation.

The lack of association with disease characteristics supports the suggestion that the etiology of fatigue in these patients is multifactorial and disease-associated inflammation plays only a small part.

For patients in the high and moderate baseline fatigue improver groups, fatigue improved with treatment, whereas for the other groups there was no change in fatigue despite treatment and improvement in disease activity. Reductions in fatigue showed no association with change in CRP, a surrogate marker of inflammation. Despite no difference in the percentage of patients in remission or disease activity at 6 months, the trajectory of fatigue differed between the 4 groups. Our original cross-sectional study showed only a small association of fatigue with inflammation. CRP was categorized as raised or normal and those with a raised CRP had a 3.7 OR with wide 95% CI (1.7–8.1)[10], and the population attributable risk was only 6%. Further, a previous publication looking at response of fatigue to treatment with anti–tumor necrosis factor medication suggested that most of the improvement was driven by improvements in pain[22]. Others have also emphasized the importance of sleep in modifying fatigue and central pain processing[23].

We and others have shown that patient-reported domains such as pain, poor sleep, and the ability to cope with illness may be more important in the development of fatigue in AAV[10] and other autoimmune conditions, such as RA[24], than disease activity[25]. Previous work in RA populations suggests that those with a history of depression are more likely to report greater fatigue in the future[26,27]. Our previous work has also suggested correlations between fatigue and anxiety and depression in patients with AAV[9]; however, this study was cross-sectional. Given the substantial effect of fatigue on both patients and society, the results support the argument that fatigue is a symptom that must be targeted in its own right rather than being improved as part of a secondary benefit to existing interventions.

There are several limitations to our study. The population included 150 patients and small effect sizes may have been missed. However, this is a rare disease; we used an incident cohort, and data were collected prospectively. Interestingly, we have found that patients in the high stable fatigue group had lower disease activity than those whose fatigue improved. This has not been shown previously, to our knowledge. The data collected did not explain this finding. We did not collect comorbidity data, including psychological comorbidity; however, this was a more homogeneous population than other studies because all patients had new-onset disease. It is recognized that these patients were recruited to clinical trials from secondary and tertiary care centers in which clinicians are experienced in the management of patients with AAV, a factor that may affect patient-reported outcomes. Despite 25% of our patients reporting a worsening of fatigue scores at 6 months, we could not identify such a group using our trajectory analysis, suggesting the study may have been underpowered and needs repeating in a larger group. In addition, although the SF-36 vitality score is a valid tool for measuring fatigue[18,19] and has

good psychometric properties[28], it may underperform at higher levels of fatigue compared to other tools in some chronic diseases[29]. Identification of those patients with a worse fatigue trajectory may require use of more sensitive fatigue measures. Our study had a short followup of only 18 months and it is unclear what happens to fatigue levels beyond this time frame. However, we did note that fatigue levels in the patients who improved did not change between 12 and 18 months. Questionnaires were administered at 6-month intervals and may have missed transitory changes in fatigue levels. However, we were interested in persistent chronic fatigue; the SF-36 vitality domain has a recall of 1 month.

The data suggest that fatigue is common in patients with AAV but average changes in fatigue are poorly informative of the variability in patterns of changes in fatigue over time. The majority of patients presenting with AAV will experience fatigue that will improve but may not return to normal levels. In addition, there is an important subgroup with high levels of fatigue at baseline who show no improvement in fatigue levels. These patients have lower levels of vasculitis activity at diagnosis. Further investigation of baseline differences in larger populations is required to understand this finding. Patients with persistent fatigue may be more likely to benefit from nonpharmaceutical interventions addressing biopsychosocial symptoms such as pain, and social function strategies, which could be commenced at 6 months when patients are in remission. Further evaluation of such interventions is essential to address the unmet need of treatment for this important problem.

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