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Management of fatigue with physical activity and behavioural change support in vasculitis: a feasibility study

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Abstract

Objective

Patients with ANCA associated vasculitis (AAV) experience high levels of fatigue, despite disease remission. This study assessed the feasibility and acceptability of a definitive randomised controlled trial of a behavioural-based physical activity intervention to support fatigue self-management in AAV patients.

Methods

AAV patients in disease remission with fatigue (Multidimensional Fatigue Inventory-20 general fatigue domain≥ 14) were randomly allocated to intervention or standard care in this single-centre open-label randomised controlled feasibility study. The intervention lasted 12 weeks and comprised eight face-to-face physical activity sessions with a facilitator and 12 weekly telephone calls. Participants were encouraged to monitor their physical activity using a tracker device (Fitbit). Standard care involved sign-posting to fatigue websites. The primary outcome was feasibility of a phase III trial assessed against three stop-go traffic light criteria, (recruitment, intervention adherence and study withdrawal). A qualitative study assessed participant views about the intervention.

Results

248 patients were screened and 134 were eligible to participate (54%). Stop-go criteria were amber for recruitment; 43/134 (32%, 95% CI 24-40) eligible participants randomised, amber for adherence; 73% of participants attended all eight physical activity sessions, but only 11/22 (50%, 95% CI 29-71%) completed the intervention as per the intended schedule, and green for study withdrawal; 2/43 participants withdrew before 24 weeks (5%, 95% CI 0-11). Qualitative results suggested the intervention was acceptable.

Conclusion

This study suggests a behavioural-based physical activity intervention targeting fatigue self-management was acceptable to patients with AAV, although recruitment and protocol adherence will need modification prior to a definitive trial.

Clinical Trial Registration Number ISRCTN11929227.

Key words

ANCA associated vasculitis, fatigue, feasibility study, physical activity, behavioural change support

Key messages

- There are no recommended therapies to treat fatigue but physical activity may improve symptoms.
- ANCA vasculitis patients with fatigue can be recruited to a physical activity intervention
- A large RCT is required to assess the clinical benefits and cost-effectiveness of a physical activity intervention.

Introduction

Despite advances in survival for patients with anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) quality of life (QoL) remains impaired, with fatigue the most important contributor[1]. Patients have identified fatigue as an important unmet need requiring research. The aetiology of fatigue is multifactorial with sleep disturbance, pain, anxiety and depression, inactivity and reduced cardiovascular fitness and, to a lesser extent, inflammation, all contributing[2, 3]. Non-pharmacological multi-disciplinary interventions to manage fatigue such as increasing physical activity (PA) and cognitive behavioural techniques have shown promise in other chronic diseases[4-8]. Patients with AAV often poorly adhere to PA advice because of fatigue and/or fear of exacerbating fatigue symptoms[9].

Interventions are required that provide a self-management tool for patients with AAV to support adherence to fatigue management advice that will build confidence and knowledge to self-manage symptoms and reduce fear of PA. Such an intervention may be enhanced by using wearable activity monitors and apps[7, 10].

The aim of this study was to assess the feasibility of undertaking a definitive randomised controlled trial (RCT) of a behaviour-based intervention to help patients self-manage fatigue symptoms.

Methods

Study design and setting

This was a single centre, open-label randomised controlled feasibility study with a nested qualitative study to explore participants' views of the study design. The trial compared a complex intervention including PA supported by behavioural change techniques, technology to assist with activity self-monitoring, and telephone support along with continued standard care compared with standard care only in patients with AAV. The full protocol has been published[11].

Sample size

As this was a feasibility study, no formal sample size calculation was performed. It was not designed or powered to detect statistically significant differences in outcomes. A recruitment target of 50 participants recruited over 9 months was set, as previously recommended[12, 13].

Eligibility

Patients were eligible if they were aged ≥18 years, had a diagnosis of AAV in remission for ≥6 months (defined by Birmingham Vasculitis Activity Score Version 3 (BVASv3)=0[14] and prednisolone dose <7.5 mg for 6 months on day of consent) and had significant fatigue levels measured by the Multidimensional Fatigue Inventory (MFI-20) general fatigue score ≥14)]; the MFI-20 has been extensively validated in a range of populations[15]. Exclusion criteria were inability to provide written informed consent, inability or unwillingness to undertake PA, comorbidities considered by their treating clinician to contraindicate an increase in PA or an inability to understand and complete questionnaires in English.

Recruitment and randomisation

Recruitment to the study was via the vasculitis service at UHB NHS Foundation Trust or response to study adverts placed in the Vasculitis UK newsletter. After confirming eligibility and obtaining informed consent, a computer-generated programme at the Birmingham Clinical Trials Unit (BCTU) randomised participants in a 1:1 ratio to either intervention or standard care. A minimisation algorithm ensured balance in the treatment allocation for age at randomisation (<65, ≥65 years).

Ethics

The West Midlands-Black Country Research Ethics Committee (ref 16/WM/0374) approved the study protocol. All participants provided written informed consent.

Interventions

Intervention group

Participants randomised to the intervention group were provided with a PA and behavioural change support programme, plus standard care; full details are published elsewhere[11]. The intervention support was provided over 12 weeks; weeks 1-8 comprised consecutive weekly face-to-face PA sessions in groups and individual telephone calls to support behaviour change and motivation, weeks 9–12 consisted of weekly individual telephone calls only. Participants were provided with wrist-worn activity trackers (Fitbit Model FB405BKL). The intervention manual is available from the corresponding author on request.

Structure of the contact sessions

The programme was individually tailored and graded, designed to be pragmatic and accessible, taking into account co-morbidities, and activity preferences with the core activity modality aerobic activity[11]. The supervised PA sessions incorporated cognitive behavioural strategies to facilitate and support behaviour change and improve self-efficacy to promote long-term PA participation. Goal setting by participants was supported by the trained facilitator with the aim of achieving at least 30 minutes of moderate intensity PA 5 days/ week, as per UK government recommendations[16], although any increase in PA was viewed positively.

Telephone contact encouraged participants to replicate the PA sessions at home and develop plans to maintain activity. The PA facilitator reviewed the impact of the intervention and management of fatigue with the participant.

Technology to support self-monitoring

The PA facilitator provided education on use of the PA tracker device and supported participants by promoting self-determination and self-regulation to set goals, maintain and monitor activity and generate plans to achieve personal goals using activity data recorded by the tracker device.

Standard care group

Participants randomised to standard care (control) group continued their usual clinical care and were sign-posted to NHS PA guidance[16] and Versus Arthritis fatigue management websites[17].

Study procedures

Data were collected at baseline prior to randomisation, and then at 12, 24 and 52 weeks (from the first PA session for those in the intervention group and from randomisation for those in the standard care group).

Study outcomes and data analysis

Primary Outcome-stop/go criteria

The primary outcome of the trial was to determine the feasibility of undertaking a full-scale phase III RCT to assess the clinical and cost effectiveness of the intervention described. The feasibility assessment of the trial was made using a composite measure of recruitment, adherence and drop-out with predefined stop-go criteria based on a traffic light system (Table 1), developed through discussion with our patient partners and review of the literature.

Clinical and patient reported outcome measures

Participants completed a range of patient reported outcome measures (PROMS) and health-related QoL questionnaires (full details are presented in the published protocol and selected PROMS are detailed in table 3) [11] at all assessments (baseline, 12, 24 and 52 weeks); completion rates and acceptability were assessed.

Fatigue was measured using validated questionnaires including MFI-20 and the Bristol Rheumatoid Arthritis Fatigue questionnaire [18]. Disease damage, measured by Vasculitis Damage index (VDI)[19], and disease activity, using BVASv3[14], were assessed at baseline and 12 and 24 weeks (VDI was measured at baseline only). Data describing variability in fatigue measures provided estimates for use in a sample size calculation for a definitive trial.

Accelerometer

All participants were asked to wear a blinded accelerometer (GENEActiv GATV01, Activinsights, Kimbolton, UK) for 7 days at baseline, prior to randomisation, 12 and 24 weeks to provide a device-based measure of their PA levels.

GENEActiv .BIN files were processed and analysed using R-package, GGIR - version 1.11-0 (http://cran.r-project.org)[20]. The following variables were generated and averaged across all valid days: number of valid wear days; average acceleration (reflects volume of PA); and moderate-to-vigorous physical activity (MVPA) using a cut-point of 100m*g*[21]. Calculation of MVPA was as total MVPA and in bouts of one and ten minutes. Participants were included in the analysis if they provided at least one valid day of accelerometer data.

Safety data

At 12 and 24 weeks follow-up cardiovascular adverse events, disease relapse and muscle or bone injury requiring medical attention as reported by the patient were recorded. Throughout the trial serious adverse events were collected.

Health economics

Detailed data collection of resources required to deliver the intervention allowed an analysis of the costs of implementing the intervention in a full-scale RCT. Data collected directly from the trial determined the resources required for delivering the supervised PA and telephone support calls. Resources included staff costs, any equipment/consumables needed, printed material, telephone call costs, staff training costs and infrastructure (e.g. room space). Number of patient contacts, length of time for face-to-face and telephone contacts and group size for the supervised PA sessions was collected. Standard unit costs were applied[22], with local costs sought from participating healthcare providers. Sensitivity analysis estimated costs with changes to costing assumptions, for example, staff grade, and group size.

Qualitative methods

All study participants received invitations to attend focus groups to collect data on their experiences and suggestions for improvements to the study and the intervention. Focus groups were conducted at the end of the trial. Semi-structured one-to-one telephone interviews were conducted with people who did not wish to participate in the trial. Focus groups and interviews were recorded and transcribed verbatim. QSR NVivo 8 was used for data management and the data were analysed thematically using a Framework methodology[23]. A pragmatic approach was adopted that focussed on key themes which would contribute to refinement of the intervention and design of any future RCT. Interviews were analysed separately by two authors (IL & SG) with discrepancies and overall interpretations discussed and agreed with all authors[24].

Statistical analysis

Baseline characteristics were summarised with numbers and percentages for categorical variables, means and standard deviations (SD) for normally distributed continuous variables, or medians and interquartile ranges for non-normal continuous variables.

The primary stop-go criteria were reported using descriptive statistics and analysed by pooling the two randomised groups and presenting overall estimates with 95% confidence intervals (CI), computed from a binomial normal approximation. Assessment of adherence to the intervention was described for the intervention group only.

For continuous outcome measures (e.g. PROMS and accelerometery data), which were deemed to be normally distributed, a linear model was fitted to generate adjusted mean differences between treatment groups (and 95% confidence intervals (CI)) at each time-point, adjusting for age and baseline score (where available). For the IPAQ tool, unadjusted differences in medians between treatment groups were produced with 95% CIs using bootstrapping methods. Binary outcome measures were summarised using number of responses and percentages. Where appropriate, a log-binomial model was used to generate adjusted relative risks (and 95% CIs), at each time-point, adjusting for age.

All analyses were based on the intention to treat principle and performed using SAS (version 9.4) and Stata (version 14.2). Differences between groups, along with 95% CI, are reported at each time point; no p-values are reported. The 24-week assessment is the proposed primary analysis time point for the phase III RCT.

Results

Recruitment and participant characteristics

Between November 2016 and December 2017, 248 patients were screened, 134 were eligible and of those, 43 (32%, 95% CI 24-40%) consented to participate in the study. The CONSORT diagram (Figure 1) describes the flow of participants through the trial and reasons for ineligibility and non-participation. Reasons for ineligibility included lack of fatigue symptoms; reasons for non-participation were mainly logistic.

Baseline participant characteristics are provided in Table 2. Participants had mean age of 62 years (range 28-78 years), 58% were male, and 65% had PR3-AAV. Participants had a high level of co-morbidity and mean VDI score was 3 (range 0-9).

Intervention adherence

Eleven of 22 participants (50%, 95% CI 29-71%) in the intervention group attended the PA sessions and accepted the telephone support calls as per the protocol schedule. Participants reported attending eight face-to-face consecutive weekly PA sessions was not always possible. To facilitate participant completion of PA sessions, attendance was allowed over 12 weeks. This resulted in 19 of the 22 participants (86%) in the intervention group attending four or more PA sessions, with 73% attending all eight sessions. Eighty two per cent of participants received at least 75% of calls in weeks 1-12 (Supplementary Table 1).

Participant Withdrawal

Withdrawal from the study was low; two participants in the intervention group withdrew prior to 24 weeks (5%, 95% CI 1-11). There was one participant withdrawal in the standard care group between 24 and 52 weeks.

Stop-go criteria to proceed to a phase III trial

The recruitment rate (32%) and the adherence rate (50%) both met the amber level of the stop/go criteria suggesting a future phase III RCT would need protocol modifications to address and improve recruitment and intervention adherence. The withdrawal rate (5%) was met at green level.

Patient reported outcome measures

The MFI-20 was well completed in all domains of returned questionnaires (≥85%). HADS, AAV-PRO and EQ5D were all well completed when returned (>90%). COPE and BRAF-MDQ were completed variably (58-91%), this was attributed to the version and format of the documentation used. We amended delivery of the questionnaires used for the PROMS for the week 52 follow-up by using a booklet containing all the questionnaires, and this resulted in higher completion rates in all tools (≥85%) (Supplementary Table 2).

Table 3 provides details of the data collected on the main behavioural and clinical PROMS at baseline and throughout the study. Participants had high levels of fatigue and poor quality of life. A measure of fatigue is proposed as the primary outcome for the phase III RCT. At 24 weeks, the adjusted mean difference between groups was -0.7 (95% CI: -2.7 to 1.4) for the MFI-20 general fatigue domain and was 5.3 (95% CI: -6.4 to 16.9) for the BRAF-MDQ total score.

Physical activity data

Baseline levels of PA were similar in both groups (Table 4). Of the 43 randomised participants, at 12 weeks, 67% provided at least one valid day of accelerometer data, and 63% provided at least four valid days. At 24 weeks, 63% provided at least one valid day of accelerometer data, and 60% provided at least four valid days (Table 4). The self-reported moderate intensity activity levels, measured using the IPAQ tool, were very high.

Sample size of a future trial

We used a minimum clinically important difference in the MFI-20 general fatigue score of two as previously described[15], to provide an estimate of the sample size of a future phase III RCT. Our feasibility study showed the MFI-20 general fatigue score to have a SD of 3.1 (80% CI: 2.6 to 4.0). If a SD of 4.0, the upper limit of the 80% CI, is assumed this gives a standardised effect size of 0.5 (considered credible in other pragmatic effectiveness studies[25]), meaning a trial with 90% power (2 sided p=0.05) requires 172 participants. Adjusting for a 15% attrition rate, 204 participants (102 each group) are required.

Safety

One cardiovascular event was reported in the standard care group. Nine participants reported experiencing a musculoskeletal injury during the trial (6 in the intervention group and 3 in the standard care group), of which one required hospitalisation (intervention group not related to intervention). Four participants reported serious adverse events, none of which were considered related to the intervention (intervention group n=3; neutropenia, pulmonary embolism, admission following a car accident, standard care n=1; admission to hospital on 2 occasions with diarrhoea). No participant's disease relapsed during the study period.

Intervention costings

Assuming every patient attended eight one-hour PA sessions and received 12 telephone calls (lasting 17.5 minutes), the total cost of the intervention per patient was approximately £541. This base-case estimate assumes two patients/PA session facilitated by grade 4 staff. If patients attend PA sessions on a one-to-one basis, this rises to £669/patient. Using patient level information from 22 intervention patients and taking into account actual numbers of telephone calls and PA sessions attended, the base case mean cost per patient was £482. The main drivers of costs are staff and use of the facility where the PA intervention was delivered.

Qualitative results

Three focus groups were conducted; two consisting of participants in the intervention group (7 participants) and one involving standard care participants (8 participants). In addition, semi-structured interviews with 8 non-participants were conducted. Key findings relating to the intervention and design of the trial are described. Specific patient comments are included in supplementary Table 3.

Recruitment

The potential benefits for the individual participant and other patients with disease influenced the decision to participate. Participants hoped to improve evidence for treatment of fatigue and reported participation as a way of saying thank you for the care received. Other motivations included wishing to increase levels of PA, previously inhibited by a lack of support or guidance. The decision not to participate was often due to logistic reasons, commonly because of the time and resource required to attend sessions. Some non-participants felt the study was no longer relevant to them.

Experiences of participating in the intervention

In general, participant feedback suggested the intervention was well accepted. A number of participants struggled to adhere to the intervention due to existing commitments. Participants suggested specific alterations to the protocol to increase flexibility in delivery of the intervention (supplementary Table 3).

Participants were particularly positive about the PA tracker and described how they used the step count as a way of monitoring and making decisions about activity. Many continued to use the activity tracker beyond the study end. Participants cited the importance of their relationship with the intervention facilitator as a significant source of motivation. They described the value of the weekly follow-up phone calls, which provided opportunities to discuss concerns about the intervention or PA. Some participants described improvements in fatigue symptoms and psychological benefits from study participation.

Discussion

The primary objective of this study was to assess the feasibility of a definitive RCT investigating a multi-component self-management intervention that targeted an increase in physical activity to improve fatigue for patients with AAV in disease remission and high fatigue levels. Based on our pre-defined stop/go criteria,

recruitment and adherence protocol targets were met at amber levels. A future RCT would thus need modifications to the protocol to increase recruitment and improve adherence. Withdrawal rates were low (green level). Despite the adherence rate achieved at amber level, the qualitative study reported that participants viewed the intervention positively, which is supported by the high attendance at the face-to-face PA sessions; 73% of those randomised to the intervention attended all eight face-to-face PA sessions.

The trial recruitment rate of 32% is similar to studies of PA interventions in patients with cancer[26]. Patient reported barriers to recruitment included time constraints and difficulties travelling to the hospital for the face-to-face PA sessions. Patient recruitment increased when we offered appointments outside normal working hours. However, we were unable to provide the intervention close to the participant's home. A future trial should consider delivery of the intervention virtually or using community facilities to increase recruitment.

Our study did not achieve the green target for adherence. .We used a much stricter definition of adherence than is usually used for PA intervention studies; which generally report mean number of sessions attended. In our study, attendance at PA sessions were similar to other studies[27].. Participant focus groups identified that the PA sessions were acceptable but also highlighted the need for more flexibility in scheduling the intervention to improve adherence. Increasing the flexibility in the protocol is likely to increase adherence.

Several patient outcomes were included to assess completion rates for use in a subsequent effectiveness RCT. The PROMS were well completed and the two specific measures of fatigue reported similarly high levels of fatigue. Self-reported PA levels using the IPAQ were extremely high compared with device measured activity, similar to previous research[28]. Baseline accelerometer data showed low levels of overall activity (i.e., average acceleration) in this population. The lack of agreement between these measures suggests an objective measure of PA is required for a future trial. Average acceleration for the intervention and control

group was 20.8 and 19.5 m*g* respectively, well below that reported for the UK Biobank population[46]. This reinforces the need for PA promotion in patients with AAV. Although this study was not intended to show efficacy, PA levels in the intervention group did increase during the intervention, although not significantly.

Although the watches provided a device measured assessment of PA, the number of participants with valid data was lower than anticipated. This was a result of logistical and procedural issues with mailing out the watches and extracting useable data from the watches. These processes will require improvement in a definitive trial.

Studies using patient level data from participants with cancer and fatigue suggest that although PA effects on fatigue are small to moderate, greatest gain is found in those with highest fatigue levels[29, 30]. This study contributes novel data by focusing on patients with AAV and high fatigue levels. We also developed an early estimate of cost to provide preliminary evidence to support a future trial. The preliminary costs of the intervention described are similar to indicative costs of delivering a cardiac rehabilitation service, recognised to improve quality of life and reduce readmissions[31].

Limitations of the study include its modest recruitment rate. This is similar to other PA interventions but may also reflect the focus on patients with high fatigue levels. The range of baseline participant activity was wide and any future RCT may need to exclude patients with high activity levels. The sample size, although small and from a single centre, was representative of individuals attending renal and rheumatology AAV clinics with a high burden of co-morbidity in the study population[32, 33].Patients had to be able to understand and converse with the facilitator in English. Future studies may require cultural adaption for an ethnically diverse population where English is not their first language.

As this was a feasibility study, we do not suggest that the findings show benefit for the intervention. The intervention should not be generally applied until a large randomised trial has proven benefit by reducing fatigue levels. Fatigue is a complex symptom with multiple components, such as sleep disturbance, pain,

mood disturbance and other factors influencing the severity of fatigue[2]. The current intervention targeted PA as a tool for patients to self-manage their symptoms. Physical activity may improve sleep, mood and pain but some patients may also require additional support to manage their fatigue, such as cognitive behavioural therapy[5].

This feasibility study suggests that the outcome measures used appeared appropriate and acceptable to participants. Participants recognised there were additional health benefits to increasing activity despite their fatigue, suggesting they may be interested in participating in a large-scale trial. Before advising patients to increase PA to self-manage fatigue a large clinical trial is required to demonstrate efficacy on fatigue levels and patient quality of life. Our feasibility study suggests such a trial is possible but the protocol would require modification so that it was more flexible, for example allowing patients to attend 8 sessions over 12 weeks rather than consecutively. Delivery of the intervention locally involving voluntary organisations or remotely using an internet-based approach may also increase recruitment.

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The Birmingham Clinical Trials Unit co-ordinated the study: Hannah Bensoussane, Hollie Caulfield, Alexandra Enocson, Catherine Hewitt, Barbara Hilken, Nicholas Hilken, Natalie Ives, Gurmail Rai, Sukhwant Sehmi, Sarah Tearne.

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Data Availability

The anonymised data underlying this article will be shared on reasonable request to the corresponding author.

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Table 1: Stop/Go criteria for progression to definitive RCT

	Recruitment rate[1]	Adherence rate[2]	Dropout rate[3]
Green target (feasible trial progress without protocol modification)	>50%	>75%	<15%
Amber (protocol needs modification but trial considered feasible)	30-50%	50-75%	15-30%
Red (trial considered not feasible)	<30%	<50%	>30%

[1]Recruitment rates were calculated as the proportion of eligible patients randomised into the study.

[2]Adherence to the intervention was defined as attendance at a minimum of four weekly physical activity direct contact sessions within the first 8 weeks of the intervention, and acceptance of a minimum of 3 of the 4 telephone support calls in weeks 9–12.

[3]Study dropout was defined as complete withdrawal from the study (≤24 weeks), with no further data collected from the participant.

Table 2: Baseline characteristics

		Intervention N=22	Standard Care N=21
Age at randomisation[1] (years)	<65	12 (55%)	10 (48%)
	≥65	10 (45%)	11 (52%)
	Mean (SD)	60.7 (11.6)	62.8 (12.0)
Gender	Male	12 (55%)	13 (62%)
	Female	10 (45%)	8 (38%)
Disease type	PR3-ANCA	13 (59%)	15 (71%)
	MPO-ANCA	6 (27%)	5 (24%)
	EGPA	3 (14%)	1 (5%)
BMI (kg/m^2)-Mean (SD, N)		29.0 (5.2, 22)	30.9 (5.4, 21)
Waist circumference (cm)-Mean (SD, N)		101.4 (17.4, 17)	108.1 (14.5, 19)
Co-morbidity	Diabetes	3 (14%)	5 (24%)
	Ischemic cardiac disease or procedure	0 (-)	4 (19%)
	Cerebrovascular Disease (TIA/Stroke)	1 (5%)	2 (10%)
	Hypertension	10 (45%)	10 (48%)
	Neuropathy	4 (18%)	5 (24%)
	Peripheral vascular disease	0 (-)	0 (-)
	Thromboembolic disease	1 (5%)	1 (5%)
	Vasculitis Damage Index score[2]-Mean (SD, N)	3.0 (2.0, 22)	3.0 (2.2, 21)
Blood Pressure	Systolic (mmHg)-Mean (SD, N)	128.8 (17.3, 21)	135.3 (15.2, 21)
	Diastolic (mmHg)-Mean (SD, N)	76.1 (11.3, 21)	81.4 (11.5, 21)
Laboratory results	Haemoglobin (g/L)-Mean (SD, N)	133.5 (12.6, 22)	139.9 (13.1, 20)

eGFR (ml/minute/1.73²)-Mean (SD, N)	63.3 (25.1, 20)	61.4 (19.5, 20)

[1]Minimisation variable.

[2]The Vasculitis Damage Index score ranges from 0-64, where a higher score indicates more organ damage.

Abbreviations: SD, standard deviation; N, number; BMI, Body Mass Index ; PR3-ANCA patients diagnosed with proteinase 3-Anti-neutrophil cytoplasm antibody positive vasculitis; MPO-ANCA, patients diagnosed with myeloperoxidase Anti-neutrophil cytoplasm antibody positive vasculitis; EGPA patients diagnosed with eosinophilic granulomatosis with polyangiitis; TIA, transient ischaemic attack; eGFR, estimated glomerular filtration rate.

Table 3: Patient reported outcome measures

	Baseline		12 weeks			24 weeks			52 weeks		
	Intervention	Standard Care	Intervention	Standard Care	Adjusted mean difference[1] (95% CI)	Intervention	Standard Care	Adjusted mean difference[1] (95% CI)	Intervention	Standard Care	Adjusted mean difference[1] (95% CI)
MFI-20: General fatigue	16.3 (2.6, 22)	16.9 (2.1, 19)	14.2 (3.0, 19)	15.5 (3.6, 20)	-0.8 (-3.1, 1.6)	13.4 (2.7, 17)	14.3 (3.1, 18)	-0.7 (-2.7, 1.4)	13.8 (4.0, 14)	14.7 (2.8, 18)	-0.6 (-3.3, 2.1)
BRAF-MDQ: Total	34.1 (12.1, 17)	35.6 (11.7, 18)	26.3 (13.9, 16)	27.5 (12.9, 15)	-2.9 (-11.9, 6.2)	31.0 (17.2, 12)	29.2 (14.4, 13)	5.3 (-6.4, 16.9)	31.0 (13.6, 12)	30.4 (13.7, 19)	3.2 (-6.0, 12.4)
SF-36: General Health	42.4 (19.0, 19)	34.0 (16.1, 21)	46.6 (19.7, 19)	39.3 (18.6, 21)	-0.1 (-10.2, 10.1)[2]	47.8 (22.0, 18)	38.7 (18.9, 19)	1.0 (-10.9, 12.9)[2]	39.2 (22.0, 13)	38.9 (24.0, 19)	-14.5 (-27.9, -1.0)[2]
HADS: Depression	5.0 (3.3, 20)	6.5 (3.5, 21)	4.2 (3.0, 17)	5.9 (3.2, 20)	-1.0 (-2.9, 0.8)	5.1 (4.0, 19)	5.7 (4.1, 18)	0.3 (-1.8, 2.4)	5.5 (3.5, 14)	5.7 (4.3, 19)	0.7 (-1.4, 2.8)
HADS: Anxiety	6.5 (3.0, 21)	7.3 (4.3, 20)	6.4 (3.0, 18)	6.6 (4.4, 20)	0.1 (-1.8, 2.0)	6.9 (4.4, 19)	5.7 (4.5, 18)	1.8 (-0.7, 4.2)	7.2 (4.6, 14)	6.1 (4.7, 19)	1.8 (-0.7, 4.3)
PSQI: Global	9.50 (3.84, 18)	9.45 (4.21, 20)	8.45 (4.94, 20)	8.47 (4.91, 17)	1.07 (-0.82, 2.96)	8.64 (4.31, 14)	8.06 (4.78, 17)	0.59 (-1.71, 2.89)	8.77 (3.83, 13)	7.5 (4.49, 18)	1.95 (0.01, 3.88)

[1]Adjusted for age and baseline score. Adjusted mean differences <0 favour intervention group for MFI-20, BRAF-MDQ, HADS and PSQI. [2]Adjusted mean differences >0 favour intervention group for SF-36.

Data presented as Mean (SD, N), adjusted mean difference presented as mean difference (95% CI)

MFI domain scores range from 4 to 20, where higher scores suggest a higher degree of fatigue. SF-36 domain scores range from 0 to 100, where lower scores suggest greater presence of limitations in that domain. BRAF-MDQ total score ranges from 0 to 70, where higher scores suggest a higher degree of fatigue. HADS domain scores range from 0 to 21, a score of <7 in either anxiety or depression subscale is regarded as normal, a score of 8–10 is suggestive of the presence of the respective mood disorder and a score of ≥11 indicating the probable presence of mood disorder. PSQI global score ranges from 0 to 21, and a score >5 indicates overall poor sleep quality.

Abbreviations: MFI-20, Multi-dimensional Fatigue Inventory 20; BRAF-MDQ, Bristol Rheumatoid Arthritis Fatigue-Multidimensional Questionnaire; SF-36, Short Form-36; HADS, Hospital Anxiety and Depression Score; PSI, Pittsburgh Sleep Index; SD, standard deviation; N, number; CI, confidence interval.

Table 4: Activity data

	Baseline		12 Weeks			24 Weeks		
	Intervention	Standard Care	Intervention	Standard Care	Adjusted Mean Difference[1] (95% CI)	Intervention	Standard Care	Adjusted Mean Difference[1] (95% CI)
Accelerometry: Number of valid days								
Mean (SD, N)	5.3 (1.4, 18)	5.6 (0.9, 20)	5.2 (1.6, 18)	5.5 (1.0, 11)		5.5 (1.3, 13)	5.9 (0.5, 14)	
Minimum-Maximum	1-6	3-6	1-7	4-7	-	3-7	5-7	-
Accelerometry: Average acceleration mg/day								
Mean (SD, N)	20.8 (7.7, 18)	19.5 (6.4, 20)	24.5 (8.4, 18)	21.7 (8.7, 11)		22.6 (6.8, 13)	20.9 (7.9, 14)	
Minimum-Maximum	11.1-39.9	7.3-31.9	11.5-46.8	8.4-38.6	-0.6 (-4.8, 3.5)	10.4-34.1	8.2-36.3	-0.9 (-5.8, 4.0)
Accelerometry: Number of minutes/day of MVPA								
Mean (SD, N)	64.3 (45.3, 18)	56.0 (37.5, 20)	79.3 (47.4, 18)	63.8 (44.5, 11)		70.5 (36.9, 13)	66.1 (48.3, 14)	
Minimum-Maximum	14.8-188.1	1.3-122.8	12.5-226.6	1.9-132.6	-0.2 (-23.0, 22.6)	19.5-135.0	1.0-162.7	-9.8 (-36.5, 16.9)
Accelerometry: Number of minutes/day of MVPA (1 minute bouts)								
Mean (SD, N)	20.3 (20.0, 18)	16.5 (18.7, 20)	32.3 (23.3, 18)	18.9 (17.0, 11)		24.7 (24.0, 13)	17.3 (19.9, 14)	
Minimum-Maximum	0.7-59.3	0-68.7	0-90.8	0-47.5	11.8 (-0.7, 24.4)	2.0-87.9	0-70.5	-0.6 (-12.3, 11.0)

Table 4: Activity data

	Baseline		12 Weeks			24 Weeks		
	Intervention	Standard Care	Intervention	Standard Care	Adjusted Mean Difference[1] (95% CI)	Intervention	Standard Care	Adjusted Mean Difference[1] (95% CI)
Accelerometry: Number of minutes/day of MVPA (10 minute bouts)								
Mean (SD, N)	8.7 (12.7, 18)	7.6 (16.2, 20)	14.3 (15.7, 18)	6.4 (9.9, 11)	9.3	11.8 (20.9, 13)	6.6 (15.5, 14)	-1.3
Minimum-Maximum	0-35.9	0-60.9	0-49.9	0-31.2	(0.1, 18.6)	0-69.8	0-58.4	(-11.6, 8.9)
IPAQ: Moderate activity (MET minutes/week)								
Median (IQR, N)	675 (60-1380, 14)	720 (100-3488, 16)	510 (225-2389, 16)	720 (180-2745, 17)	-210[2]	840 (180-2420, 17)	2520 (1350-3780, 15)	-1680[2]
Minimum-Maximum	0-2940	0-10140	0-3788	0-9450	(-2079, 1659)	0-4020	0-9900	(-3181, -179)
IPAQ: Vigorous activity (MET minutes/week)								
Median (IQR, N)	0 (0-240, 18)	0 (0-0, 18)	0 (0-120, 17)	0 (0-0, 18)	0[2]	0 (0-0, 17)	0 (0-0, 18)	0[2]
Minimum-Maximum	0-5760	0-1080	0-5760	0-0	(-147, 147)	0-7200	0-2400	(-57, 57)

[1]Values >0 favour intervention. Adjusted for age and baseline score.

[2]Unadjusted difference in medians. Values >0 favour intervention.

Abbreviations: MVPA, Moderate or vigorous activity; IPAQ, International Physical Activity Questionnaire; SD, standard deviation; N, number; CI, confidence interval.

Figure Legend

Figure 1 Consort diagram