The Birmingham Vasculitis Activity Score as a Measure of Disease Activity in Patients with Giant Cell Arteritis

Tanaz A. Kermani, David Cuthbertson, Simon Carette, Gary S. Hoffman, Nader A. Khalidi, Curry L. Koening, Carol A. Langford, Kathleen McKinnon-Maksimowicz, Carol A. McAlear, Paul A. Monach, Philip Seo, Kenneth J. Warrington, Steven R. Ytterberg, Peter A. Merkel, and Eric L. Matteson, for the Vasculitis Clinical Research Consortium

ABSTRACT. ***Objective.*** To evaluate the performance of the Birmingham Vasculitis Activity Score (BVAS) in the assessment of disease activity in giant cell arteritis (GCA).

Methods. Patients with GCA enrolled in a prospective, multicenter, longitudinal study with symptoms of active vasculitis during any visit were included. Spearman's rank correlation was used to explore the association of the BVAS with other measures of disease activity.

Results. During a mean (SD) followup of 2.3 (1.6) years, symptoms of active GCA were present in 236 visits in 136 subjects (100 female, 74%). Median (range) BVAS1 (new/worse symptoms) was 1 (0-10) and median (range) BVAS2 (persistent symptoms) was 0 (0-5). Median (range) physician's global assessment (PGA) was 4 (0-9) for disease activity in the past 28 days and 2 (0-9) for activity on the day of the visit. Important ischemic manifestations of active vasculitis not recorded by the BVAS included tongue/jaw claudication (27%), upper extremity claudication (15%), lower extremity claudication (5%), carotidynia (7%), and ischemic retinopathy (5%). During 25 visits (11%) with active disease, all symptoms of active vasculitis were placed in the "Other" category yet still resulted in a BVAS1 and BVAS2 of 0. BVAS1 moderately correlated with PGA for the past 28 days (Spearman's correlation 0.50) and physician-rated disease activity for the past 28 days (Spearman's correlation 0.46).

Conclusion. The BVAS has limited utility in GCA. Patients with active GCA can have a BVAS of 0. Many important ischemic symptoms attributable to active vasculitis are not included in the composite score. (J Rheumatol First Release April 1 2016; doi:10.3899/jrheum.151063)

Key Indexing Terms:
GIANT CELL ARTERITIS DISEASE ACTIVITY COHORT STUDY
BIRMINGHAM VASCULITIS ACTIVITY SCORE

Giant cell arteritis (GCA) is a chronic granulomatous vasculitis affecting the aorta and its primary branches. Extracranial manifestations of GCA, which occur in about one-third of patients, include large-artery stenosis and aortic

From the Division of Rheumatology, University of California, Los Angeles, Los Angeles, California; Department of Biostatistics, University of South Florida, Tampa, Florida, USA; Division of Rheumatology, Mount Sinai Hospital, Toronto, Ontario, Canada; Center for Vasculitis Care and Research, Cleveland Clinic, Cleveland, Ohio, USA; Division of Rheumatology, St. Joseph's Healthcare, McMaster University, Hamilton, Ontario, Canada; Division of Rheumatology, University of Utah, Salt Lake City, Utah; Division of Rheumatology, University of Pittsburgh, Pittsburgh, Pennsylvania; Division of Rheumatology and Clinical Immunology, University of Pennsylvania, Philadelphia, Pennsylvania; The Vasculitis Center, Section of Rheumatology, and the Clinical Epidemiology Unit, Boston University School of Medicine, Boston, Massachusetts; Division of Rheumatology, Johns Hopkins University, Baltimore, Maryland; Division of Rheumatology, Mayo Clinic College of Medicine, Rochester, Minnesota, USA.

Dr. Kermani was supported through a Vasculitis Fellowship by the Vasculitis Clinical Research Consortium (VCRC). The VCRC has received support from the US National Institute of Arthritis and Musculoskeletal and Skin Diseases (U54AR057319), the US National Center for Research Resources (U54 RR019497), the Office of Rare Diseases Research, and the US National Center for Advancing Translational Science. The VCRC is part of the Rare Diseases Clinical Research Network.

T.A. Kermani, MD, MS, Division of Rheumatology, University of California, Los Angeles; D. Cuthbertson, MS, Department of Biostatistics, University of South Florida; S. Carette, MD, FRCPC, Division of Rheumatology, Mount Sinai Hospital; G.S. Hoffman, MD, MS, Center for Vasculitis Care and Research, Cleveland Clinic; N.A. Khalidi, MD, FRCPC, Division of Rheumatology, St. Joseph's Healthcare, McMaster University; C.L. Koening, MD, MS, Division of Rheumatology, University of Utah; C.A. Langford, MD, MHS, Center for Vasculitis Care and Research, Cleveland Clinic; K. McKinnon-Maksimowicz, DO, Division of Rheumatology, University of Pittsburgh; C.A. McAlear, MA, Division of Rheumatology and Clinical Immunology, University of Pennsylvania; P.A. Monach, MD, PhD, The Vasculitis Center, Section of Rheumatology, and the Clinical Epidemiology Unit, Boston University School of Medicine; P. Seo, MD, MHS, Division of Rheumatology, Johns Hopkins University; K.J. Warrington, MD, Division of Rheumatology, Mayo Clinic College of Medicine; S.R. Ytterberg, MD, Division of Rheumatology, Mayo Clinic College of Medicine; P.A. Merkel, MD, MPH, Division of Rheumatology and Clinical Immunology, University of Pennsylvania; E.L. Matteson, MD, MPH, Division of Rheumatology, Mayo Clinic College of Medicine.

Address correspondence to Dr. T.A. Kermani, University of California, Los Angeles, 2020 Santa Monica Blvd., Suite 540, Santa Monica, California 90404, USA. E-mail: kermani.tanaz@yahoo.com

Accepted for publication February 26, 2016.

disease[1]. Glucocorticoids remain the mainstay of treatment for patients with GCA, but treatment is associated with morbidity in the majority of patients[2]. Additionally, relapses are common[2,3,4,5,6,7,8,9,10]. Several randomized controlled trials have been conducted to evaluate other immunosuppressive therapy in patients with GCA[11,12,13,14,15,16,17,18,19]. A problem common to trials in GCA is the lack of commonly accepted standardized measures of disease activity[20]. Almost all trials have used some measurement of disease activity such as "relapse," "recurrence," "flare," or "remission," but the definitions of these disease states are not uniformly applied across studies, making comparisons challenging[20].

The Birmingham Vasculitis Activity Score (BVAS) is a validated tool for assessment of disease activity in patients with many different forms of vasculitis[21,22,23]. The BVAS includes scored items grouped into 9 organ systems that identify a broad spectrum of clinical manifestations from vasculitis. Only features attributed to active vasculitis are considered. The BVAS is part of the Outcome Measures in Rheumatology Clinical Trials core outcome measures for use in clinical trials of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis[24]. Previous validation studies of the BVAS included only a small number of patients with large-vessel vasculitis. The aim of our study was to evaluate the BVAS as a measure of disease activity in a prospective observational cohort of patients with GCA. Information gained from such a study could inform future efforts to develop disease activity measures in GCA and clinical trial design.

MATERIALS AND METHODS

All data for this study were collected from patients enrolled between 2006 and 2013 in the Vasculitis Clinical Research Consortium Longitudinal Study of Giant Cell Arteritis, a multicenter, prospective, observational cohort. All patients in this cohort meet the 1990 American College of Rheumatology classification criteria for GCA[25], which was modified to include patients with large-vessel vasculitis by angiography or biopsy. Inclusion criteria were age above 50 years with ≥ 2 of the following features: (1) new localized headache, (2) temporal artery abnormality on examination, (3) erythrocyte sedimentation rate (ESR) > 40 mm/h by Westergren method, (4) abnormal temporal artery biopsy, and (5) large vessel vasculitis by angiography or biopsy. All subjects were followed prospectively with standardized clinical assessments including symptoms attributable to vasculitis (over the past 28 days, on the day of evaluation), laboratory findings, BVAS (version 2, which includes 66 items grouped into 9 organ systems), and physician's global assessment (PGA, scale of 0-10). Disease activity was also assessed categorically by the treating physician at each visit as remission or active (low, moderate, or high). Disease activity was defined as the presence of new or worsening symptoms attributable to active vasculitis in the 28 days prior to evaluation or on the day of evaluation.

Information was reviewed on symptoms, laboratory evaluation, PGA, and BVAS during any period of disease activity in the 28 days prior to the visit, or on the date of the visit. The distribution of organ involvement as documented in the BVAS was collected. The investigator completing the BVAS separates symptoms that are new or worse from those that have been present within the last 3 months and continue to be present (persistent). There are 2 final BVAS scores: BVAS1 (new/worse) and BVAS2 (persistent). Additional symptoms attributed to vasculitis that were not recorded by the BVAS except in the "Other" category were also collected. Manifestations of active vasculitis placed under the "Other" category of BVAS do not add to the total BVAS and are scored as 0. Descriptive statistics were used. Spearman's rank correlation was used to evaluate the correlation of the BVAS in patients with active disease with other measures of disease activity including PGA, physician-rated disease activity (remission, low, moderate or high), ESR, and C-reactive protein (CRP). JMP, Version 11, SAS Institute Inc., was used for all analyses.

The study was approved by institutional review boards at each participating site. All participants provided informed consent.

RESULTS

Data were available for 136 subjects: 100 (74%) female, mean (SD) age at study entry of 71.7 (9.3) years with a mean (SD) followup of 2.3 (1.6) years. Symptoms of active GCA were present in 236 visits. Median (range) BVAS1 (new or worse symptoms) was 1 (0-10) and median (range) BVAS2 (persistent symptoms) was 0 (0-5) in the 236 visits with active disease. Median (range) PGA was 4 (0-9) for disease activity in the past 28 days and 2 (0-9) for activity on the day of the visit. Disease activity for the past 28 days was characterized as remission for 7 visits, low for 75 visits, moderate for 72 visits, and high for 32 visits. Disease activity on the day of evaluation was categorized as remission in 48 visits, low in 124 visits, moderate in 51 visits, and high in 10 visits (data missing in 3 cases). On the day of evaluation, median (range) ESR was 21 (1-126) mm/h, with median (range) CRP of 6.65 (0-211.7) mg/l.

In 51 patients (38% of patients in this study) with active disease at the time of enrollment, the diagnosis of GCA was made within 3 months of enrollment into the cohort. In these patients, median (range) BVAS1 at first visit was 3 (0-9), and with BVAS2, 0 (0-5). Disease activity for the past 28 days was rated as low in 1 patient, moderate in 24 patients, and high in 24 patients (data missing in 2 patients). Disease activity on day of evaluation (study enrollment) was categorized as remission in 15 patients, low in 16 patients, moderate in 13 patients, and high in 6 patients. Median (range) PGA for past 28 days was 7 (2-9) and 2 (0-9) for the day of the visit (at study enrollment).

Symptoms of active vasculitis during the 236 visits with active disease and whether they were identified on BVAS are summarized in Table 1. Clinical manifestations of active disease as collected by BVAS for the 236 visits are in Table 2. The BVAS was also separately analyzed for 51 patients with GCA diagnosed within 3 months of enrollment into the cohort (Table 3).

The most-used categories of BVAS were the "General" category, followed by "Other," and "Mucus Membranes/Eyes." Forty-eight (73%) of the 66 items in the 9 organ systems were never used. Further, 57 (86%) of the 66 items in the 9 organ systems were recorded in < 3% of visits when active disease was present. The different categories of the individual questions in the BVAS that were applicable to any encounter with symptoms of active vasculitis are given in Figure 1. All of the components in the General section of the BVAS were applicable to patients with GCA while none

Table 1. Symptoms of active giant cell arteritis.

Symptoms	236 Encounters in 136 Patients with GCA		51 Patients with a New Diagnosis of GCA			Identified on BVAS
	Past 28 Days	Today	At Diagnosis	Past 28 Days	Today	
Weight loss	17	13	8	8	5	Yes
Fever	7	11	3	3	0	Yes
Headache	98	53	33	32	11	Yes
Scalp tenderness	66	30	27	24	6	Yes (as headache)
New temporal artery pain	43	17	20	18	3	Yes (as headache)
Carotidynia	16	7	9	10	5	No
Jaw/tongue claudication	64	29	26	27	9	No
Ischemic retinopathy	14	5	10	10	5	No
Partial vision loss	14	7	5	8	5	Yes
Severe vision loss	5	3	5	5	3	Yes
Diplopia	9	1	8	8	0	No
Polymyalgia rheumatica	79	53	16	17	10	Yes
Arthralgia/arthritis	28	40	11	10	3	Yes
Upper extremity claudication	35	29	9	9	8	No
Lower extremity claudication	12	9	4	4	3	No
Transient ischemic attack	1	0	0	0	0	No
Light-headedness	5	5	0	0	0	No
Mesenteric ischemia	1	1	1	1	0	Yes
Other (fatigue, cough, night sweats, anorexia)	21	15	4	4	1	Yes for fatigue and cough

GCA: giant cell arteritis; BVAS: Birmingham Vasculitis Activity Score.

of the components in the Renal section were applicable to patients with active GCA.

In 25 visits (11%) of active disease, all the symptoms of active vasculitis were placed only in the Other category, resulting in both BVAS1 and BVAS2 of 0. Manifestations of active vasculitis not recorded by the BVAS in these 25 visits were tongue/jaw claudication (5 cases, 20%), upper extremity claudication (14 cases, 56%), lower extremity claudication (6 cases, 24%), diplopia (1 case, 4%), and light-headedness (1 case, 4%). Median PGA in these 25 encounters was 3 (0-8) for the past 28 days and 3 (0-7) for the day of the evaluation. Disease activity for the past 28 days in these 25 encounters was rated as remission in 2 visits, low in 8 visits, moderate in 8 visits, and high in 1 visit, while disease activity for the day of the evaluation was rated as remission in 4 visits, low in 15 visits, moderate in 5 visits, and high in 1 visit.

Correlation of the BVAS with other commonly used measures of PGA is in Table 4. Neither the BVAS nor the PGA correlated well with ESR or CRP.

DISCUSSION

In this large cohort of patients with GCA, the BVAS had limited utility in the assessment of disease activity. Most categories of the BVAS were not applicable in patients with GCA. Additionally, because many components of active vasculitis in GCA were placed in the Other category on the BVAS and do not contribute to the total BVAS, some patients had a BVAS of 0 despite active disease. This analysis raises concerns for use of the BVAS in clinical trials of new treatments for GCA.

There are numerous challenges in the clinical assessment of disease activity and an objective measure would be beneficial. Presently, there are no standardized measures of disease activity in GCA. Previous clinical trials have used terms such as *relapses, recurrences, flares*, or *remission* to define disease activity and often take into consideration markers of inflammation[11,12,13,14,15,16,17,18,19]. GCA is a chronic granulomatous vasculitis, with observational cohorts reporting at least 1 disease relapse in 28%-64% of patients[2,3,4,5,7,9,10]. While markers of inflammation such as ESR and CRP are neither sensitive nor specific in the assessment of disease activity[8,26,27], they are frequently used to assess disease activity in patients with GCA and may influence treatment decisions. Suspected relapses are often treated with higher doses of glucocorticoids, which are associated with significant morbidity in this population of patients[2,3]. The BVAS is a validated tool for assessment of disease activity for systemic vasculitis[21,22,23]. However, previous validation studies evaluating the BVAS for assessment of disease activity in systemic vasculitis have included only a small number of patients with GCA[21,23]. Additionally, in a validation study of BVAS version 3, patients with GCA were excluded because of homogeneity of clinical manifestations and a limited range of abnormalities that would be measured by the BVAS items[23]. Few studies have used BVAS in the assessment of disease activity in

Table 2. Frequency of clinical manifestations in 236 encounters of giant cell arteritis with active disease during observation, as captured by the Birmingham Vasculitis Activity Score (BVAS).

BVAS Items (by organ system)	New/worse Symptoms*	Persistent Symptoms*
General, n = 188		
Malaise	57	17
Myalgia	51	7
Arthralgia/arthritis	47	17
Headache	108	9
Fever (< 38.5°C)	4	1
Fever (> 38.5°C)	2	2
Weight loss (≥ 2 kg)	20	0
Maximum allowable score on BVAS	3	2
Median (range) BVAS for category	1 (0–3)	0 (0–2)
Cutaneous, n = 2		
Ulcer	2	0
Maximum allowable score on BVAS	6	3
Median (range) BVAS for category	0 (0–4)	0 (0–0)
Mucous membranes/eyes, n = 35		
Mouth ulcers	0	1
Blurred vision	24	1
Sudden vision loss	19	0
Maximum allowable score on BVAS	6	3
Median (range) total BVAS for category	0 (0–6)	0 (0–2)
Ear, nose, and throat, n = 1		
Sinus involvement	0	1
Maximum allowable score on BVAS	6	3
Median (range) total BVAS for category	0 (0–0)	0 (0–1)
Chest, n = 9		
Persistent cough	8	1
Maximum allowable score on BVAS	6	3
Median (range) total BVAS for category	0 (0–2)	0 (0–1)
Cardiovascular, n = 2		
Congestive heart failure	0	2
Maximum allowable score on BVAS	6	3
Median (range) BVAS for category	0 (0–0)	0 (0–2)
Abdominal, n = 1		
Severe abdominal pain	1	0
Maximum allowable score	9	4
Median (range BVAS for category)	0 (0–3)	0 (0–0)
Renal, n = 0		
Maximum allowable score on BVAS	12	6
Median (range) BVAS for category	0 (0–0)	0 (0–0)
Nervous system, n = 4		
Organic confusion/dementia	2	0
Stroke	1	0
Sensory peripheral neuropathy	0	1
Maximum allowable score on BVAS	9	6
Median (range) BVAS for category	0 (0–9)	0 (0–3)
Other, n = 85	63	22
Total		
Maximum allowable score	63	33
Median (range) total BVAS	1 (0–10)	0 (0–5)

*Values are number of encounters during active disease with symptoms identified by that item. All median BVAS are scores for 236 encounters with active disease. n = total number with any clinical manifestation in that organ system.

patients with GCA and again included a small number of patients[28,29]. Our study evaluated BVAS version 2 in a large, multicenter cohort of patients with GCA.

In our study, the total BVAS in patients with GCA during active disease was low, with a median score of 1. Even in the subset of patients with newly diagnosed GCA, the BVAS at diagnosis was low despite disease activity being rated by the evaluating physician as moderate to high in most of these patients. Additionally, in the majority of the encounters with active disease, symptoms were new rather than persistent;

Table 3. Frequency of active disease in 51 patients with newly diagnosed giant cell arteritis, as identified by the Birmingham Vasculitis Activity Score (BVAS). All median BVAS are scores for 236 encounters with active disease.

BVAS Items (by organ system)*	New/worse Symptoms	Persistent Symptoms
General, n = 43		
Malaise	16	3
Myalgia	11	0
Arthralgia/arthritis	9	1
Headache	36	1
Fever (< 38.5°C)	1	1
Fever (> 38.5°C)	1	1
Weight loss (≥ 2 kg)	10	0
Median (range) BVAS for category	1 (0–3)	0 (0–2)
Mucous membranes/eyes, n = 18		
Blurred vision	16	0
Sudden vision loss	12	0
Retinal hemorrhage	1	
Median (range) total BVAS for category	0 (0–6)	0 (0–0)
Chest, n = 5		
Persistent cough	4	1
Median (range) total BVAS for category	0 (0–2)	0 (0–1)
Cardiovascular, n = 1		
Congestive heart failure	0	1
Median (range) BVAS for category	0 (0–0)	0 (0–2)
Other, n = 19	19	0
Total median (range) BVAS	3 (0–9)	0 (0–5)

*No symptoms were found for these BVAS items: cutaneous; ear, nose, and throat; abdominal; renal; and nervous system. n: total number with any clinical manifestation in that organ system.

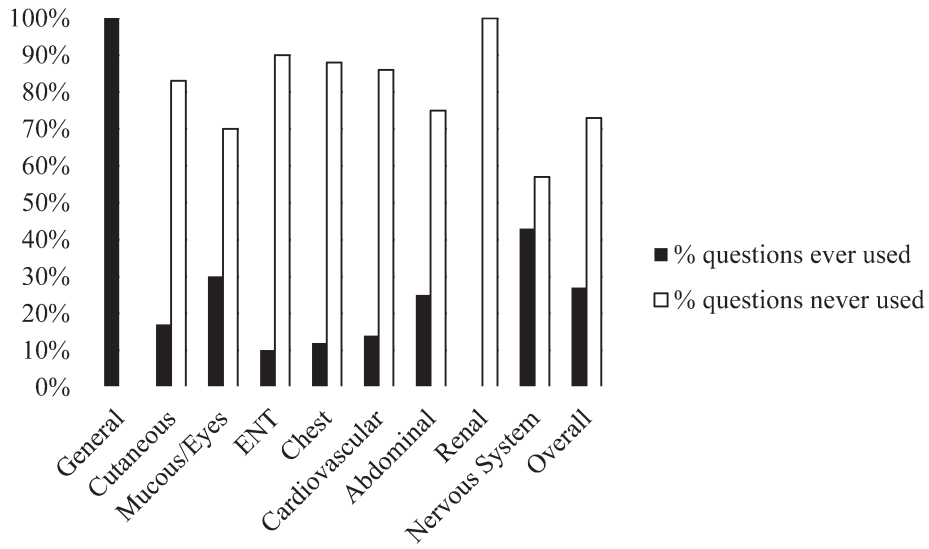

Figure 1. Percentage of BVAS questionnaire components, arranged by category, that were applicable to any patient with giant cell arteritis and active disease. ENT: ear, nose, and throat; BVAS: Birmingham Vasculitis Activity Score.

thus the BVAS2 was not applicable in most patients with active GCA.

Most categories in the BVAS are not applicable to patients with GCA. The majority of symptoms of active GCA were recorded in 2 of the 9 categories on the BVAS (General and Mucus Membranes/Eyes) and many symptoms fell into the Other category, which does not contribute to the final score. Nearly 75% of the questions in the BVAS did not apply to any patient with GCA who had active disease, and > 85% of the questions were used in < 3% of visits when active disease was present.

Further, several common manifestations of GCA are not

Table 4. Spearman's correlations of BVAS with other measures used to assess disease activity in GCA.

	BVAS1	p	BVAS2	p	PGA 28 Days	p	PGA Today	p
PGA past 28 days	0.50	< 0.001	–0.20	0.003	—	—	—	—
PGA today	0.01	0.62	–0.08	0.26	0.29	< 0.001	—	—
ESR	0.02	0.80	–0.12	0.08	0.08	0.22	0.41	< 0.001
CRP	0.02	0.77	–0.01	0.93	–0.01	0.9	0.36	< 0.001
Disease activity past 28 days*	0.46	< 0.001	–0.18	0.001	0.90	< 0.001	—	—
Disease activity today	0.05	0.40	–0.04	0.50	—	—	0.93	< 0.001

* Rated by evaluating physician as remission, low, medium, or high. BVAS: Birmingham Vasculitis Activity Score; BVAS1: score for new/worse disease activity; BVAS2: score for persistent disease activity; GCA: giant cell arteritis; PGA: physician's global assessment; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

included among the core elements on the BVAS. For example, ischemic manifestations such as limb claudication, jaw/tongue claudication, carotidynia, ischemic retinopathy, and diplopia were not identified except in the Other category. A further potential weakness of the BVAS is that the category "Headache" likely lacks specificity for GCA because this term must be used to mean scalp tenderness and temporal artery pain, 2 symptoms that may not be perceived by patients or physicians as "Headache." Many symptoms of active GCA were not identified by the BVAS (except in the Other category). In 11% of cases of active disease, the BVAS was 0. The median PGA for the patients with a BVAS = 0 was 3, with physician-categorized disease activity being rated as low or moderate in the majority of the cases.

There is also not a strong correlation of the BVAS with other commonly used measures to assess disease activity in GCA[21,22,23]. In one study evaluating magnetic resonance imaging and positron emission tomography, activity scores from imaging findings were compared to clinical measures including BVAS and markers of inflammation[28]. Imaging findings showed poor correlation with other clinical measures of disease activity including BVAS and markers of inflammation[28]. In the current study, BVAS correlated well with PGA and physician categorical ratings of disease activity, but only for disease activity in the past 28 days and not for disease activity on the day of evaluation. Treatment changes made before the patient was evaluated may account for this finding. Alternately, symptoms may have spontaneously improved or abated by the time of evaluation. Neither BVAS nor PGA/disease activity in the past 28 days correlated with markers of inflammation, which again may reflect treatment changes made by the physician based on the patient's symptoms prior to the evaluation visit. In the current study, PGA on the day of activity was the only variable of disease activity that correlated with ESR and CRP.

The strengths of our study include the prospective design with standardized serial assessments including the BVAS and detailed questionnaires about symptoms at each visit. This enabled more detailed analysis of symptoms recorded during active disease and comparison to what is collected on BVAS. Details on symptoms were available at different timepoints including "in the past 28 days," and "today" (on the day of evaluation). As a result, symptoms of active vasculitis were identified, including new symptoms that may have resolved by the time of evaluation. The data gathered in a longitudinal manner on each patient in the cohort are more comprehensive and complete than would be available during routine clinical assessment. BVAS version 2 was used because that was the version available at the time the cohort was first established. BVAS version 3 has fewer items and a single box for persistent activity but is otherwise similar to the original BVAS[22]. Therefore, use of the older version of BVAS should not affect the validity of our findings. Additionally, in a study evaluating different measures of disease activity for ANCA vasculitis, the different measures showed high correlation[30]. Additional strengths of our study include the large cohort size, helping to ensure that uncommon manifestations of GCA were assessed. The conduct of the study at multiple centers in North America adds to the generalizability of the results.

Our study has some limitations to consider. The project was not able to assess interobserver reliability of the BVAS in GCA, although this has been studied in the past[21,22,23]. Symptoms attributed to active GCA by the evaluating clinician were identified as active disease but it is possible that manifestations could be related to other causes in this elderly population. The character of the cohort is such that the effect of treatment on changes in the BVAS could not be established.

Objective, standardized methods of assessing disease activity in patients with large-vessel vasculitis are greatly needed[20,31]. The BVAS has played an important role in clinical trials in ANCA-associated vasculitis and remains an important contribution in the development of outcome measures in systemic vasculitis. The present study highlights the limitations of this tool in the evaluation of patients with GCA and provides data on aspects of clinical manifestations during active disease in GCA that may be important to include in future measures of disease activity. These findings highlight why other approaches to disease assessment in

GCA are needed and are helpful in informing future efforts to develop and validate measures of disease activity in large-vessel vasculitis.

REFERENCES

1. Salvarani C, Cantini F, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis. Lancet 2008;372:234-45.
2. Proven A, Gabriel SE, Orces C, O'Fallon WM, Hunder GG. Glucocorticoid therapy in giant cell arteritis: duration and adverse outcomes. Arthritis Rheum 2003;49:703-8.
3. Alba MA, Garcia-Martinez A, Prieto-Gonzalez S, Tavera-Bahillo I, Corbera-Bellalta M, Planas-Rigol E, et al. Relapses in patients with giant cell arteritis: prevalence, characteristics, and associated clinical findings in a longitudinally followed cohort of 106 patients. Medicine 2014;93:194-201.
4. Garcia-Martinez A, Hernandez-Rodriguez J, Espigol-Frigole G, Prieto-Gonzalez S, Butjosa M, Segarra M, et al. Clinical relevance of persistently elevated circulating cytokines (tumor necrosis factor alpha and interleukin-6) in the long-term followup of patients with giant cell arteritis. Arthritis Care Res 2010;62:835-41.
5. Hachulla E, Boivin V, Pasturel-Michon U, Fauchais AL, Bouroz-Joly J, Perez-Cousin M, et al. Prognostic factors and long-term evolution in a cohort of 133 patients with giant cell arteritis. Clin Exp Rheumatol 2001;19:171-6.
6. Liozon E, Roblot P, Paire D, Loustaud V, Liozon F, Vidal E, et al. Anticardiolipin antibody levels predict flares and relapses in patients with giant-cell (temporal) arteritis. A longitudinal study of 58 biopsy-proven cases. Rheumatology 2000;39:1089-94.
7. Martinez-Lado L, Calvino-Diaz C, Pineiro A, Dierssen T, Vazquez-Rodriguez TR, Miranda-Filloy JA, et al. Relapses and recurrences in giant cell arteritis: a population-based study of patients with biopsy-proven disease from northwestern Spain. Medicine 2011;90:186-93.
8. Weyand CM, Fulbright JW, Hunder GG, Evans JM, Goronzy JJ. Treatment of giant cell arteritis: interleukin-6 as a biologic marker of disease activity. Arthritis Rheum 2000;43:1041-8.
9. Nesher G, Nesher R, Mates M, Sonnenblick M, Breuer GS. Giant cell arteritis: intensity of the initial systemic inflammatory response and the course of the disease. Clin Exp Rheumatol 2008;26:S30-4.
10. Kermani TA, Warrington KJ, Cuthbertson D, Carette S, Hoffman GS, Khalidi NA, et al. Disease relapses among patients with giant cell arteritis: a prospective, longitudinal cohort study. J Rheumatol 2015;42:1213-7.
11. Hunder GG, Sheps SG, Allen GL, Joyce JW. Daily and alternate-day corticosteroid regimens in treatment of giant cell arteritis: comparison in a prospective study. Ann Intern Med 1975;82:613-8.
12. Schaufelberger C, Andersson R, Nordborg E. No additive effect of cyclosporin A compared with glucocorticoid treatment alone in giant cell arteritis: results of an open, controlled, randomized study. Br J Rheumatol 1998;37:464-5.
13. De Silva M, Hazleman BL. Azathioprine in giant cell arteritis/polymyalgia rheumatica: a double-blind study. Ann Rheum Dis 1986;45:136-8.
14. Jover JA, Hernandez-Garcia C, Morado IC, Vargas E, Banares A, Fernandez-Gutierrez B. Combined treatment of giant-cell arteritis with methotrexate and prednisone. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 2001;134:106-14.
15. Spiera RF, Mitnick HJ, Kupersmith M, Richmond M, Spiera H, Peterson MG, et al. A prospective, double-blind, randomized, placebo controlled trial of methotrexate in the treatment of giant cell arteritis (GCA). Clin Exp Rheumatol 2001;19:495-501.
16. Hoffman GS, Cid MC, Hellmann DB, Guillevin L, Stone JH, Schousboe J, et al. A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. Arthritis Rheum 2002;46:1309-18.
17. Schaufelberger C, Mollby H, Uddhammar A, Bratt J, Nordborg E. No additional steroid-sparing effect of cyclosporine A in giant cell arteritis. Scand J Rheumatol 2006;35:327-9.
18. Hoffman GS, Cid MC, Rendt-Zagar KE, Merkel PA, Weyand CM, Stone JH, et al. Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis: a randomized trial. Ann Intern Med 2007;146:621-30.
19. Martinez-Taboada VM, Rodriguez-Valverde V, Carreno L, Lopez-Longo J, Figueroa M, Belzunegui J, et al. A double-blind placebo controlled trial of etanercept in patients with giant cell arteritis and corticosteroid side effects. Ann Rheum Dis 2008;67:625-30.
20. Direskeneli H, Aydin SZ, Kermani TA, Matteson EL, Boers M, Herlyn K, et al. Development of outcome measures for large-vessel vasculitis for use in clinical trials: opportunities, challenges, and research agenda. J Rheumatol 2011;38:1471-9.
21. Luqmani RA, Bacon PA, Moots RJ, Janssen BA, Pall A, Emery P, et al. Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis. QJM 1994;87:671-8.
22. Mukhtyar C, Lee R, Brown D, Carruthers D, Dasgupta B, Dubey S, et al. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). Ann Rheum Dis 2009;68:1827-32.
23. Suppiah R, Mukhtyar C, Flossmann O, Alberici F, Baslund B, Batra R, et al. A cross-sectional study of the Birmingham Vasculitis Activity Score version 3 in systemic vasculitis. Rheumatology 2011;50:899-905.
24. Merkel PA, Aydin SZ, Boers M, Direskeneli H, Herlyn K, Seo P, et al. The OMERACT core set of outcome measures for use in clinical trials of ANCA-associated vasculitis. J Rheumatol 2011;38:1480-6.
25. Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum 1990;33:1122-8.
26. Kyle V, Cawston TE, Hazleman BL. Erythrocyte sedimentation rate and C reactive protein in the assessment of polymyalgia rheumatica/giant cell arteritis on presentation and during follow up. Ann Rheum Dis 1989;48:667-71.
27. Pountain GD, Calvin J, Hazleman BL. Alpha 1-antichymotrypsin, C-reactive protein and erythrocyte sedimentation rate in polymyalgia rheumatica and giant cell arteritis. Br J Rheumatol 1994;33:550-4.
28. Both M, Ahmadi-Simab K, Reuter M, Dourvos O, Fritzer E, Ullrich S, et al. MRI and FDG-PET in the assessment of inflammatory aortic arch syndrome in complicated courses of giant cell arteritis. Ann Rheum Dis 2008;67:1030-3.
29. Henes JC, Mueller M, Pfannenberg C, Kanz L, Koetter I. Cyclophosphamide for large vessel vasculitis: assessment of response by PET/CT. Clin Exp Rheumatol 2011;29 Suppl 64:S43-8.
30. Merkel PA, Cuthbertson DD, Hellmich B, Hoffman GS, Jayne DR, Kallenberg CG, et al. Comparison of disease activity measures for anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis. Ann Rheum Dis 2009;68:103-6.
31. Aydin SZ, Direskeneli H, Sreih A, Alibaz-Oner F, Gul A, Kamali S, et al. Update on Outcome Measure Development for Large Vessel Vasculitis: Report from OMERACT 12. J Rheumatol 2015; 42:2465-9.