Assessing the Performance of the Birmingham Vasculitis Activity Score at Diagnosis for Children with Antineutrophil Cytoplasmic Antibody-associated Vasculitis in A Registry for Childhood Vasculitis (ARChiVe)

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ABSTRACT. ***Objective.*** There are no validated tools for measuring disease activity in pediatric vasculitis. The Birmingham Vasculitis Activity Score (BVAS) is a valid disease activity tool in adult vasculitis. Version 3 (BVAS v.3) correlates well with physician's global assessment (PGA), treatment decision, and C-reactive protein in adults. The utility of BVAS v.3 in pediatric vasculitis is not known. We assessed the association of BVAS v.3 scores with PGA, treatment decision, and erythrocyte sedimentation rate (ESR) at diagnosis in pediatric antineutrophil cytoplasmic antibody-associated vasculitis (AAV).

Methods. Children with AAV diagnosed between 2004 and 2010 at all ARChiVe centers were eligible. BVAS v.3 scores were calculated with a standardized online tool (www.vasculitis.org). Spearman's rank correlation coefficient (r_s) was used to test the strength of association between BVAS v.3 and PGA, treatment decision, and ESR.

Results. A total of 152 patients were included. The physician diagnosis of these patients was predominantly granulomatosis with polyangiitis (n = 99). The median BVAS v.3 score was 18.0 (range 0–40). The BVAS v.3 correlations were $r_s = 0.379$ (95% CI 0.233 to 0.509) with PGA, $r_s = 0.521$ (95% CI 0.393 to 0.629) with treatment decision, and $r_s = 0.403$ (95% CI 0.253 to 0.533) with ESR.

Conclusion. Applied to children with AAV, BVAS v.3 had a weak correlation with PGA and moderate correlation with both ESR and treatment decision. Prospective evaluation of BVAS v.3 and/or pediatric-specific modifications to BVAS v.3 may be required before it can be formalized as a disease activity assessment tool in pediatric AAV. (J Rheumatol First Release Feb 15 2012; doi:10.3899/jrheum.111030)

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Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of primary systemic vasculitides predominantly affecting small- to medium-size blood vessels. Disease subtypes currently recognized include granulomatosis with polyangiitis (GPA; previously known as Wegener's granulomatosis)[1], microscopic polyangiitis (MPA), Churg-Strauss syndrome (CSS), and limited pauci-immune glomerulonephritis (pauciimmune GN)[2]. The current treatment strategy for these diseases is to induce and maintain remission of disease. It is therefore essential to be able to determine the level of disease activity in individual patients.

The Birmingham Vasculitis Activity Score (BVAS) and the Vasculitis Activity Index are 2 disease assessment tools that have been validated in adult patients with vasculitis[3,4]. The BVAS is considered to be the more objective tool and European League Against Rheumatism recommendations have advocated its use as the standard tool in clinical trials[5].

The BVAS was developed by consensus and validated as a comprehensive multisystem clinical disease activity assessment tool for primary systemic vasculitis in adults. The score is based on the assessment of 9 organ systems [general, cutaneous, mucous membrane/eyes, ear/nose/throat, chest (pulmonary), cardiovascular, abdominal, renal, and nervous system], with weighted items and a maximum ceiling score for each organ system. After its original validation in 1994, there were 2 modifications[6,7] and a disease-specific modification for GPA (BVAS-GPA; formerly referred to as BVAS-WG)[8]. The most recent version, BVAS v.3, correlates strongly with physician's global assessment of disease activity (PGA; $r_s = 0.91$) and with treatment decision ($r_s = 0.66$), and moderately with C-reactive protein (CRP) levels ($r_s = 0.43$) in adult vasculitis patients[7]. Neither the BVAS nor any other disease activity measurement tool has been validated for use in children, although some pediatric studies have used this adult tool[9,10].

Reported differences between adult and pediatric patients with GPA include a higher frequency of subglottic stenosis and nasal deformities[11] and higher frequency of renal and pulmonary involvement compared to adults[12,13]. Applying BVAS to pediatric patients, therefore, may not completely reveal the extent of clinical involvement or the degree of disease activity seen in these patients. Thus there is an important need to evaluate the utility of BVAS in assessing disease activity in pediatric patients with chronic systemic vasculitis. The aim of our study was to investigate the relationship of BVAS v.3 scores with PGA, initial treatment decision, and erythrocyte sedimentation rate (ESR) at the time of diagnosis, in the largest contemporary registry of childhood AAV.

MATERIALS AND METHODS

ARChiVe (A Registry for Childhood Vasculitis: e-entry) is a contemporary inception cohort of patients that was established in collaboration with members of the Childhood Arthritis and Rheumatology Research Alliance (CARRA). A list of collaborating centers and investigators in the ARChiVe network is given in the Appendix. Since inception in March 2007, pediatric rheumatologists at 36 CARRA-associated institutions in the United States (n = 32) and Canada (n = 4) have contributed patients. Eligible subjects were children diagnosed with GPA, MPA, CSS, and ANCA-positive pauci-immune GN before their eighteenth birthday and after January 1, 2004, who were then followed at the participating institutions between March 2007 and June 2010. Children with ANCA-positive unclassified small to medium vessel systemic vasculitis were also included in this cohort. The diagnosis was established by the treating pediatric rheumatologist at each of the ARChiVe network sites and was entered in the database as the "MD diagnosis." Formal diagnostic criteria for each type of vasculitis were not specified. Subjects were excluded if there were insufficient data to determine BVAS v.3 score. The study protocol was approved by the local research ethics board at each participating center. Informed consent for participation was obtained from parents, and informed consent or assent was obtained from patients for both retrospective and prospective recruitment as applicable.

For children diagnosed between January 2004 and the launch of ARChiVe in March 2007, data were collected by retrospective review of available medical records. For children diagnosed between March 2007 and June 2010, data were collected prospectively. In all cases, data collected were for the period from clinical onset until 2 months after diagnosis. ARChiVe uses a Web-based interface for entry of the following data: MD

diagnosis; date of symptom onset; demographic data; family and patient's medical history; presenting/diagnostic features; physical examination findings; results of laboratory testing (including ANCA specificities); and results of diagnostic imaging or other procedures such as biopsies and bronchoscopy and pulmonary function tests; in addition, data are collected on initial therapy including the use of oral prednisone [mg/kg/day, recorded as low (< 0.5), medium (0.5–1.5), high (> 1.5)] and intravenous (IV) corticosteroids, cyclophosphamide (oral or IV), other disease-modifying drugs, "biologic" therapies, other concurrently used medications (anticoagulants, antihypertensives), and other interventions such as the need for dialysis or mechanical ventilation.

Data collection items in the registry included all elements of BVAS v.3 and a PGA determined by an onsite rheumatologist at diagnosis (determined on a standard 10-cm visual analog scale). The following modifications were necessary to apply BVAS v.3 directly to pediatric data: hypertension was defined as blood pressure above pediatric-specific normal values instead of as diastolic pressure > 95 mm Hg; mildly elevated serum creatinine (up to 30% above upper normal limit for age) was treated as equivalent to adult serum creatinine 125–249 μmol/l; moderately to severely elevated serum creatinine (over 30% above upper normal limit for age) was treated as equivalent to adult serum creatinine 250–499 μmol/l; renal failure requiring dialysis was treated as equivalent to adult serum creatinine ≥ 500 μmol/l. Weight loss was considered to be present if the patient had lost > 2 kg, or more than 3% of body weight.

Both CRP and ESR levels at the time of diagnosis were collected in ARChiVe; however, ESR was chosen instead of CRP as a laboratory marker of inflammation because CRP was measured only as normal or abnormal. ESR was measured as normal (< 20 mm/h), moderately elevated (20–50 mm/h), or high (> 50 mm/h). Treatment at the time of diagnosis was categorized as follows: (1) Limited, if it included corticosteroids with or without nonsteroidal antiinflammatory drugs, hydroxychloroquine, and/or trimethoprim-sulfamethoxazole; (2) Moderate, if it included a disease-modifying agent other than cyclophosphamide; and (3) Aggressive, if it included cyclophosphamide. These treatment categories differ from those discussed in recent BVAS v.3 studies that assessed disease activity in a non-inception cohort[7,14].

BVAS v.3 items were extracted from the database and individual patient scores were calculated by 1 author (KM) using a standardized online calculator (www.vasculitis.org). Spearman rank correlation coefficient (r_s) was used to test the statistical significance of associations between BVAS v.3 scores and PGA, treatment decision, and ESR at the time of diagnosis. The statistical analysis was performed using SPSS version 19 (SPSS, Chicago, IL, USA).

RESULTS

A total of 153 pediatric patients with an AAV were recruited into the ARChiVe cohort during the study period. One patient was excluded from analyses because data were insufficient to score the BVAS v.3. Of the remaining 152 patients, 104 (68.4%) were female and 48 (31.6%) were male. The MD diagnoses of patients in the cohort were GPA (n = 99), MPA (n = 25), CSS (n = 3), ANCA-positive pauciimmune GN (n = 6), and unclassified vasculitis (n = 19).

The median BVAS v.3 at diagnosis for these 152 patients was 18.0 (range 0–40), with the lowest median BVAS v.3 found for CSS (10 ± 9.9) and highest for GPA (19.0 ± 8.2). PGA scores were available for 150 patients. The median PGA for the group was 7.0 ± 2.6 cm (range 0–10). Table 1 shows the frequency of involvement of different organ systems scored by BVAS v.3 for each AAV subtype. Arthralgia was found in 50% or more of patients of all subtypes. Cutaneous, ENT, renal, and chest manifestations were commonly found in almost all subtypes. Abdominal involvement was rare and cardiac involvement uncommon except for CSS and unclassified vasculitis.

Sixty-four (42.1%) of the 152 patients (18 MPA, 39 GPA, 5 ANCA-positive pauciimmune GN, 2 unclassified) had the renal ceiling score of 12. Nearly all these patients had multiple manifestations that would have given them higher scores if there had been no ceiling. These included 17 of the 18 MPA patients, 38 of the 39 GPA patients, and all of the ANCA-positive pauciimmune GN patients. A combination of hematuria and proteinuria (total of 10 BVAS v. 3 points) with even a small elevation of serum creatinine or hypertension was common and resulted in the maximum renal score of 12. Such patients with milder renal disease could not be distinguished from those with endstage renal disease requiring dialysis. Sixty-seven patients (44.1%) had the maximum chest ceiling score of 6 (11 MPA, 48 GPA, 6 unclassified, 1 ANCA-positive pauciimmune GN, 1 CSS). Again, nearly all of these patients would have had higher scores if there had been no ceiling, including all of the MPA and unclassified vasculitis patients, and 44 of the 48 GPA patients. The chest ceiling score did not distinguish between patients with alveolar hemorrhage versus patients with a cavitary lesion(s) and an effusion, or other mild pulmonary disease.

Table 1. Percentage of patients with different organ involvement as scored by Birmingham Vasculitis Activity Score v.3 for ANCA-associated vasculitis subtypes.

Vasculitis Subtype (n)	Fever	Weight Loss	Arthalgia	Cutaneous	Mucous Membrane/Eye	ENT	Chest	Cardiovascular	Abdominal	Renal	Nervous System
ANCA-positive GN (6)	16.7 (1)	33.3 (2)	50 (3)	33.3 (2)	33.3 (2)	50 (3)	16.7 (1)	16.7 (1)	0	100 (6)	33.3 (2)
CSS (3)	33.3 (1)	0	66.7 (2)	100 (3)	0	100 (3)	100 (3)	33.3 (1)	0	33.3 (1)	0
MPA (25)	24 (6)	28 (7)	56 (14)	32 (8)	8 (2)	32 (8)	56 (14)	8 (2)	0	96 (24)	16 (4)
Unclassified (19)	36.8 (7)	10.5 (2)	68.4 (13)	63.2 (12)	31.6 (6)	15.8 (3)	36.8 (7)	21.1 (4)	10.5 (2)	57.9 (11)	26.3 (5)
GPA (99)	22 (22)	33 (33)	59 (59)	46 (46)	31 (31)	81 (81)	68 (68)	6 (6)	3 (3)	68 (68)	15 (15)

ANCA: antineutrophil cytoplasmic autoantibody; GN: glomerulonephritis; CSS: Churg-Strauss syndrome; MPA: microscopic polyangiitis; GPS: granulomatosis with polyangiitis.

The correlation between BVAS v.3 and PGA scores was $r_s = 0.379$ (95% CI 0.233 to 0.509, $p < 0.0001$; Figure 1). One hundred forty-two of the 152 patients had a recorded ESR value. The correlation between BVAS v.3 and ESR levels was $r_s = 0.403$ (95% CI 0.253 to 0.533, $p < 0.0001$; Figure 2). The correlation between BVAS v.3 and initial treatment category was $r_s = 0.521$ (95% CI 0.393 to 0.629, $p < 0.0001$; Figure 3).

DISCUSSION

The BVAS represents a powerful tool and allows rapid, accurate, and reliable assessment of disease activity in adults with vasculitis. It also enables data-driven clinical decision making, and permits comparative therapeutic trials. In the adult validation study of BVAS v.3, where half (155) of the 313 patients with chronic vasculitis had GPA, the scores correlated strongly with PGA (concurrently scored by the same investigator completing the BVAS; $r_s = 0.91$) and treatment decision ($r_s = 0.66$), and moderately with CRP levels ($r_s = 0.43$)[7]. When applied to the cohort of children with vasculitis in our study, the median BVAS v.3 at the time of diagnosis (18.0 ± 8.0) was similar to the mean BVAS v.3 reported in patients with adult vasculitis at diagnosis (18.92, SD 6.06)[7]. In addition, BVAS v.3 demonstrated similar correlation when compared against the initial treatment decision ($r_s = 0.521$) and acute-phase reactant levels ($r_s = 0.403$) described in BVAS v.3 adult validation studies.

However, a marked disparity was noted between BVAS v.3 scores and PGA in our pediatric cohort ($r_s = 0.379$). A recent abstract of 796 pediatric patients with vasculitis (mostly Henoch-Schönlein purpura, and only 25 with GPA) documented a moderate correlation ($r_s = 0.49$) between BVAS v.3 and PGA (recorded by separate investigators, as in ARChiVe)[15]. There are a variety of possible explanations for why BVAS correlates much better with PGA in adult compared to pediatric patients. First, it should be noted that the original BVAS study did not demonstrate any significant correlation with PGA (Kendall's tau = 0.35, $p = 0.1$)[4]. Validation studies of subsequent versions showed increasing strength of correlation between BVAS scores and a PGA where they were recorded concurrently by the same investigator. The BVAS-GPA in 2001 demonstrated a correlation with PGA of $r_s = 0.81$[8], and the BVAS v.3 in 2008 demonstrated a correlation with PGA of $r_s = 0.91$[7]. After over a decade of routine use in adult clinical practice, the BVAS has arguably influenced how physicians score PGA in their adult patients, and PGA has evolved over time to reflect the BVAS. In contrast, the lack of a standardized measure of

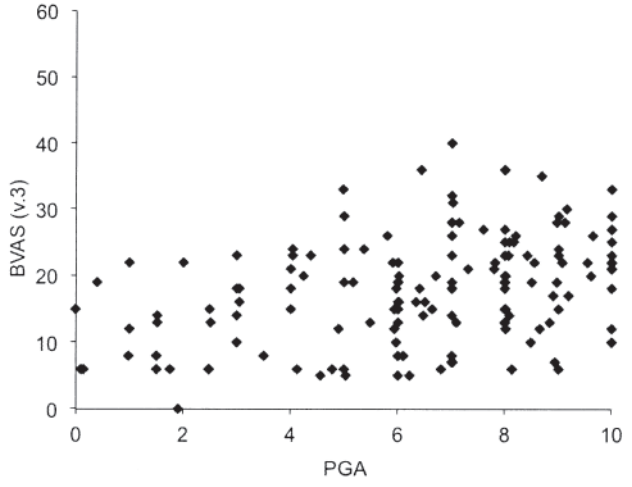

Figure 1. Correlation between Birmingham Vasculitis Activity Score v.3 (BVAS; scored 0–63) and physician's global assessment (PGA) scored on a 10-cm visual analog scale.

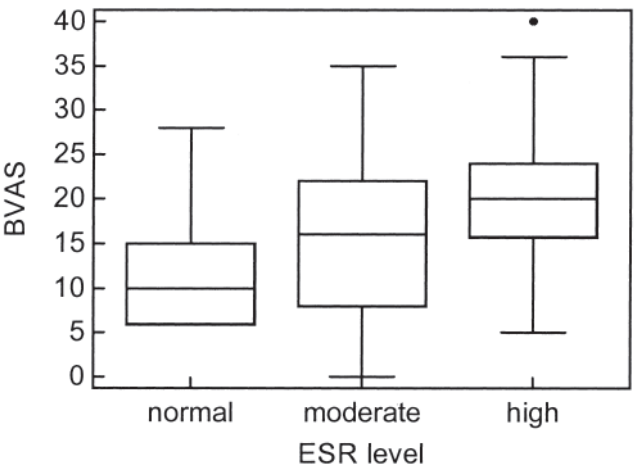

Figure 2. Correlation between Birmingham Vasculitis Activity Score (BVAS) v.3 and erythrocyte sedimentation rate (ESR); ESR levels (mmol/h) defined as normal < 20, moderate 20–50, high > 50.

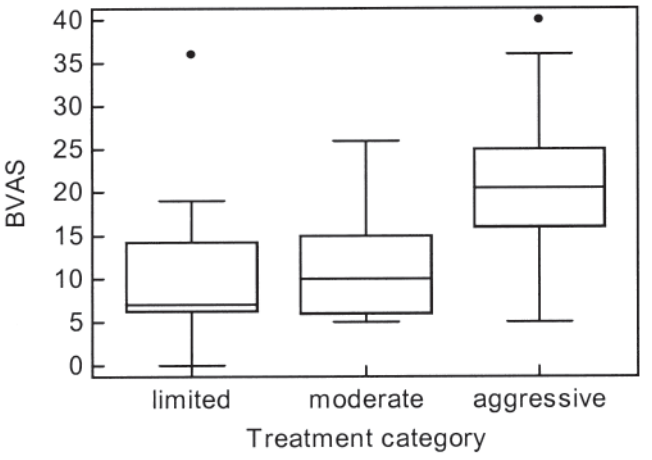

Figure 3. Correlation between Birmingham Vasculitis Activity Score (BVAS) v.3 and treatment category, defined as limited (if it included corticosteroids with or without nonsteroidal antiinflammatory drugs, hydroxychloroquine, and/or trimethoprim-sulfamethoxazole); moderate (if it included a disease-modifying agent other than cyclophosphamide); or aggressive (if it included cyclophosphamide).

disease activity in pediatric vasculitis may result in variable and nonsystematic approaches to assigning PGA scores to pediatric patients that may not be based on objective criteria. Moreover, because most pediatric rheumatology centers care for only a few patients with AAV, a physician's clinical "gestalt" in establishing a PGA may be based on very limited clinical experience. Vasculitis patients account for < 5% of all patients seen at pediatric rheumatology centers in the United States and Canada[16,17] (and unpublished CARRAnet data).

Second, it is possible that for pediatric vasculitis patients, physicians are basing their global assessment on factors not currently contained within the BVAS v.3, or they are informally assigning values to certain disease features that are weighted differently by BVAS. Although children with vasculitis are at risk of developing all disease manifestations observed in adults, there are variations in rates of such manifestations and differing perceptions regarding the effects of similar disease manifestations in a child compared to an adult[11,12]. In the ARChiVe cohort a high proportion of patients were at the ceiling score level for renal and pulmonary involvement, and the majority of these patients would have had higher scores had there not been a ceiling. It is possible that certain items or combinations of items indicating renal and/or pulmonary involvement (or other organ involvement) had an influence on PGA scoring that was not reflected in the BVAS v.3 score. For example, a child with isolated hematuria in the absence of an elevation in serum creatinine might be assessed to have more active disease than an adult with isolated hematuria because most children have underlying healthy kidneys and an elevation in serum creatinine is not necessarily seen until a significant injury has occurred. Whether differences in weighting or changes to ceiling scores are necessary will depend to some extent on whether these differences have any influence on outcomes and must be considered in future longitudinal studies of BVAS.

Finally, in our study, PGA and BVAS v.3 scores were ascertained by different investigators in ARChiVe. BVAS v.3 was applied retrospectively to time-of-diagnosis data entered in the ARChiVe registry. This methodology and weak correlation approximates the finding in the initial adult BVAS validation study (Kendall's tau = 0.35, p = 0.1) that was attributed to BVAS score and PGA being ascertained by different investigators[4]. Although BVAS is calculated using objective clinical data, it is possible that incomplete or inaccurate data could influence the accuracy of BVAS scoring. In addition, investigators were generally not trained in the use of BVAS v.3, and this may have affected whether items were entered as intended by BVAS v.3.

Although this study did not demonstrate a strong correlation between BVAS v.3 and PGA, there is a sound rationale for applying adult-based disease activity measures to pediatric patients, recognizing that modifications may be necessary to improve their performance in children. Considerable overlap exists between disease activity measures for adults and children with other chronic rheumatic conditions. When compared directly, the American College of Rheumatology (ACR) 20% response criteria for rheumatoid arthritis and the ACR 30% response criteria for juvenile idiopathic (formerly rheumatoid) arthritis consist of remarkably similar core criteria[18,19]. A precedent for use of adult disease activity metrics in children exists in the study of patients with juvenile systemic lupus erythematosus. Lupus disease activity tools such as the Systemic Lupus Erythematosus Disease Activity Index, Systemic Lupus Activity Measure, and European Consensus Lupus Activity Measurement index were all initially developed for use in adults with SLE but are now incorporated as core criteria in the overall assessment of disease activity in children with SLE[20,21]. Given the similarity of disease manifestations and successful use of adult disease metrics in pediatric conditions, it would seem reasonable to apply existing disease activity measures for assessment of children with systemic vasculitis. Finally, using similar disease activity metrics for children and adults with rare rheumatologic conditions will make it easier to collect accurate longterm data on disease activity and outcomes.

The field of pediatric vasculitis has benefited recently from many important advances. Formal validated classification criteria now exist for chronic vasculitis in children[22]. Our study demonstrates the potential use of the BVAS v.3 as a disease activity measure in children with ANCA-associated systemic vasculitis. A better assessment of BVAS will come with studying how well it correlates with changes in disease activity over time. The focus of further research should be to investigate the performance of BVAS v.3 prospectively along with other potential markers of disease activity over the course of the disease and across a broader spectrum of pediatric vasculitis diagnoses. With each subsequent step forward, the field of pediatric vasculitis draws closer to the possibility of comparative therapeutic trials, the potential to standardize therapy, and most importantly, the potential to significantly improve outcomes for children with these rare and life-threatening conditions.

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APPENDIX

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