Performance of the Birmingham Vasculitis Activity Score and Disease Extent Index in childhood vasculitides

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ABSTRACT

Objectives. *To evaluate the performance of the Birmingham Vasculitis Activity Score (BVAS) v3 and the Disease Extent Index (DEI) for the assessment of disease activity in 4 primary childhood (c-) systemic vasculitides.*

Methods. *Patients fulfilling the EULAR/PRINTO/PRES (Ankara) c-vasculitis classification criteria for Henoch-Schönlein purpura (HSP), childhood (c) polyarteritis nodosa (c-PAN), c-Wegener's granulomatosis (c-WG) and c-Takayasu arteritis (c-TA) with disease duration at the time of diagnosis ≤3 months were extracted from the PRINTO database. The performance of the BVAS and DEI were examined by assessing convergent validity, the pattern of disease involvement, and responsiveness. We also evaluated alternative unweighted scoring methods for both tools.*

Results. *The analysis set included 796 patients with 669 HSP, 80 c-PAN, 25 c-WG and 22 c-TA. The median age at diagnosis was 6.9 years (6.6–12) and median delay in making the diagnosis from the onset of signs/symptoms was 0.01 (0.003-0.027) years. A strong correlation was found between the BVAS and DEI (r_s=0.78) while correlation with the physician global assessment was moderate (r_s=0.48) with BVAS and poor with DEI (r_s=0.25). Both the BVAS and DEI sub-scores and total scores were able to descrive the disease involvement in the 4 childhood vasculitides. Responsiveness was large (>1.5) for both tools. The performance characteristics of the BVAS and DEI with the unweighted methods were comparable.*

Conclusion. *This study demonstrates that both the BVAS and DEI are valid tools for the assessment of the level of disease activity in a large cohort of childhood acute and chronic vasculitides.*

Introduction

The primary systemic vasculitides in children are clinically distinct diseases characterised by inflammation of the vessel wall without identifiable cause. The complexity of assessing disease activity or disease status in the vasculitides reflects the multi-systemic character of the pathologic manifestations of these illnesses (1).

Although recent series have documented an improvement in long-term outcome and survival of primary systemic vasculitis during childhood, clinical trials and long-term studies are lacking (2-7). This is mainly due to the low prevalence of the diseases, difficulties in the classification systems, as well as the lack of validated instruments to reliably assess disease activity and damage.

Recently, in Ankara, the European League Against Rheumatism (EULAR), the Paediatric Rheumatology International Trials Organisation (PRINTO) (8) and the Paediatric Rheumatology European Society (PRES) validated the classification criteria for the major primary systemic childhood vasculitides, namely Henoch-Schönlein purpura (HSP), childhood polyarteritis nodosa (c-PAN), c-Wegener's granulomatosis (c-WG), and c-Takayasu arteritis (c-TA)

(9, 10). For the assessment of disease activity, EULAR has recommended the use of the Birmingham Vasculitis Activity Score (BVAS) (11-13) and the Disease Extent Index (DEI) (14) for conducting clinical studies and/or clinical trials in systemic chronic vasculitis for adults; however, these tools have not been systematically used for studies in childhood vasculitis.

The primary objective of this *post hoc* study was to evaluate the performance of the BVAS and DEI for the evaluation of disease activity in acute and chronic childhood vasculitides. The secondary objective was to explore alternative simplified scoring systems for the BVAS and DEI.

Patients and methods

The PRINTO database (Fig. 1) contains data on children with age at diagnosis ≤18 years, diagnosed as HSP, c-PAN, c-WG, c-TA or other c-primary systemic vasculitis as previously described (9, 10). In brief, the database includes demographic data, clinical diagnosis and a comprehensive list of 70 signs/symptoms in 12 broad organs/systems, laboratory parameters, physician global assessment of disease activity on a 10 cm visual analogue scale (VAS), biopsy findings and imaging reports. Data have been collected by chart review, before or at the time of diagnosis and at least 3 months later (exact time not recorded). Items definitions were adapted from the BVAS glossary (11, 12, 15) to reflect paediatric specificities such a hypertension, haematuria, proteinuria, fall in creatinine clearance. For instance weight loss was defined in the original BVAS form as loss of dry body weight without dieting ≥2 kg however in our CRF we defined it more than or equivalent to 5% body weight.

For the purposes of this analysis we extracted all patients who fulfilled the HSP, c-PAN, c-WG and c-TA EULAR/PRINTO/PRES paediatric vasculitis classification criteria, with disease duration of ≤3 months at the time of diagnosis. Patients with a probable or definite diagnosis of cutaneous PAN, microscopic polyangiitis (just few patients), and unclassified vasculitis were excluded. Kawasaki disease the other major acute pediatric vasculitis was not part of the initial effort being studied by another group.

The study was approved by the ethics committee and consent obtained from parent(s) as required by the national law in each participating country.

BVAS and DEI tools

The BVAS was recently modified (version 3) and validated in adult patients with different forms of systemic vasculitis (12). This instrument is a 1-page form comprising 56 predefined items attributable to active vasculitis and grouped into 9 organ systems (general, cutaneous, mucous membranes/eyes, ears/nose/throat, chest, cardiovascular, abdominal, renal, nervous system, and other). Each item has 2 distinct scales (persistent or new/worse) with its own weight (from 1 to 9), and each of the 9 organ systems has its own maximum score (from 2 to 12). The score of each area is then summed up to give the total score. In addition there is a "persistent disease only"; this box is marked, only if every disease manifestation is attributable to persistent disease. If any of the items marked are new/worse, all items are weighted as new/worse. The score for BVAS may reach a maximum of 63 if there are new/worse items recorded and 33 if all items are scored as persistent.

The DEI (14) has been developed as a complementary measure to evaluate disease activity. The DEI is a 1-page form listing 11 predefined organ manifestations (ears/nose/throat and upper airways, inflammatory eye lesions, heart, lung and lower airway, kidney, gastrointestinal tract, peripheral nervous system, central nervous system, skin, arthralgias/arthritides, constitutional symptoms) with definitions of signs and symptoms that can be attributed to active vasculitis; manifestations not listed can also be scored if they are clearly attributable to active vasculitis. Each item, if positive, is scored as 2 with the exception of constitutional symptoms which are scored as 1. The total score for the DEI is from 0 to 21. There is no distinction between new, worse or persistent disease; however, previous activity or damage should not be counted.

Scoring of the BVAS and DEI using the PRINTO database

In order to obtain the total score of the BVAS and DEI we extracted all related items from the PRINTO database. For each item three Authors (ED, SO and PD) checked the corresponding items in the glossary used for the childhood vasculitis project (9, 9) and those present in the BVAS and DEI glossaries. In addition to calculate the scores as per the original instructions, we hypothesised that a simplified method (unweighted score) for the scoring calculation would have comparable properties. To test this hypothesis, we empirically chose to score dichotomously each item as yes/no (1 or 0) depending on presence or absence of the individual item. For the BVAS unweighted calculation we scored persistent disease and new/worse disease items equally. The total score resulted from the sum of all positive items, 0-56 for the BVAS and 0-11 for the DEI.

The total BVAS and DEI scores (original and unweighted) were automatically calculated, at the time of diagnosis and at least 3 months thereafter, using a computerised algorithm developed by the PRINTO webmaster and validated independently by a statistician (RG).

Performance characteristics

The evaluation of the performance characteristics was done by evaluating the following properties.

Feasibility or practicality of the measures was determined by addressing the percentage of missing values.

Convergent construct validity, which is a form of validation that seeks to examine whether the construct in question is related to other reference measures in a manner consistent with *a priori* prediction, was also investigated. As surrogate measures, we chose the physician's global assessment of the patient's overall disease activity, CRP and ESR. We calculated the Spearman's rank correlation (where a value of >0.7 was considered high, a value of 0.4 to 0.7 was moderate, and a value of <0.4 was low) (16). We predicted that the correlation of BVAS and DEI with the surrogate measure would be at least in the moderate range.

The issue of collinearity (or redundancy) of variables was investigated by means of Spearman's correlation coefficient; a coefficient ≥0.7 was considered to represent evidence of collinearity.

We then evaluated the ability of the BVAS and DEI sub-scores and total scores to describe the pattern of disease involvement (activity status) detected by the DEI sub-scores in the 4 disease groups. The purposes of this exercise was to evaluate if the BVAS and DEI contains items that are relevant for the evaluation of acute (HSP) and chronic vasculitides.

Responsiveness (sensitivity to change) was examined by determining the ability of each category of the scales to detect any clinically important change between the assessment done at the time of diagnosis and the second assessment after at least 3 months. It was calculated through the standardised response mean (SRM) calculated as the absolute mean change in score divided by the SD of that score; 95% confidence interval (95% CI) were also provided (17-19). An SRM value <0.5 is considered small, ≥0.5 <0.8 moderate, and values ≥ 0.8 represent large effect (20-22).

Statistics

Descriptive statistics were reported as medians and 1st, 3rd quartiles (1st; 3rd q), whereas categorical variables were reported as absolute frequencies and percentages. Laboratory values were standardised based on the normal values provided by each local laboratory as previously described (23). Comparison of frequencies were made by the chi-square or the Fisher's exact test, while the Mann-Whitney U-test was used for comparisons of medians. For multiple comparisons Bonferroni's correction was applied as appropriate. A non parametric analysis of variance (Kruskal-Wallis test) was employed for the ability to differentiate the 4 vasculitides, with the Dunn test used *post hoc*. There was no imputation for missing data.

Data were entered in an Access XP database and analysed with Excel XP (Microsoft), XLSTAT 6.1.9 Addinsoft, Statistica 6.0 (StatSoft, Inc), and Stata 7.0 (Stata Corporation).

Results

As shown in Figure 1 of the 1,399 patients available in the database, 940 (67%) fulfilled the EULAR/PRINTO/PRES c-vasculitides classification criteria (9, 10). A total of 796 (57%) patients with disease for ≤3 months at the time of diagnosis were included. When we compared the demographic characteristics between the included and excluded patients we did not find any statistically significant difference except for the age at onset for c-PAN patients (p<0.01).

The male to female ratio was 0.96:1. There were 669 (84%) HSP, 80 (10%) c-PAN, 25 (3%) c-WG, and 22 (3%) c-TA. The median age at diagnosis was 6.9 (6.6; 12) years and median delay in diagnosis from the onset of signs or symptoms was 0.01 (0.003; 0.03) years. Median age for onset of signs or symptoms were 6.6 years (5; 8.8), 9.4 (6.4; 12), 13.3 (10.8; 15.5) years and 12 (8.8; 14.5) years for the HSP, c-PAN, c-WG and c-TA, respectively.

Convergent validity and collinearity

Table I depicts the convergent validity and collinearity of the BVAS and DEI with the selected surrogate markers. The correlation with the physician global assessment of disease activity was moderate for the BVAS original and unweighted scores (0.48 and 0.53 respectively) and poor for the DEI original and unweighted, and with CRP and ESR.

As expected, the BVAS and DEI original score were highly collinear (redundant) with their respective unweighted scores (0.92 and 0.98, respectively). Collinearity was also observed between the BVAS and DEI with both scoring methods.

We then repeated the analysis for the 4 vasculitides separately, the correlations between the BVAS original and unweighted with the physician global assessment of disease activity remained moderate for HSP (N=669, 0.42-0.42). For the group of c-WG, c-PAN, c-TA taken separately the correlation with the physician global assessment of disease activity was poor with a trend toward better correlation for the BVAS unweighted scoring and for c-TA. In or-

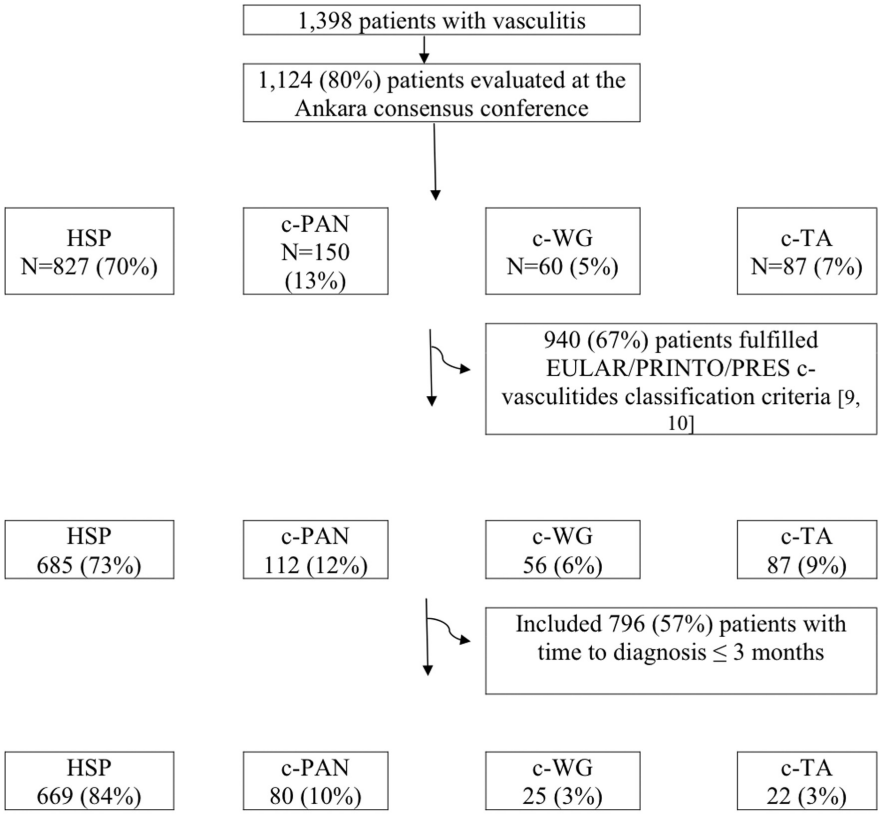

Fig. 1. Flow chart of the patients.

Table I. Spearman correlation coefficients for the evaluation of convergent validity and collinearity.

	Physician Global assessment of disease activity	BVAS	BVAS unweighted	DEI	DEI unweighted	CRP
BVAS original	0.48					
BVAS unweighted	0.53	0.92				
DEI original	0.25	0.78	0.73			
DEI unweighted	0.27	0.76	0.74	0.98		
CRP	0.34	0.34	0.43	0.18	0.21	
ESR	0.37	0.31	0.39	0.13	0.15	0.66

Table II. Pattern of disease involvement detected by the BVAS organ systems sub-scores in the 4 disease groups. Data are medians (1st; 3rd q).

	All patients n=796	HSP n=669	c-PAN n=80	c-WG n=25	c-TA n=22	*p*-value*
1. General	1 (1-3)	1 (1-3)	3 (2-3)	3 (2-3)	2 (2-3)	<0.0001
2. Cutaneous	2 (2-2)	2 (2-2)	4 (2-4)	2 (0-2)	0 (0-0)	<0.0001
3. Mucous membranes/eyes	0 (0-0)	0 (0-0)	0 (0-0)	2 (0-3)	0 (0-0)	<0.0001
4. Ears/nose/throat	0 (0-0)	0 (0-0)	0 (0-0)	4 (2-6)	0 (0-0)	<0.0001
5. Chest	0 (0-0)	0 (0-0)	0 (0-0)	6 (0-6)	0 (0-0)	<0.0001
6. Cardiovascular	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	4 (0-6)	<0.0001
7. Abdominal	6 (0-6)	6 (0-6)	6 (0-9)	0 (0-6)	0 (0-6)	<0.0001
8. Renal	0 (0-6)	0 (0-6)	4 (0-10)	10 (4-12)	4 (0-4)	<0.0001
9. Nervous system	0 (0-0)	0 (0-0)	3.5 (0-9)	0 (0-0)	0.5 (0-1)	<0.0001

*Kruskal-Wallis ANOVA with Dunn test as *post hoc*.

Table III. Pattern of disease involvement detected by the DEI sub-scores in the 4 disease groups. Data are medians (1st; 3rd q).

	All patients n=796	HSP n=669	c-PAN n=80	c-WG n=25	c-TA n=22	*p*-value*
1. Ears/nose/throat and upper airway	0 (0-0)	0 (0-0)	0 (0-0)	2 (2-2)	0 (0-0)	<0.0001
2. Inflammatory eye lesions	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	NS
3. Heart	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-2)	NS
4. Lung and lower airway	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-2)	0 (0-0)	<0.0001
5. Kidney	0 (0-2)	0 (0-2)	0 (0-2)	0 (0-2)	0 (0-0)	0.0007
6. Gastrointestinal tract	2 (0-2)	2 (0-2)	2 (0-2)	0 (0-2)	0 (0-2)	<0.0001
7. Peripheral nervous system	0 (0-0)	0 (0-0)	0 (0-2)	0 (0-0)	0 (0-0)	<0.0001
8. Central nervous system	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	NS
9. Skin	2 (2-2)	2 (2-2)	2 (0-2)	0 (0-2)	0 (0-0)	<0.0001
10. Arthralgias/arthritides	2 (2-2)	2 (2-2)	2 (2-2)	2 (0-2)	0 (0-2)	<0.0001
11. Constitutional symptoms	1 (0-1)	0 (0-1)	1 (0.5-1)	1 (1-1)	1 (1-1)	<0.0001

*Kruskal-Wallis ANOVA with Dunn test as *post hoc*. NS: non significant.

der to evaluate the existence of possible selection bias from the undue influence of the large sample of HSP patients, an acute form of vasculitis, the correlation table was also repeated without HSP patients and all correlations became poor (data not shown) with the exception of the correlation between BVAS and DEI which was ≥0.8.

Pattern of disease involvement as detected by the BVAS and DEI in the 4 childhood vasculitides

Tables II and III show the pattern of disease involvement for the 9 organ systems that compose the BVAS and the 11 items of the DEI. All 9 organ systems sub-scores are able to differentiate one vasculitis from the other (all *p*-values <0.0001). In particular for the BVAS (Table II) the active features within general, cutaneous, abdominal and renal organ systems are common in all 4 forms of vasculitis, while mucous membranes/eyes, ears/nose/throat, chest features are specific for c-WG, cardiovascular for c-TA, and nervous system for either c-PAN and c-TA.

Similarly, in Table III, for the corresponding 11 items of the DEI, 5 items (kidney, gastrointestinal tract, skin, constitutional symptoms and arthralgias/arthritis) are active features present in all 4 types of vasculitides. Ear/nose/throat, lung and lower airways are typically affected in c-WG and heart in c-TA. Inflammatory eye lesions and central nervous system show median values of 0 (0;0) for all 4 forms of vasculitis, indicating their rarity in these forms of childhood vasculitis.

The evaluation of disease activity in the 4 c-vasculitides for the BVAS and DEI plus the surrogate measures is reported in Table IV. All summary measures showed statistically significant ability to differentiate the 4 vasculitides (all *p*-values <0.0001). Higher disease activity scores were present for both original and unweighted BVAS and DEI scoring system for c-WG followed by c-PAN, c-TA and HSP. The same hierarchical order was observed for the physician global assessment of disease activity, for ESR and CRP (although there is a significant amount of missing data of 25% and 43%, respectively, particularly evident for HSP).

Responsiveness

Table V shows the responsiveness, as measured by the SRM, by comparing the disease activity status at the time of diagnosis (within 3 months from the disease onset) and at least 3 months thereafter. Both original and unweighted scoring system showed an excellent responsiveness with a larger effect (>2) for the DEI. Large effect ≥0.8 was shown also by the physician global assessment of disease activity and ESR while CRP responsiveness was small.

Discussion

The availability of new drugs and of adequate measures to assess response

Table IV. Evaluation of disease activity by the different tools in c-vasculitides. A non-parametric (Kruskal-Wallis) ANOVA with the Dunn test as post hoc test was performed. Data are medians (1st; 3rd q).

	n.	All patients 796	HSP 669	c-PAN 80	c-WG 25	c-TA 22	*p*-value
BVAS original	796	11 (8-17)	10 (7-15)	19.5 (12.5-25)	23 (19-29)	15 (11-20)	<0.0001
BVAS unweighted	796	4 (3-5)	4 (3-5)	7 (5-9)	10 (7-12)	4.5 (3-6)	<0.0001
DEI original	796	6 (5-7)	6 (5-7)	6.5 (5-9)	9 (7-9)	3 (2-5)	<0.0001
DEI unweighted	796	3 (3-4)	3 (3-4)	3.5 (3-5)	5 (4-5)	2 (1-3)	<0.0001
Physician Global assessment of disease activity	715	5 (3-7)	4 (2.5 - 6)	7 (7-8)	8.5 (8-9)	8 (7-8.5)	<0.0001
ESR	596	29 (14-52)	22 (12-37)	86 (53-115)	76.5 (58-108)	48 (40-72)	<0.0001
CRP	457	1.4 (0.5-4.3)	1 (0.5-2.2)	8.14 (4.5-16.4)	9.8 (5.4-16.4)	4.6 (2.2-8.5)	<0.0001

to therapy, such as the BVAS, has provided the clinical and methodological pre-requisite for an evidence-based treatment and management of adult vasculitides (5-7, 24-27). Progress in the management of childhood vasculitides requires parallel improvements in the ability to measure and record vasculitis activity in a uniform manner. This report describes the first study of BVAS and DEI for the evaluation of disease activity, and hence response to therapy, for the 4 systemic c-vasculitides in the largest paediatric vasculitis cohort of 796 recently diagnosed patients. This cohort closely mimics the type of population typically enrolled in a clinical trial where patients with uncontrolled disease activity are normally considered.

Because no objective markers are currently available to accurately quantify the level of disease activity as surrogate measures, we chose the physician's global assessment of the patient's overall disease activity and CRP and ESR. The correlation with the physician global assessment of disease activity was moderate in our series, similar to the data reported in the original BVAS paper by Luqmani *et al*. where the correlation was poor (11). However more recently the same group reported higher correlation between BVAS and the physician global assessment of disease activity (0.91) (12). The lower correlation with the physician global assessment of disease activity in our series is probably related to the retrospective nature of the PRINTO database that hampered a direct evaluation of the disease activity status of the patients; in addition another difference was related to a predominance of HSP patient in our series and of Wegener patients in the population reported by Luqmani *et al*. (12). The present study demonstrated that the BVAS and DEI correlated poorly with ESR and CRP and the correlation did not improve when the analysis was repeated without the HSP patients that are known to have normal or low level of inflammation. The correlation with CRP level in the recent paper by Luqmani *et al*. (12, 28) was moderate to poor (0.43 and 0.18 respectively) probably due to an over-representation of WG patients with respect to our case series. On the other hand, there was a good correlation among these two instruments suggesting that the simplest DEI might be interchangeably used as an alternative measure to assess the disease activity in vasculitis at least in children (14, 29). However, compared to BVAS, the DEI lacks the fine details to document abnormalities.

Table V. Responsiveness of all activity instruments. All values are median (1st; 3rd q).

	n.	3 months before or at the time of diagnosis	3 months after diagnosis	SRM (95% CI)
BVAS original	796	11 (8-17)	0 (0-0)	1.63 (1.53-1.63)
BVAS unweighted	796	4 (3-5)	0 (0-0)	1.61 (1.47-1.74)
DEI original	796	6 (5-7)	0 (0-2)	2.37 (2.18-2.56)
DEI unweighted	796	3 (3-4)	0 (0-0)	2.30 (2.10-2.50)
Physician Global assessment of disease activity	507	4 (3 - 7)	0 (0-2)	1.3 (1.18-1.46)
ESR	328	38 (19-63)	15 (9-20)	0.85 (0.76-0.94)
CRP	267	1.84 (0.7-6.3)	1 (0.5-5)	0.03 (-0.1-0.16)

While instruments to assess disease activity can be specific for each type of vasculitis, an ideal tool, besides being simple, should have also the ability to differentiate between different disease status (*e.g*. active *vs*. remission, low grade disease activity, change over time) and describe the disease activity pattern of one form of vasculitis from another. Our data suggest that indeed both the tools were able to differentiate between the 4 childhood acute and chronic vasculitides either at the level of the 9 organ systems of BVAS or the 11 organ manifestations of the DEI.

An important parameter for the applicability of a tool in a clinical trial is the ability of the instrument to evaluate change over time to estimate the effect of treatment. Our database contains disease activity parameters at the time of diagnosis, within 3 months from onset, as well as at least 3 months later. Even if information on drug treatment were not part of the case report forms we hypothesised that treatment was given to the patients and that the effect could have been observed in the following months; the observed changes were presumably due to treatment of chronic vasculitides (c-PAN, c-WG and c-TA) while for HSP the change was primary related to the natural history of the disease which is self-limiting without any therapy in the majority of cases. Our results confirmed this hypothesis and showed an important improvement as evaluated by the decrease in the BVAS and DEI score as well as in the physi-

cian global assessment of disease activity and ESR and CRP. With the SRM, a large effect was observed for the DEI and BVAS, but also for the physician global assessment of disease activity while ESR and CRP responsiveness was small. The small effect observed for CRP was also found by Luqmani *et al*. (12) who did not find a relationship between the magnitudes of change for the BVAS and the CRP levels. Similar to our study recent reports on adult patients with TA indicated that most of the 11 organ systems in BVAS were not involved in adult TA (30-32).

The use of questionnaires for the assessment of disease status in routine clinical practice by busy health professionals is always hampered by the length of the tool and the complexity in the scoring system. The novelty of this study is that we propose an alternative simpler method to score both the BVAS and DEI while maintaining the validity of the instruments. In particular the 2 scoring methods (original and unweighted score) had a Spearman correlation higher than 0.9 (redundancy) and maintained the ability to differentiate between different diseases as well as the sensitivity to change. The use of BVAS in children is hampered by the differences in both the spectrum of active disease manifestations as well as in some of the item definitions; this problem was overcome by some modifications of the BVAS glossary to take into account paediatric specificities.

As in adults, differentiating the disease activity from the effects of chronic damage, dysfunction and infection is also important in children to avoid inappropriate use of immunosuppressive and toxic drugs (33). There is no single clinical, serologic or radiological marker that can assess objectively the level of disease activity. Therefore the validation of the BVAS and DEI has to be considered the first step for the proper evaluation of disease activity. The lack of objective indicators should prompt the community to evaluate disease activity, and hence response to therapy, from different perspective such as a questionnaire for the quantification of the disease activity level, evaluation by either health professional and parents or children themselves, as well as the quantification of physical disability and health related quality of life. A multidomain approach for the assessment of disease activity and damage indeed has been proven to be the best way to follow patients with the other major paediatric rheumatic diseases and their adult counterparts (23, 34-44).

In conclusion, our study demonstrated that the BVAS and DEI have adequate convergent validity, ability to differentiate among different types of childhood vasculitis, and good responsiveness to change. Our results also suggest that an unweighted scoring method may be a useful alternative especially for clinical settings. We speculate that further specific modifications to the adult instruments would enhance their use in children and a project is currently on going to validate a paediatric version of BVAS.

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