Optimisation of vasculitis disease assessments in clinical trials, clinical care and long-term databases

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Received on September 20, 2014; accepted in revised form on September 27, 2014.

Clin Exp Rheumatol 2014; 32 (Suppl. 85): S118-S125.

Key words: vasculitis, patient outcome assessment, clinical trials, databases, registries

Funding: NIHR Rare Diseases Translational Research Collaboration and the Oxford NIHR Musculoskeletal Biomedical Research Unit, University of Oxford provide funding for RUDY and C. Ponte's clinical research fellowship.
Competing interests: none declared.

ABSTRACT

The systemic vasculitides are a group of rare, chronic, relapsing, but often progressive inflammatory conditions. They are associated with a significant burden of morbidity both due to scarring from the disease itself and as a consequence of treatment with glucocorticoids and other potent immunosuppressive agents. Careful assessment of disease activity is critical to guide appropriate use of these potentially toxic therapies. It is also important to differentiate features of active disease from those attributable to damage, which will not respond to immunosuppression. As these are chronic complex conditions, the impact on a patient's functional ability and quality of life are also important considerations. Given the lack of a reliable biomarker for assessment of disease activity or damage in systemic vasculitis, clinical tools developed and validated for use initially in clinically trials are key outcome measures in the evaluation of these patients. While the conduct of randomised clinical trials in vasculitis has been significantly enhanced by the development and use of validated outcome measures, regular use of validated disease activity and damage measurements as part of routine care offers a structured approach, which can serve as the basis of justifying treatment decisions. The authors review the concepts of clinical assessment tools used in the evaluation of patients with systemic vasculitis in the setting of clinical practice, clinical trials and long term databases with particular emphasis on disease activity, damage, prognosis and function.

Introduction

Systemic vasculitides are a group of multisystemic diseases with diverse organ manifestations, severity, morbidity and outcomes. Although mortality has significantly decreased in recent years (1), the total burden of the disease remains high, comprising relapsing and refractory disease (2-4), drug toxicity, infections, development or exacerbation of comorbid conditions (*e.g.* cardiovascular disease, diabetes, osteoporosis or malignancies), and other forms of damage related to the disease or its treatment (5-8). In addition, the patient's ability to function and manage everyday life can be significantly impaired in vasculitis (9, 10). Disease assessment should target four main domains of the condition: activity, damage, prognosis and functional outcome (11). Table I provides an overview of the clinical tools available in these domains.

Laboratory tests can aid in diagnosis and management of certain patients with vasculitis, but no serological markers are available as a *gold standard* to assess disease activity or determine damage. ESR and CRP are not specific for vasculitis, antineutrophil cytoplasmic antibody (ANCA) titres often fail to predict relapse and imaging techniques have low value in small vessel vasculitis. The main outcome measures used for monitoring of vasculitis are based on comprehensive clinical checklists that were originally developed and validated for clinical trials. With the advent of biological, mechanism-based treatment in vasculitis (*e.g.* Rituximab in ANCA associated vasculitis), where there is a recognised need for accurate disease assessment to guide treatment decisions, and with the significant improvement in survival, where controlling damage is now becoming the main concern, the use of structured clinical assessment is becoming mandatory to record disease course in daily practice and long term databases. We will review the concepts of clinical assessment of systemic vasculitis in these three settings (Fig. 1).

Clinical trials

In the last decade the number and quality of clinical trials focused on vasculitis

Table I. Summary of vasculitis assessment tools.

Assessment Tool	Overview
ACTIVITY	
Physician Global Assessment (PhGA) (12, 13)	- Global evaluation by the treating physician of the overall disease activity at the time of assessment using a 10cm visual analogue scale or a 5-point Likert Scale.
Birmingham Vasculitis Activity Score (BVAS v1-3) (14-16)	- 9 weighted organ systems based on expert consensus - Symptoms and signs of organ involvement recorded if attributable to current/active vasculitis - Based on intention to treat
BVAS/WG (17)	- Addition of disease items more specific for GPA (Wegener's) - Only validated for use in GPA
Disease Extent Index (DEI) (18)	- Scoring based on signs, symptoms and diagnostic procedures - 10 weighted organ based systems + constitutional symptoms - Developed in GPA
Japanese vasculitis activity score (19)	- Composite prognostic outcome measure including creatinine, CRP, age and the presence or absence of lung involvement - Only for use in MPA - Predicts mortality
Paediatric Vasculitis Activity Score (PVAS) (20)	- Based on modification of BVAS v3 - A number of items redefined/ added for use in a paediatric population - Validated
Disease Extent Index Takayasu (DEI Tak) (21)	- Derived from BVAS - Assessment of disease activity - 59 items, 11 organ based systems - Clinical findings only, no imaging required
Indian Takayasu Clinical Activity Score (ITAS 2010) (22)	- Original ITAS derived from disease manifestations in DEI Tak - ITAS 2010, 44 items with 7 key items weighted - Validated
Vasculitis Activity Index (VAI) (23)*	- 9 rating scales for separate organ system involvement - Laboratory tests used
Groningen Index (24)*	- Scoring based on clinical signs and histology - Developed in GPA
**The VAI & Groningen Index have been superseded by BVAS*	
DAMAGE	
Vasculitis Damage Index (VDI) (25)	- Measures any chronic damage/scarring that has occurred since the onset of vasculitis, irrespective of the aetiology of that damage - 64 items in 11 organ systems - Non-weighted - Validated in different types of vasculitis - Currently undergoing revision
Paediatric VDI	- Paediatric modification of adult version - In development
Combined Damage Assessment (CDA) (26)	- 135 non-weighted items in 17 organ-based systems - Graded according to severity - Has not outperformed VDI; more sensitive but complex and has decreased reliability
AVV Instrument of Damage (AVID) (27)	- Specific for AAV - Left and Right sides are scored separately for eyes and ears - Not validated
Takayasu Damage Score (TADS) (28)	- 42 items in 7 systems - Scoring of DEI Tak features present for 6 months
FUNCTION & QUALITY OF LIFE (QoL)	
Health Assessment Questionnaires (HAQ, HAQII, MDHAQ) (29-31)	- Designed initially for use in Rheumatoid Arthritis - Measure of physical function and disability
Short Form 36 (SF-36) (32)	- Generic assessment of function, health and wellbeing - 36 questions across 8 health domains including physical function, role limitations, energy/fatigue, emotional well-being, social functioning, pain and general health
EuroQol 5D (EQ-5D) (33)	- Generic measure of health status - 5 dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression
AVQoL /AAV PRO	- Quality of life assessment score for AAV - In development
Hospital Anxiety and Depression Scale (HADS) (34)	- 14 items, scored 0-3 - Designed to determine levels of anxiety , depression or emotional distress amongst patients who are being treated for a wide variety of clinical problems
PROGNOSTIC	
Five Factor Score (FFS) (35, 36)	- The original FFS referred to EGPA, MPA and PAN. Revised version was also validated in GPA and current five factors (each +1 point) are following: age >65, renal impairment, cardiac insufficiency, GI tract involvement, and absence of ENT symptoms - FFS =0; 5 year mortality 9% - FFS =1; 5 year mortality 21% - FFS ≥ 2; 5 year mortality 40%
Vasculitis Damage Index (VDI) (25)	- Higher VDI scores (≥5) prior to starting immunosuppression and at 6 months have been shown to predict higher mortality

ANCA: Antineutrophil cyytoplasm antibody; AAV. ANCA-associated vasculitis; CRP: C-reactive protein; EGPA: Eosinophilic granulomatosis with polyangitiis; ENT: Ear, nose and throat; GI: Gastrointestinal; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; PAN: Polyarteritis nodosa.

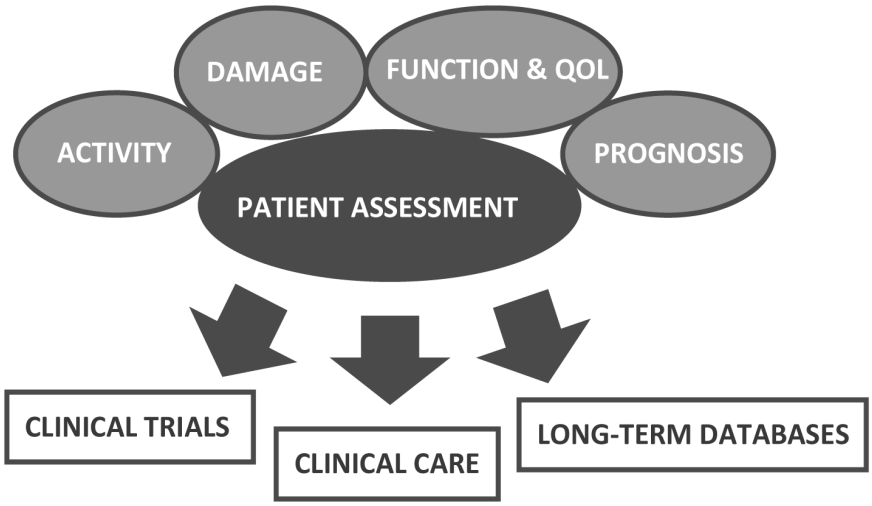

Fig. 1. Disease assessment domains in clinical trials, daily practice and long term databases.

have been increasing, accompanied by the development and validation of new disease assessment tools (37). As a result of international collaboration, there have been a number of randomised clinical trials (RCT) for several types of vasculitis, particularly ANCA-associated vasculitis (AAV), which have changed clinical care in vasculitis and also subsequently provided the opportunity to improve and validate reliable outcome measures for these diseases (11).

The Outcome Measures in Rheumatology (OMERACT) Vasculitis Working Group, formed in 2004, has brought together different investigative groups to establish research agendas and define core sets of outcome measurements considered crucial to be used in clinical trials (38, 39). In AAV, the approved core set includes validated measures of disease activity (3 versions of the Birmingham Vasculitis Activity Score), damage (Vasculitis Damage Index), patient-reported outcome (Short Form-36) and death (Fig. 2). A vasculitis disease-specific patient-reported outcome (PRO) for AAV is under development and is scheduled for completion and validation by January 2015, so that it can be considered for addition to this AAV core set. Additional methods of disease assessment, such as the use of novel biomarkers, may also be added in the future. In Table II we summarise the most recent RCTs in AAV vasculitis, in which clinical tools used to define disease states, damage and function.

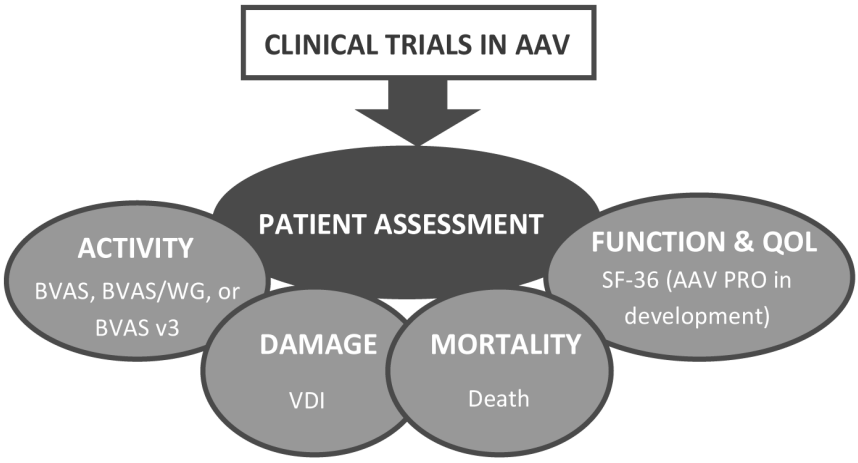

Fig. 2. OMERACT core set of domains and outcome measures for clinical trials in AAV.
AAV: ANCA-associated vasculitis; BVAS: Birmingham Vasculitis Activity Score; BVAS/WG: BVAS for Wegener's granulomatosis; PRO: Patient-reported outcomes; SF-36: Medical Outcome Study Short-Form 36 survey; VDI: Vasculitis Damage Index.

After success in AAV, the OMERACT group started to focus on the development of a core set of outcomes measures in large-vessel vasculitis (LVV) (40). However, the literature review has shown that there are still no widely accepted outcome tools for disease assessment in LVV. Monitoring response to therapy through imaging (*e.g.* ultrasound) is commonly used in clinical care, but still needs a validated and standard approach to be used in research. The Indian Takayasu Clinical Activity Score (ITAS2010) (22) is a simple tool, fully developed and validated for disease assessment in Takayasu using data from Indian patients, but further studies in patients with a wider ethnic and regional background are required before it can be considered a standard tool for clinical research in TAK (41). A Delphi exercise with investigators from different countries is on the research agenda to establish the intended core set of validated outcome measures in LVV for clinical trials.

In addition, in Behçet's disease there are no standardised outcome measures accepted for randomised controlled trials (RCTs) (42). A systematic literature review has been performed and the OMERACT working group are planning a Delphi exercise comprising the opinion of investigators from different countries and medical specialities to reach consensus on outcomes of interest in this disease.

Clinical care

The vasculitides are a complex set of conditions and therefore the way to assess them in daily practice is necessarily challenging and complex. In addition to patients' clinical symptoms and signs, physicians tend to rely on inflammatory markers, such as CRP and ESR, to monitor their disease activity and response to therapy; however, although they are useful additional tests, they are affected by other causes, especially infection, which may mimic vasculitis or co-exist in patients with established

Table II. Overview of the clinical assessment tools used in randomised controlled trials of AAV.

		CLINICAL ASSESSMENT TOOL USED	TRIAL
DISEASE ACTIVITY	**To define remission**		
	Total remission	No new/worse BVAS items or ≤1 persistent item	CYCAZAREM, CYCLOPS, NORAM
		BVAS= 0	BREVAS#*, IMPROVE LEM, MAINRITSAN MYCYC, REMAIN# RITUXVAS, SPARROW#* WEGENT
		DEI=0	LEM
		BVAS/WG=0	PEXIVAS#, RAVE RITAZAREM#*, WGET
	Partial remission	BVAS/DEI stable for ≥3 months	LEM**
	To define relapse		
	Relapse	BVAS/WG ≥1	RAVE, WGET
		BVAS/WG ≥1 major item or ≥3 minor items	RITAZAREM#
		BVAS ≥1	RITUXVAS, WEGENT
		≥1 major BVAS item or BVAS >6	BREVAS#
	Major relapse	≥1 major BVAS item	BREVAS#, CYCAZAREM CYCLOPS, MYCYC
	Minor relapse	≥3 minor BVAS items	CYCAZAREM, CYCLOPS MYCYC
	To define response to treatment		
	Refractory disease	BVAS ≥1 at 6 weeks	RITUXVAS
	Treatment response	≥50% reduction in BVAS from baseline	IVIG for persistent AAV MAINRITSAN
	Treatment failure	New organ involvement defined by original FFS ≥1	MAINRITSAN
DAMAGE	**To assess damage accrual**		
	Secondary outcome measure	VDI	CHUSPAN2#, CLEAR# CYCAZAREM, CYCLOPS IMPROVE, MAINRITSAN MEPEX, MYCYC NORAM, RAVE REMAIN#, RITUXVAS SPARROW#, WGET
		CDA	PEXIVAS#, RITAZAREM#
FUNCTION & QoL	**To assess patient-reported outcomes**		
	Secondary outcome measure	SF-36	BREVAS#, CHUSPAN2 CYCAZAREM, LEM MAINRITSAN, MEPEX MYCYC, NORAM PEXIVAS#, RAVE RITAZAREM#, RITUXVAS SPARROW#, WGET
		HAQ	CHUSPAN2, MAINRITSAN
		EQ5D	RITAZAREM#1

#ongoing trials; *with stable prednisone dose of ≤ 10 mg/day; **along with improvement in disease activity.

BREVAS (46): belimumab + azathioprine vs azathioprine + placebo (maintenance); CHUSPAN2 (59): corticosteroid +azathioprine *vs*. corticosteroid + placebo (induction); CLEAR (60): C5a receptor inhibitor *vs*. placebo (induction); CYCAZAREM (43): cyclophosphamide *vs*. azathioprine (maintenance); CYCLOPS (44): cyclophosphamide IV *vs*. oral (induction); IMPROVE (47): mycophenolate mofetil *vs*. azathioprine (maintenance); LEM (48): leflunomide *vs*. methotrexate (maintenance); MAINRITSAN (49): rituximab *vs*. azathioprine (maintenance); MEPEX (61): plasma exchange vs high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis; MYCYC (50): mycophenolate mofetil *vs*. cyclophosphamide (induction); NORAM (45): methotrexate *vs*. cyclophosphamide (induction); PEXIVAS (55): plasma exchange *vs*. standard treatment (induction); RAVE (56): rituximab *vs*. cyclophosphamide (induction); REMAIN (51): long-term *vs*. short-term azathioprine (maintenance); RITAZAREM (57): rituximab *vs*. azathioprine (maintenance); RITUXVAS (52): rituximab *vs*. cyclophosphamide (induction); SPARROW (53): gusperimus + glucocorticoids *vs*. standard treatment + glucocorticoids (induction); WEGENT (54): azathioprine *vs*. methotrexate (maintenance); WGET (4): etanercept *vs*. standard therapy (induction).

vasculitis. In AAV, ANCA titres have not proved to be valuable in predicting relapse and rising titres may occur in up to 40% of patients who do not subsequently demonstrate any change in clinical features to suggest reactivation of disease (8, 62). Emerging new markers elevated in severe active AAV, such as CXCL13, MMP-3 and TIMP-1, could potentially be helpful in assessment of disease activity and prognosis in the future (63). In LVV, raised serum IL-6 levels have been recognised in patients with active giant cell arteritis and Takayasu, however, its clinical usefulness as a biomarker is yet to be established (64-66). Imaging modalities, which can guide treatment decisions in LVV, such as ultrasound, MRA or PET-CT, are not yet validated and have no role in assessment of disease in small vessel vasculitis.

Given there are no universally applicable biomarkers to assess disease activity or determine chronic sequelae in all patients with most forms of vasculitis, clinical tools play a very important role in the clinical practice setting. Their regular use as part of routine care offers a structured approach which can guide treatment decisions. In the recent British Society of Rheumatology (BSR) guidelines for the management of ANCA-associated vasculitis (67) BVAS is used to define patients' disease states (remission, major/minor relapse, active or refractory disease), and therefore treatment requirements, especially important when justifying the introduction of biologic treatment (*e.g*. Rituximab). In addition, BVAS has capacity to provide clinicians with a useful checklist to help them remember the most common manifestations of vasculitis when assessing patients with suspected or diagnosed disease.

In some countries, such as Germany, there are financial incentives to health care providers for use of structured assessment in rheumatic diseases, including BVAS in vasculitis. In keeping with other rheumatic diseases, a 0–100 mm visual analogue scale of physician's global assessment (PhGA) has been used in granulomatosis with polyangiitis (GPA) (68). However, it failed to correlate well with BVAS when both

were performed independently (14). Additionally, a patient-based disease measure, also using a 0–100 mm visual analogue scale (PtGA: Patient global assessment), has been developed to overcome the issue of BVAS being only based on physician's judgment, but solely showed modest correlation with other outcome measures (13). In assessment of damage, VDI items are recorded cumulatively from the onset of vasculitis and do not discriminate between the effects of previous disease activity, treatment toxicity or co-existing comorbidities. Given the reduction in mortality in vasculitis it is very important to record the presence of damage and to take it into account when managing patients in daily practice, especially to adjust treatment according to individual needs (*e.g.* add a steroid sparing agent in patients who develop diabetes, high blood pressure or cataracts) or to avoid over treatment (*e.g.* to avoid increasing immunosuppression in a patient who has stable chronic kidney impairment).

As in all rheumatic diseases, tools in vasculitis that were developed for clinical trials and specialised centres, are yet to be fully transposed from research to the clinical setting. The vasculitides are particularly problematic, given they comprise a heterogeneous group of diseases (managed by a variety of different specialists) with different manifestations and severity, making it difficult to have a simplified assessment tool, quickly applicable in routine care. Like SLEDAI for Systemic Lupus Erythematosus, BVAS is the most widely accepted tool for disease activity assessment in the clinical setting. It includes most of the different features seen in vasculitis. It is validated for small and medium-vessel vasculitis, but it has been applied to other disease categories such as LVV (69) or cryoglobulinaemic vasculitis (70).

VDI is the main tool available to assess damage in vasculitis. One of the key issues to encourage wider use of both these tools is to ensure proper training. BVAS and VDI online training are now available (71) (www.bvasvdi.org) for all clinicians involved in the care of patients with vasculitis. Serial disease assessment using these instruments in clinic will provide physicians with quantitative and qualitative scores of the patient's condition. In addition, use of structured assessments should raise greater awareness of clinical research opportunities such as research registries and clinical trials. Figure 3 proposes an approach to standard assessment in clinical practice.

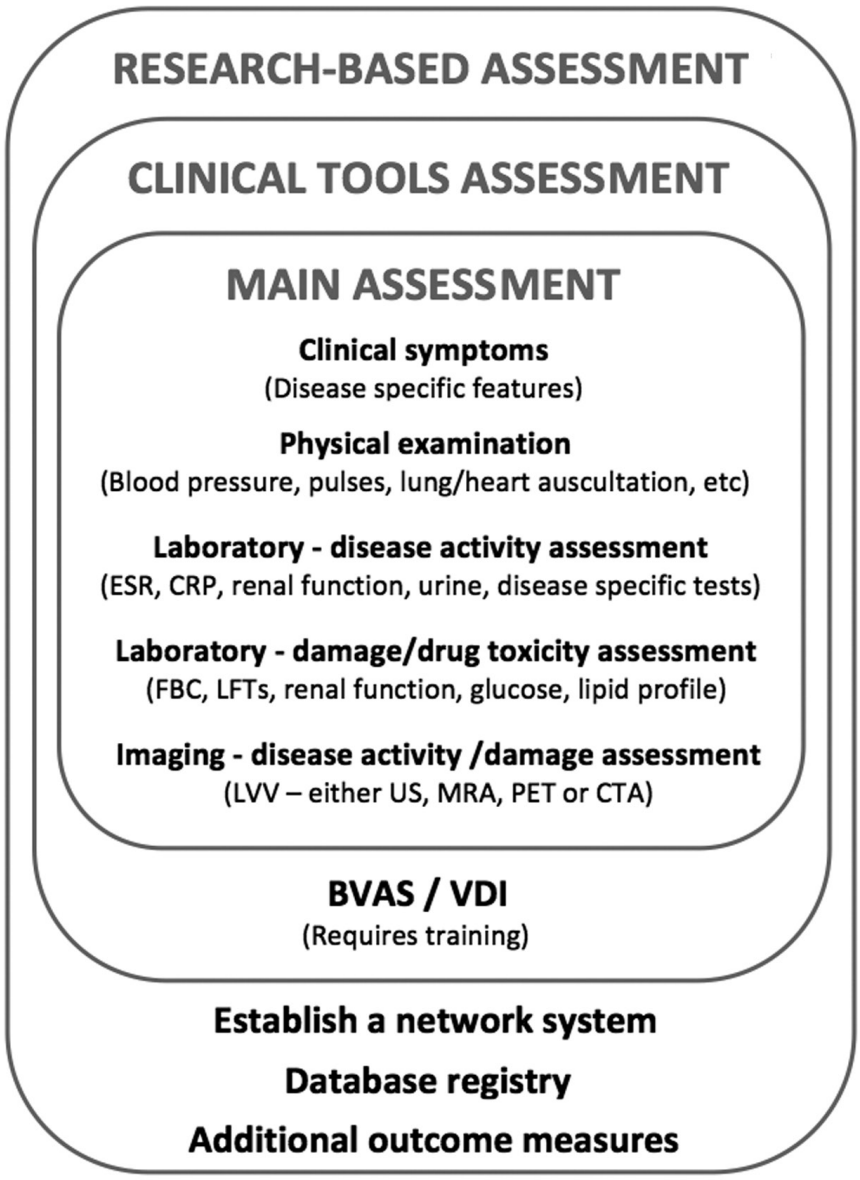

Fig. 3. Disease assessment in clinical practice.
BVAS: Birmingham Vasculitis Activity Score; CRP: C-reactive protein; CTA: Computed tomography angiography; ESR: Erythrocyte sedimentation rate; FBC: Full blood count; LFTs: Liver function tests; LVV: Large-vessel vasculitis; MRA: Magnetic resonance angiography; PET: Positron emission tomography; US: Ultrasound; VDI: Vasculitis Damage Index.

Long-term databases

The increasing number of clinical trials in vasculitis, new therapeutic options (albeit with potential side effects), and the wide variety of clinical manifestations in a group of relatively rare diseases, has led to the development of disease registries in vasculitis. Most of the existing registries are intended solely for research. Structured clinical information from routine care is recorded in the database. The UKIVAS registry is an example of a research database with clinical information on over 1000 vasculitis patients collected from a number of centres around the UK and Ireland. Its aim is to archive

longitudinal clinical data to enable identification of cohorts for potential recruitment to clinical trials and biomarker evaluation studies (72).

RUDY is a recent UK research registry for rare bone diseases and vasculitis, linked with UKIVAS, with a strong emphasis on patients' self-reported outcomes (https://research.ndorms.ox.ac.uk/rudy/). Similar to UKIVAS, the Glomerular Disease Collaborative Network (GDCN) inception cohort, from the southeastern USA, includes a large number of vasculitis patients with therapeutic interventions and frequency of clinical evaluations not determined by protocol; however, patients' selection is less broad and mainly comprises new cases of AAV with biopsy-proven renal involvement (73-76).

By contrast, Reuma.pt/vasculitis in Portugal is designed to allow clinicians to be able to record clinical data and adverse effects of treatment while at the outpatient clinic (77, 78). This different type of registry enables a structured approach to be adopted in clinical practice, providing an opportunity to record the most important outcome measures to characterise the natural history of vasculitis.

Long-term observational cohorts of vasculitis patients recruited from clinical trials and enrolled into registries provide an opportunity to search for biomarkers, study the natural course of the disease and determine long term outcomes. The medical community has worked towards this aim and has established large collaborative networks (79). The European Vasculitis Study Group (EUVAS), currently known as the European Vasculitis Society, is an open collaboration of clinicians interested in research and education in vasculitis that oversees multicentre RCTs in patients with GPA and MPA (5). Long-term follow up of patients participating in EUVAS clinical trials showed that higher BVAS scores were associated with higher mortality in 5 years. In the first year infection (48%) and active vasculitis (19%) were the major causes of death and thereafter cardiovascular disease (26%), malignancy (22%) and infection (20%) (1). VDI analysis of the same cohort (of more than 500 patients) revealed that over a 7-year follow-up around one-third of patients had ≥5 items of damage across a variety of organs and systems (5). Risk factors such as old age, poor renal function, high cumulative doses of glucocorticoids, high disease activity and disease relapse were identified has being associated with damage accrual (80). Selective analysis of BVAS and VDI items allowed the study of the incidence and prevalence of peripheral neuropathy in vasculitis and the creation of a cardiovascular risk model in AAV (81, 82), proving that individual components of clinical assessment instruments are valuable predictor variables for long term outcomes of vasculitis. Other well-established vasculitis consortia include the French Vasculitis Study Group (FVSG), Italian Vasculitis Study Group (IVSG), and the Vasculitis Clinical Research Consortium (VCRC). Although they function independently, their real value lies in the increasingly cross-collaborative projects, which has significantly improved our knowledge in vasculitis.

It is important that all the newly developing databases should share a core set of assessments equal in all registries; however, given the variety of existing databases, this can be challenging. In order to be able to continue strong international collaboration, providing robust data on long term outcomes in vasculitis; at a minimum, databases should have a uniform structure with compatible datasets, including standardized demographics, diagnosis, clinical features, medications and side effects, and clinical assessment tools.

Conclusion

Patients with vasculitis are a complex group in need of careful systemic evaluation to accurately assess disease activity, severity, damage and prognosis, as well as the effects on physical function and quality of life.

In clinical practice, tools to evaluate disease activity/damage are reliable if used by trained assessors and can be used to guide treatment decisions. Funding agencies are increasingly mandating formal documentation of disease status for patients treated with expensive and potentially toxic therapies. Online training is available for BVAS & VDI, the two most widely used assessments of disease activity and damage, both of which can easily be incorporated into routine clinical practice.

Long-term databases of patients with systemic vasculitis have been established; many based on international collaborations. Included in their key objectives are the development and validation of new outcome measures for use in systemic vasculitis and the re-evaluation of existing measures. They also provide an opportunity to search for potential biomarkers and study long-term outcomes. Ideally all databases in systemic vasculitis would share identical core sets of assessments to facilitate comparison between databases, thus promoting international collaborative efforts. Along with the development of prospective multicentre registries for vasculitis, patients should be considered for inclusion in therapeutic RCTs, thereby allowing clinicians accumulate experience in both the management and clinical assessment in these rare heterogeneous diseases.

The comprehensive set of validated clinical tools outlined in this article, used to assess disease states and predict outcomes, are strongly recommended for use in clinical trials, long-term databases and increasingly in clinical practice.

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