THE DIAGNOSIS, ASSESSMENT AND OUTCOMES OF PRIMARY SYSTEMIC VASCULITIS

By

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For my father

Bhikhubhai Ratilal Mukhtyar

April 1, 1931 – March 7,1985

&

Bina, Aanya, and Sasha with love

Abstract

We have created definitions for ultrasonographic abnormalities of Giant Cell Arteritis. The 'halo' sign is a '*homogenous, hypoechoic wall thickening, well delineated towards the luminal side, visible both in longitudinal and transverse planes, most commonly concentric in transverse scans.'* At the superficial temporal artery, the interobserver reliability in acquired and dynamic images has a κ = 0.87 and 0.60 respectively; the intraobserver reliability in acquired images and live exercises has a κ = 0.88 and 0.71 respectively. Ultrasonography is more reliable (κ = 0.8) than temporal artery biopsy (κ = 0.4) when compared against physician verified diagnosis at 100-week follow-up. Ultrasonography of 25 patients may be enough for service validation if audited against biopsy and long-term outcomes.

Activity and Damage form the twin sides of vasculitis assessment. We have validated the Birmingham Vasculitis Activity Score v3 in two separate studies with convergent validity against treatment decision (ρ = 0.54) and excellent interobserver reliability (ICC = 0.996). A new Combined Damage Assessment index had lower interobserver (ICC = 0.78) and intraobserver reliability (ICC = 0.87) vs the Vasculitis Damage Index (ICC = 0.94 and 0.92 respectively).

Granulomatosis with Polyangiitis, Microscopic Polyangiitis and Eosinophilic Granulomatosis with Polyangiitis have remission rates of 30%-93%, 75%-89% and 81%-91% respectively. The 5-year survival is 74%-91%, 45%-76% and 60%-97% respectively. At diagnosis, the quality of life as measured by the Short Form – 36 is worse than normative data. Older age and neurologic involvement at baseline are associated with lower physical composite scores.

My work has resulted in improvements in the diagnosis of Giant Cell Arteritis, assessment of primary systemic vasculitis and understanding outcomes in Antineutrophil Cytoplasm Antibody associated vasculitis. They have also informed the research agenda for further developments in the field.

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List of Abbreviations

AAV	ANCA Associated Vasculitis
ANCA	Anti Neutrophil Cytoplasm Antibody
cANCA	cytoplasmic ANCA
pANCA	perinuclear ANCA
MPO ANCA	myeloperoxidase ANCA
PR3 ANCA	proteinase 3 ANCA
BDCA	Behçet's Disease Current Activity
BVAS	Birmingham Vasculitis Activity Score
CDA	Combined Damage Assessment
CI	Confidence Interval
CRP	C-Reactive Protein
CT	Computed tomography
EGPA	Eosinophilic Granulomatosis with PolyAngiitis
ELISA	Enzyme Linked Immunosorbent Assay
EULAR	European League Against Rheumatism
EUVAS	European Vasculitis Study Group
FDG	Flurodeoxyglucose

GBM	Glomerular Basement Membrane
GCA	Giant Cell Arteritis
GPA	Granulomatosis with PolyAngiitis
ICC	Intraclass Correlation Coefficient
IgA	Immunoglobulin A
MPA	Microscopic PolyAngiitis
MR	Magnetic Resonance
OMERACT	Outcome MEasures in Rheumatoid Arthritis Clinical Trials
PAN	PolyArteritis Nodosa
PET	Positron Emission Tomography
PGA	Physician Global Assessment
PMR	PolyMyalgia Rheumatica
QOL	Quality of Life
SD	Standard deviation
TAB	Temporal Artery Biopsy
VAI	Vasculitis Activity Index
VDI	Vasculitis Damage Index

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Chapter 1 The diagnosis, assessment, and outcomes of primary systemic vasculitis: a narrative review

Introduction

The primary systemic vasculitides are a group of rare conditions that produce inflammation of blood vessels. Depending upon the calibre of the blood vessel affected, they have been divided into 'Large', 'Medium' and 'Small' vessel vasculitis (1). In this context, large-sized vessels are those that are present outside an organ, medium-sized vessels are macroscopic intra-organ vessels, and small-sized vessels are microscopic and always contained in an organ. The large vessel vasculitides are Takayasu arteritis and Giant Cell Arteritis (GCA). The medium vessel vasculitides are Kawasaki disease and Polyarteritis Nodosa (PAN). The small vessel vasculitides are divided into those which are related to immune-complex deposition - Immunoglobulin A (IgA) vasculitis, Cryoglobulinemic vasculitis, Anti-Glomerular Basement Membrane (GBM) disease and Hypocomplementemic Urticarial Vasculitis; and those associated with Anti-Neutrophil Cytoplasm Antibody (ANCA) - Granulomatosis with Polyangiitis (GPA), Microscopic Polyangiitis (MPA) and Eosinophilic Granulomatosis with Polyangiitis (EGPA). Other rarer forms of primary systemic vasculitis which have variable vessel involvement include Behçet's disease and Cogan's syndrome.

Depending upon the calibre of the affected blood vessel and the organs involved, primary systemic vasculitis can produce myriad manifestations. Their rarity and variety of presentations create challenges in their early recognition. The delay in diagnosis may lead to organ or life-threatening situations. For example, a delay in the recognition of GCA can lead to permanent blindness; ANCA associated vasculitis (AAV) can become life-threatening due to renal or heart failure. Early diagnosis can therefore be of great value in preventing morbidity and mortality. Since 2009, there have been international recommendations on the management of these conditions

(2, 3). These recommendations have been updated in the last few years (4, 5). The pharmacotherapy of these conditions includes immunosuppression in most cases and most individuals suffer relapse. Assessment of activity and damage related to either disease or treatments is therefore of great value. In this introductory chapter, we will discuss the current standards in diagnostics and assessment of the primary systemic vasculitides and the outcomes of interest.

Diagnosis of vasculitis

Tissue

Histological examination allows observation of anatomical and immunological changes in a specimen and therefore allows a definitive diagnosis based upon the appreciation of mechanisms of disease. Statistically, it is highly specific as a diagnostic modality. However, this is of greater value in the primary systemic vasculitides where there is organ specific involvement.

In the large vessel vasculitides, a large vessel must be sampled directly since there is no intra-organ involvement. This can therefore only happen in areas where there is anatomical collateral circulation, for example, in the scalp. Biopsy of the superficial temporal artery has been the method of choice for diagnosis of GCA up to 2018, when an international recommendation advocated imaging as an alternative first test (6). There is evidence that the yield of a temporal artery specimen is related to length of the specimen and the number of levels at which the specimen is examined (7, 8). Immune staining for $CD3^+$ cells, which appear to have an important role in the pathogenesis of GCA, in addition to standard histological examination may improve the sensitivity of temporal artery biopsy (TAB) (9). Efforts to increase the diagnostic yield by studying the cytokine expression for interleukin-6 have not been successful (10). With the availability of an alternate modality of diagnosis and evidence that a negative biopsy does not change the clinical decision making process (11), TAB is of

value as a second test in the presence of a high pre-test probability and a negative imaging test (Figure 1).

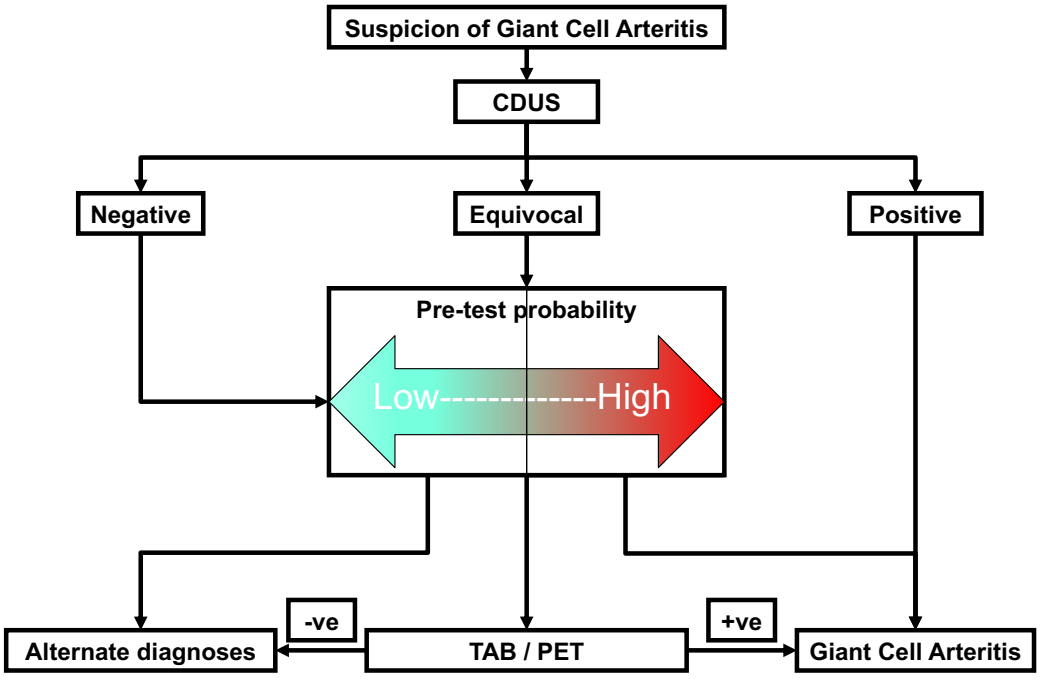

Figure 1 An example of a diagnostic algorithm for GCA showing the place of colour doppler ultrasonography (CDUS), temporal artery biopsy (TAB) and positron emission tomography (PET)

Small and Medium vessel vasculitis can involve any organ. The demonstration of fibrinoid necrosis, microaneurysms, perivascular granulomatosis or pauci-immune glomerulonephritis are all highly specific for a diagnosis of systemic vasculitis. In AAV, the kidneys, chest and the nose are all portals for histological sampling (12). Clinically, it is appropriate to target any involved organ. Renal biopsies have a higher yield for making a diagnosis and where indicated are thought to offer a better choice over chest or nasal sampling (12). Renal tissue in AAV can also offer prognostic information. There is evidence that individuals with sclerotic glomeruli have a lower survival over those who only have focal or crescentic involvement (13). A risk stratification score which predicts prognosis for end-stage renal disease or death has been proposed based on features of renal biopsy (proportional of normal glomeruli

and proportion of tubular atrophy / interstitial fibrosis) (14). Currently this is of academic interest till validation in a large cohort provides evidence for practical use.

Serological markers

There are no serological markers that are diagnostic for primary systemic vasculitis. However, several markers contribute to strengthen the diagnostic certainty.

Immunoglobulin A

Mesangial deposition of IgA in the context of an individual presenting with cutaneous or renal manifestations suggestive of IgA vasculitis can be considered to be diagnostic (15). There is evidence that even normal appearing skin demonstrates IgA deposition in individuals with renal IgA vasculitis (16). The levels of circulating IgA are higher in individuals with IgA vasculitis as compared to healthy controls and serve as a supportive diagnostic marker (17). There is emerging academic interest in the role and circulating levels of a subtype of IgA – galactose deficient IgGA1, which appears to be raised in all IgA vasculitis, but more so in those with associated nephritis (17).

Cryoglobulins

Immunoglobulins that precipitate reversibly when exposed to temperatures below 37°C are termed cryoglobulins. Lerner and Watson coined the term on identifying the proteins in an individual with purpura (18). Cryoglobulins of mixed immunoglobulin classes – typically IgM and IgG, have been known to be involved in the deposition of immune complexes in small blood vessels causing a vasculitis. Their presence is not always associated with vasculitis and therefore the terms ‘cryoglobulinemia’ and ‘cryoglobulinemic vasculitis’ cannot be used interchangeably. Their presence in individuals with clinical or laboratory evidence of definite small vessel vasculitis has diagnostic value.

Anti C1q antibody

The presence of low levels of C1q in the context of a systemic vasculitis associated with urticaria, arthralgia, abdominal pain and glomerulonephritis were reported in 1977 (19). Its presence as a case definition for a diagnosis of hypocomplementemic urticarial vasculitis became cemented with a report of 18 individuals with the clinical syndrome (20). Its presence is not diagnostic and it has been found in other conditions including SLE (21), rheumatoid arthritis (22) and chronic hepatitis C (23).

Anti GBM antibody

A new specific antibody deposited in the glomerulus of individuals with renal diseases was described in 1967 (24). The affinity for the glomerular basement membrane was further established in the same year (25). The antibody may not always be present in the sera even when there is demonstrable presence of antibody deposition in the glomerular basement membrane (26). Data from Israel including 1772 samples analysed in commercially available ELISA kits concluded that the test has only 41% sensitivity and 85% specificity (27). The antibody titres do not correlate with survival (27).

Antineutrophil cytoplasm antibodies

Antibodies directed against any antigen contained within neutrophil cytoplasm are termed ANCA. They were first discovered in the 1980's in individuals with renal vasculitis and GPA (28). These antibodies were detected using indirect immunofluorescence. The uptake of the fluorescent marker was seen to be in two specific patterns – in a perinuclear distribution or diffuse cytoplasmic distribution. These two patterns were called pANCA and cANCA respectively. In 1988, Falk and Jennette identified that the ANCA could be subdivided into those that were directed against myeloperoxidase (MPO ANCA) or otherwise (29). In 1990, Ludemann et al described antigenic specificity of cANCA to the third neutral serine proteinase enzyme present in neutrophil cytoplasm (30). This was termed PR3 ANCA. Enzyme-

linked immunosorbent assays (ELISA) for the detection of MPO ANCA and PR3 ANCA were standardized in 1996 (31). Since then, highly sensitive and specific third generation ELISA have replaced the need for indirect immunofluorescence (32). There was an international consensus in 2017 that ANCA testing with high quality commercially available ELISA is the preferred method of testing ANCA without there being a categorical need for the more time-consuming and less specific indirect immunofluorescence (32).

Antiphospholipid antibodies

Antibodies directed against phospholipids in the cell membrane are termed antiphospholipid antibodies. Their presence is associated with antiphospholipid antibody syndrome with or without accompanying systemic lupus erythematosus. Antiphospholipid antibodies predispose to thrombosis and therefore, there has been interest in their presence in systemic vasculitides where large vessel thrombosis is an integral part of disease manifestation. Bang et al found that 3/69 patients with Behçet's disease had lupus anticoagulant (33). There is limited evidence that anticardiolipin antibodies are present in the serum of individuals with Behçet's disease with retinal involvement (34, 35) and cerebrospinal fluid of individuals with neuro-Behçet's disease (36). In a meta-analysis including 380 patients with Behçet's disease and 619 controls, the prevalence of anticardiolipin antibodies and anti -β2 glycoprotein 1 was statistically higher in cases than controls (37). There is similar evidence of their presence in GCA (38, 39) and Takayasu arteritis (40). Antiphospholipid antibodies are not diagnostic and there is no conclusive evidence that their presence is associated with definite raised risk of thrombotic events. Currently, they remain of academic interest.

Imaging

There are many diagnostic imaging modalities to choose from. The choice of the investigation should be made wisely to optimise resources and get the best

diagnostic yield. The current common diagnostic modalities are discussed below; but in general, all patients with suspected vasculitis should at least have a chest X-ray. Further choice depends on the nature of the suspected vasculitis. Like in the acquisition of tissue, in large vessel vasculitis there will need to be direct imaging of the blood vessel and, in small and medium vessel vasculitis the imaging modality of choice will be one that is able to give the best resolution of an involved organ. It is interesting that each of the last four decades has brought us a new imaging modality – Computed Tomography (CT) scanning for small and medium vessel vasculitis first started in the 1980's (41), Magnetic resonance (MR) imaging for intracranial vasculitis in the 1990's (42), positron emission tomography (PET) for extracranial vasculitis in 2000's (43) and ultrasonography for cranial vasculitis in 2010's (44). The 2020's promise us new modalities like optical coherence tomography of the retina for GCA (45) and 3-dimensional dark blood MR imaging using 3 Tesla machines for viewing the lumen of extracranial vessels (46).

Chest X-ray

A plain X-ray exposure of the chest is an investigation that has stood the test of time. Chest radiography has been a favoured modality for quick recognition of nodulo-cavitary lesions (47, 48), pleural abnormalities (48, 49) and alveolar haemorrhage (50). It is not a sensitive test during an acute presentation, even in individuals with a predominant chest vasculitis like EGPA (51), but there is evidence that most individuals with AAV will demonstrate a chest X-ray abnormality during the course of having AAV (52). Abnormalities of the contour of the aorta are reliable radiological signs of Takayasu arteritis (53), but chest X-rays are not sensitive at picking up pulmonary arterial involvement in Takayasu arteritis (54). In almost every instance of suspected chest involvement in primary systemic vasculitis, current practice would be to perform a CT scan of the chest irrespective of the results of the chest X-ray (55, 56).

Computed tomography

CT scanning of the nose, paranasal sinuses and the chest is of great value in diagnosis of vasculitis, particularly AAV. Soft tissue changes in the sinus, sinus wall thickening, mucosal thickening, sclerosing osteitis, bone destruction are common features on CT imaging of the nose and paranasal sinuses in granulomatous AAV (57-60). In granulomatous AAV with lung disease, CT scanning can pick up nodulo-cavitary lesions as small as 0.3 mm in diameter (61, 62). The nodules are usually multiple, bilateral, and sub-pleural (63). Other chest lesions seen in AAV include infarcts (61), air-bronchograms (61), infiltrates (64), ground glass opacities (65), endobronchial lesions (66) and pleural lesions (56, 61). The presence of infiltrates should raise suspicion of alveolar haemorrhage (64). Pulmonary artery aneurysms (67, 68) and superior vena cava thrombosis (69) are rare manifestations picked up on CT scanning in Behçet's disease. CT scanning is a hugely contributory investigation in the diagnosis of primary systemic vasculitis but is only of relevance in the appropriate clinical context.

Magnetic Resonance Imaging

MR imaging is the imaging modality of choice for finding intracranial lesions in primary systemic vasculitis. Cortical changes (70), white matter changes in the hemispheres (70-72), brain stem involvement (70), meningeal involvement (71), optic nerve involvement (73) and isolated spinal cord involvement (73) can be visualised using different MR imaging sequences. The hemispheric white matter changes are best seen using fluid attenuated inversion recovery sequences (74). The anatomy in a small area like orbital involvement in GPA is seen very well using unenhanced, non-fat-suppressed T1-weighted sequences (75). Cardiac MR has been used increasingly in recent years to demonstrate cardiac involvement in GPA (76) and EGPA (77). MR imaging has been used to show structural changes in the wall and lumen of large vessels in individuals with Takayasu arteritis (78), but PET is a better modality to diagnose Takayasu arteritis because it can demonstrate the extent of

active disease in the arterial tree. Recently, the use of 3 Tesla magnets has successfully demonstrated GCA in cranial arteries (79), but ultrasonography is the current standard of imaging cranial involvement in GCA (80). Recent MR imaging advances which may be of promise include the ability to differentiate arteritic from non-arteritic ischaemic optic neuropathy (81); and the use of dark-blood MR angiogram to image the large blood vessels for vasculitis (82).

PET (combined with CT)

Plain X-rays, CT scans and MR imaging focus on the lumen of a blood vessel. PET allows appreciation of the metabolic activity of the vessel wall when Fluorine-18-fluorodeoxyglucose (FDG) is used as a radioactive marker. When images obtained with this technique are superimposed on those acquired by CT, the resulting images allow accurate visualisation of metabolic activity by anatomical structures. This allows for earlier diagnosis and treatment of vasculitis involving the large vessels with a high diagnostic accuracy (83). The demonstration of the entire arterial tree has made it possible to appreciate the extent of disease in the large vessel vasculitides (84, 85). It was always known that Takayasu arteritis involved the aorta and its major branches, but FDG-PET-CT scanning revealed that GCA also had widespread involvement of the arterial tree (85). FDG-PET-CT scanning has demonstrated the silent large vessel vasculitis in individuals previously thought to have polymyalgia rheumatica (PMR) (86, 87). It is now imperative that individuals thought to have PMR are now assessed for the possibility that they may have GCA. Attempts to correlate the level of tracer uptake to prognosis have not been successful (88, 89). The major pitfall of PET scanning is the ambiguity of its findings in individuals who are no longer naïve to glucocorticoid therapy. Glucocorticoid therapy rapidly switches off tissue inflammation and therefore a negative scan in individuals on those drugs has low negative predictive value. PET scanning for diagnosis of large vessel vasculitis should probably be done within 3 days of commencing prednisolone (90). The diagnostic yield may drop significantly after the first week of high-dose glucocorticoid therapy

(91). FDG-PET-CT scanning as a diagnostic modality for large vessel vasculitis has become a gold standard without undergoing formal validation.

Ultrasonography

Colour doppler ultrasonography was first used as a method of improving the sensitivity and yield of TAB (92). Schmidt et al first studied intramural changes in 10 cases and 23 controls to demonstrate a concentric hypoechoic 'halo' around the lumen of the superficial temporal artery that disappeared within 2 weeks of commencing glucocorticoid therapy (93). Chrysidis et al have proposed definitions of normal and abnormal ultrasonography findings of the superficial temporal artery after a systematic literature review of all abnormalities reported in temporal artery inflammation (94). Two findings of note that appeared to be of significance were the 'halo sign' and the 'compression sign'. They defined the 'halo sign' as a *"Homogenous hypoechoic wall thickening, well delineated towards the luminal side, visible both in longitudinal and transverse planes, most commonly concentric in transverse scans."* The compression sign was defined as *"The thickened arterial wall remains visible upon compression; the hypoechogenic vasculitic vessel wall thickening contrasts with the mid-echogenic to hyperechogenic surrounding tissue".* Colour doppler ultrasonography demonstrates moderate agreement with TAB in a pooled analysis of 12 studies including 965 individuals; the results were as in Table 1 (80). The agreement between the two diagnostic modalities as judged by Cohen's kappa (κ) was 0.44 (95% confidence interval (CI) 0.38, 0.50) (80). The interobserver reliability for halo sign and compression sign has been excellent when experienced sonographers reviewed readily acquired images (κ = 0.87 for halo sign; κ = 0.83 for compression sign) (94), and good when experienced sonographers acquired the images themselves in a dynamic exercise (κ = 0.60 for halo sign and compression sign) (95). The intraobserver reliability was excellent for 24 sonographers reviewing 150 images and videos 2 weeks apart (κ = 0.88 for halo sign and κ = 0.83 for compression sign) (94); and for 12 sonographers who acquired the images themselves in six individuals scanned few hours apart (κ = 0.76 for halo sign and κ =

0.78 for compression sign) (95). Karahaliou et al (96) scanned individuals with suspected GCA and age and gender matched controls with either diabetes mellitus or cerebrovascular accident. Of the 22 individuals with GCA, 18 demonstrated the halo sign and none of the 15 controls demonstrated any abnormality. Ultrasonographic findings in the temporal arteries are sensitive to glucocorticoid therapy. Schmidt et al (97) described that the halo disappeared at a mean of 16 days in 30 individuals with GCA. De Miguel et al (98) found that the halo disappeared in 36/38 individuals at the same time as the C-reactive protein (CRP) fell from 47.2 mg/dl to 6.8 mg/dl. Colour doppler ultrasonography is the first outcome measure that can objectively allow bedside assessment for the diagnosis of GCA. It has been validated to a high standard (80) using an internationally agreed process with demonstration of convergent validity with TAB; divergent validity to differentiate from diabetes mellitus and cerebrovascular accidents; interobserver and intraobserver reliability in static and dynamic exercises; and is eminently feasible because of ubiquitously available technology. Like all aspects in the field of medicine, this new technology requires training and experience before a diagnostic service can be offered (99). The sensitivity to change means that the scan should be performed within 7 days of commencing glucocorticoid therapy (44). Practically, this imaging modality can be recommended to be the primary diagnostic method for GCA followed by a second test if necessary (Figure 1) (6).

Table 1 Matrix of results in 965 individuals assessed by temporal artery biopsy and ultrasonography from Coath and Mukhtyar (80)

	Ultrasonography positive	Ultrasonography negative	Total
TAB positive	239	99	338
TAB negative	155	472	627
Total	394	571	965

Diagnostic criteria

There are currently no diagnostic criteria for primary systemic vasculitis. There are internationally agreed classification criteria for Takayasu arteritis (100), GCA (101), GPA (102), EGPA (103), PAN (104), IgA vasculitis (105) and Behçet's disease (106). They have found their way into textbooks and classrooms, but classification criteria are meant to be used only for research. When classification criteria are used for diagnostic purposes, they perform poorly (107). The diagnosis of the primary systemic vasculitides has heavily relied on pattern recognition of multi-system disease with different organ manifestations being present in the various vasculitis syndromes (108). The Birmingham Vasculitis Activity Score (BVAS) is a distillation of common manifestations of systemic vasculitis, each of which is assigned a value to quantify the disease activity of vasculitis (109). During the validation of the third version of the BVAS (110), the scores generated in different vasculitides were compared with other conditions presenting to the rheumatology clinic. A BVAS v3 score of $\geq$8 had a sensitivity of 0.72 and a specificity of 0.79 to allow differentiation between primary systemic vasculitis and other musculoskeletal conditions including rheumatoid arthritis. This proof of concept with the addition of many more clinical and laboratory variables has led to a large international effort to develop diagnostic criteria for primary systemic vasculitis (111).

Assessment of vasculitis

For the vasculitis physician to present a coherent management plan to the individual with systemic vasculitis, they need to be able to balance three major aspects of the clinical situation:

- Is the disease active, and therefore is there an indication to commence or increase immunosuppression?

- Is there damage related to disease or its treatment, which needs either an alteration of the immunosuppression (E.g., renal impairment), or the introduction of a new treatment plan (E.g., anti-hypertensive).
- How has the disease and its treatment impacted upon the quality of life (QOL) of the individual with vasculitis, and does it need an alteration of treatment or an introduction of a new therapy or service? (E.g., weight increase because of glucocorticoid therapy that may need an amendment to the treatment plan along with dietary advice and physiotherapy)

This tripod of 'activity', 'damage' and 'quality of life' can be assessed via clinical examination, laboratory testing and clinical tools.

Activity assessment

There are no valid biomarkers that correlate with disease activity (112). International recommendations advocate that activity assessment is done by considering relevant laboratory markers in the context of a careful clinical assessment (4, 5). PET-CT (88, 113), MR imaging (114, 115), ultrasonography (98, 116), ANCA titres (117, 118) and CRP levels (119, 120) are commonly available modalities that have some value in helping to assess disease activity of primary systemic vasculitis. The absence of valid biomarkers has necessitated the development of clinical assessment tools (Table 2). The available clinical tools have been validated to differing standards (Table 3).

Table 2 Composite indices that have undergone validation in various primary systemic vasculitides with number of cases of specific vasculitis syndromes

Clinical Tool	Tak (N)	GCA (N)	PAN (N)	GPA (N)	MPA (N)	EGPA (N)	IgA (N)	Cryo (N)	Behçet's (N)	Ref
BVAS	11	10	14	50	6				11	(109)
BDCA									19	(121)
VAI			13	35	3	3		2	7	(122)
BVAS/WG				117						(123)
BVAS v3	9		10	155	15	28	10	6	25	(110)

	6		2	149	22	23	7	9	5	(124)
DEI.TAK	155									(125)
ITAS 2010	177									(126)
MAI									177	(127)
EMRAI									73	(128)
GUSS									207	(129)

BVAS: Birmingham Vasculitis Activity Score; BDCA: Behçet's disease Current Activity Form; VAI: Vasculitis Activity Index; BVAS/WG: Birmingham Vasculitis Activity Score for Wegener's granulomatosis; BVAS v3: Birmingham Vasculitis Activity Score version 3; DEI.TAK: Disease Extent Index for Takayasu Arteritis: ITAS 2010: Indian Takayasu Arteritis Score 2010; MAI: Mucocutaneous Activity Index; GUSS: Genital Ulcer Severity Score

Table 3 Components of validation of various disease activity indices

Clinical Tool	Convergent Validity vs.	Interobserver reliability	Intraobserver reliability	Sensitivity to change	Ref
BVAS	Kallenberg Index; PGA; VAI	✓		✓	(109)
BDCA		✓			(121)
VAI	PGA	✓		✓	(122)
BVAS/WG	PGA	✓			(123)
BVAS v3	Treatment decision; BVAS v2; CRP; PGA; VAI	✓	✓	✓	(110) (124)
DEI.TAK	PGA; Kerr's criteria; Treatment decision				(125)
ITAS 2010	BVAS, PGA, ESR, CRP	✓		✓	(126)
MAI	BSAS	✓	✓	✓	(127)
EMRAI	BDCA	✓			(128)
GUSS	BDCA				(129)

BVAS: Birmingham Vasculitis Activity Score; BDCA: Behçet's disease Current Activity Form; VAI: Vasculitis Activity Index; BVAS/WG: Birmingham Vasculitis Activity Score for Wegener's granulomatosis; BVAS v3: Birmingham Vasculitis Activity Score version 3; DEI.TAK: Disease Extent Index for Takayasu Arteritis: ITAS 2010: Indian Takayasu Arteritis Score 2010; MAI: Mucocutaneous

Activity Index; EMRAI: Electronic Medical Records Activity Index; GUSS: Genital Ulcer Severity Score; BSAS: Behçet's syndrome Activity Score

The BVAS is a list of common manifestations of the primary systemic vasculitides, arranged by organ-systems. Each manifestation is assigned a score and each organ-system is assigned a ceiling score. The total score of all the organ systems represents the disease activity. There have been three versions of the BVAS, the latest one being modified and validated in 2009 (110, 130) It is the only clinical tool validated to international standards (131) in two different cohorts (110, 124) across the greatest breadth of primary systemic vasculitides (Table 2). The BVAS v3 (Appendix 1) is a list of 56 items divided into 9 organ systems with a range of possible scores between 0-63 with a higher score representing more severe activity. It has been internationally recommended as a surrogate for disease activity assessment for small and medium vessel vasculitis (2).

BVAS v3 has been used as an outcome measure in studies of large vessel vasculitis (132, 133), but its two validation studies did not include any cases of GCA and 15 cases of Takayasu arteritis (Table 2), with a limited range of disease activity scores from 0-4 (max score 63) (124). The Indian Takayasu Arteritis Score 2010 (126) has better evidence for its use in Takayasu arteritis, having been validated in a cohort of 177 cases. It has not yet found favour as an outcome measure for disease activity in randomized clinical trials of Takayasu arteritis. For Behçet's disease, there have been 4 separate outcome measure that have been developed (Table 2) The Behçet's Disease Current Activity Form (BDCA) has been used as the anchor against which two other large validation studies have been conducted for Electronic Medical Records Activity Index and Genital Ulcer Severity Score (Table 3). However, the BDCA itself has had very limited validation looking only at interobserver reliability in 19 cases. Practically, the BVAS v3 validation studies had 30 cases of Behçet's disease and a range of 0-19 (max 63) allowing for a reasonable discrimination between disease activity states (124).

The primary systemic vasculitides are rare diseases, and amongst them – anti-GBM disease, HUVS and Cogan's syndrome are rarer still. Probably because of that, these three disease groups have not been included in the development of any clinical tool. But GCA is the commonest primary systemic vasculitis, and it was not included in any validation studies. As a result, its monitoring and assessment is purely on clinical assessment. Practically, it has been suggested (80) that disease relapse in GCA can be suspected in the presence of two of the following 4 (a modification of the criteria proposed by Kerr et al for Takayasu arteritis (134)) –

1. Constitutional symptoms – Fever, Weight loss, Anorexia, Night sweats
2. Claudication symptoms – headache, jaw claudication, limb claudication
3. Acute phase response – rise in CRP
4. Imaging – point of care ultrasonographic evidence of vascular inflammation

Damage

Damage is the irreversible scar of disease or its treatment which is not going to respond to immunosuppression. It is important to look for and differentiate it from activity because it will often change the trajectory of the treatment plan. Damage can occur because of vasculitis (E.g., renal failure) or because of treatment (E.g., hypertension related to glucocorticoid therapy). Damage can have myriad presentations. There is recognition that anti-endothelial cell antibodies can be generated in primary systemic vasculitis and may be responsible for vascular injury and damage (135). But damage that is clinically recognisable and needs differentiation from activity does not have any valid biomarkers. The need for systematic clinical surveillance for damage led to the development of the Vasculitis Damage Index (VDI) (136). The VDI is a list of 64 items of damage grouped into 11 organ-systems (Appendix 2). Primarily an inventory of common and/or important items of damage, the number of items of damage accrued, and how quickly they were accrued became recognised as a prognostic marker for survival (137). That primary systemic vasculitis should be associated with an increased risk of

cardiovascular events is intuitive, but the use of VDI has allowed for systematic assessment of individuals with vasculitis and resultant evidence that cardiovascular damage occurred more commonly than damage in other organ systems in individuals with small and medium vessel vasculitis (138, 139). ENT damage is common in vasculitis, especially GPA (140). ENT damage can also be predictive of a more relapsing course (141). Historically, ENT disease in GPA has not been thought to be worth treating with intensive immunosuppression (142), but the amount of damage that ENT disease can inflict in individuals with GPA (141), and the poorer outcomes in long-term follow-up of individuals treated with less intensive immunosuppression (143), are changing the argument for treating ENT disease in GPA as aggressively as those with renal disease (144). Since the VDI has become the predominant indexing tool for assessing and recording damage, there were concerns that other manifestations might be ignored (145). The development of a more detailed clinical tool did not prove to be any more successful at recording damage, and the complexities of recording the damage made it less feasible to use (146). Specific indices have been developed for use in Large Vessel Vasculitis, Behçet's disease and Takayasu arteritis. The Large Vessel Vasculitis Index of Damage is a list of 85 items that has not undergone formal validation. In a study of 204 individuals with large vessel vasculitis, it captured a median of 3 items of damage over a mean follow-up of 3.5 years (147). The Behçet's Overall Damage Index is a list of 46 items with specificity for Behçet's disease and has been validated in an international exercise involving 228 individuals with Behçet's disease (148). The Takayasu Arteritis Damage Score is a disease specific score that has been used in clinical trials (149), but has never formally undergone validation. It may be more specific than VDI in recording disease-specific items of damage (150).

Quality of Life

QOL is a concept that reflects the standard of health and well-being. Physicians and researchers have traditionally been interested in outcomes pertaining to the absence or presence of a disease state – survival, remission, relapse etc. Arguably, individuals

with disease just want to feel better and are not concerned with whether their clinicians feel that their disease is active or not. In one survey, a cohort of individuals who had been hospitalised reported living with bladder and bowel incontinence and ventilation as outcomes worse than death (151). The QOL is impaired in all those who suffer with primary systemic vasculitis (152), but no one measurable aspect of disease singularly determines this downturn of well-being (153). The things that concern patients with vasculitis are far more mundane as compared to the scores measured by complex clinical tools. The ability to drive (154), employment status (155), energy levels (156) are of greater relevance to the well-being than achieving remission (157) and being on immunosuppressive therapy (158).

There are no validated tools to measure QOL accurately in individuals suffering with primary systemic vasculitis. Short form 36 (SF-36) is a questionnaire featuring 36 questions which allow interpretation of physical and mental health and comparison with a reference population (159). It has been used to quantify the effect of the disease and its treatment on the QOL in GCA (154), Takayasu arteritis (160), AAV (156) and Behçet's disease (161). The SF-36 is a generic tool, and it has been validated in large population studies, but it seems to lack the ability to identify differences which are intuitive. For example, Hellmann et al found that loss of vision was rated a domain of utmost importance by those suffering with GCA (162), but SF-36 scores are comparable between those with and without visual loss (154). SF-36 is a questionnaire that has been designed using American English and it relies on comparison with normative data from large population samples. These data are available for North American and European populations. The Behçet's Disease QOL tool is disease specific and validated in Turkish (163) and Korean populations (164). Even though QOL is of greater importance to patients than the concepts of disease activity and damage, there has not been a single interventional clinical trial in primary systemic vasculitis with QOL as the primary outcome measure. This suggests that as yet patients are not at the heart of clinical trials and the development of better patient reported outcome measures may help to achieve that goal.

Outcomes

Outcomes are measurable endpoints that allow us to measure the efficacy of an individual or compare the efficacies of different interventions. Prior to the advent of glucocorticoid therapy, primary systemic vasculitides were associated with a high risk of mortality. Even after the discovery and use of glucocorticoid therapy, there was a rapid realisation that these drugs simply caused suppression of disease and cure was not a realistic option (165). However, remission became the outcome to aspire for with the use of prednisolone (166, 167). But the term 'remission' has meant different things to different workers, and the terminology has been applied inconsistently (168). Remission rates in primary systemic vasculitis are a function of phenotype, serotype, treatments, and time. But they are also artefactually influenced by the way they are measured - acute phase responses are less reliable than physician verification which is less reliable unless validated by a credible disease activity assessment tool. The term 'remission' implies that the condition will relapse. This means that unless there is a validated definition of what 'relapse' means, the patient will still be deemed to remain in 'remission'. 'Remission' and 'relapse' have been the consistent primary outcome measures in all clinical trials in primary systemic vasculitis. There has been an international consensus to define remission and relapse in the different vasculitides (5, 169), but clinical trials continue having variable definitions. There are two consistent features in the definitions used – the first is the use of a validated disease activity tool like BVAS v3, and the second is the absence of a biomarker because of their unreliable nature.

Other outcomes of interest have been dialysis dependence / renal survival (170), QOL (171) and damage (172). The problems with assessing QOL and damage have been discussed above.

Conclusions

Joseph Hodgson recognised in 1815 that the vessel wall may be involved in a specific group of diseases (173). Since then, the diagnosis and assessment of vasculitis has made significant advances. Although there are no specific diagnostic biomarkers, the presence of serological markers like IgA, cryoglobulins, anti-C1q antibody, anti-GBM antibody and ANCA in the appropriate clinical context assist diagnosis. Advances in imaging mean that we can derive diagnostic information from the wall and lumen of blood vessels including bedside assessment of cranial arteries. The speed of diagnosis of GCA has led to improvements in visual outcomes and lower costs (174-176). The assessment of vasculitis cannot be with laboratory tests alone. It requires a holistic assessment involving quantification of disease activity using validated clinical tools, recognition of damage with institution of appropriate measures to ameliorate the issues, and involvement of the patient in decisions to ensure that the impact of the disease and treatments on the quality of life are discussed and considered in the long-term care of these chronic diseases. Currently activity assessment with BVAS v3 and damage assessment with VDI have been tried, tested, and found to be state-of-the-art. Quality of life measurement needs improvement because current attempts with the use of SF-36 have been sub-optimal. With the clinical tools at our disposal and the definitions of the various outcome measures of interest, giant strides have been made in recording and improving outcomes in primary systemic vasculitis via international collaboration resulting in evidence-based recommendations for the management of the primary systemic vasculitides (2-5).

Chapter 2 Diagnosis

The role of ultrasonography for diagnosis of GCA had been evolving since 1995 (93), but its exact utility was unknown. In 2006, Karahaliou et al demonstrated that the specificity of ultrasonography for diagnosis of GCA could be increased from 91% for unilateral superficial temporal artery changes to 100% if the change was demonstrable on both sides (96). At this time developments in FDG-PET-CT demonstrated that GCA involved vascular beds beyond the cranial arteries in most cases, especially the subclavian arteries (177). Further ultrasonography studies confirmed that changes like those seen in the superficial temporal artery could be seen in the subclavian and axillary arteries in 30% of cases (178). Simultaneous evolution of MR imaging techniques showed that the use of contrast-enhanced 3-Tesla magnet imaging could demonstrate increased mural thickness and reduced lumen in individuals with GCA (179) and that these changes abated with the onset of glucocorticoid therapy (180). This technique could demonstrate changes in the ophthalmic artery in individuals with ophthalmic manifestations of GCA (181). But lower resolution MR machines which are more ubiquitously available could not reproduce these results (182). With low confidence in TAB, and evolving imaging technologies, we put the validation of imaging techniques at the top of the research agenda when we published the first recommendations for the management of large vessel vasculitis in 2009 (3).

Studies of ultrasonography in GCA had been heterogenous in their design and definitions, and thus difficult to compare (183). The main ultrasonographic finding of diagnostic value had been a hypoechoic concentric halo. In 2013 Aschwanden et al reported improved results by the addition of a ‘compression sign’ to the ‘halo sign’ (184). In 2016, Diamantopoulos et al demonstrated that formal introduction of ultrasonography in a ‘fast track’ GCA service to triage patients for rapid diagnosis and treatment improved visual outcomes while improving cost-effectiveness (176). The logistics of delivering an ultrasonography service became apparent from the results

of a large clinical trial comparing ultrasonography to temporal artery biopsy (44). To recruit cases across multiple centres, a training programme was built which required novice sonographers to perform 20 normal ultrasonography examinations and 1 positive scan as evidence of expertise. This was believed to be a sub-optimal strategy (185). In the absence of certification, there was no blueprint on setting up an ultrasonography service or validating it. For FDG-PET-CT, the presence of a smooth linear or long segmental uptake that was superior to liver uptake became the de facto feature for diagnosis of extracranial large vessel vasculitis, without any further validation exercises (186). Alternative assessment using aortic to blood pool uptake ratio has been proposed but met with conflicting results (187, 188). High resolution MR imaging appeared to have high diagnostic accuracy, reliability, and sensitivity to change in a single-centre study (189)

Ultrasonography equipment is ubiquitously available as compared to 3-Tesla MR machines or FDG-PET-CT machines. It offers rapid bedside assessment without exposure to ionizing radiation. It was closest to formal validation for widespread uptake as outlined in the research agenda that we published in the 2009 research recommendations (3).

I present three papers defining my role in the translation of ultrasonography for use in clinical trials and clinical practice. The main work presented here is the validation of an ultrasonography service in a regional centre. This is supported by two other papers where I worked as part of an international consortium to develop and validate definitions for commonly encountered lesions in ultrasonography for the diagnosis of GCA. My role in the three papers is as under –

1. Validating a diagnostic GCA Ultrasonography service against temporal artery biopsy and long-term outcomes
    a. Design of study
    b. Acquisition of data including all the ultrasonography examinations
    c. Analysis

    d. First authorship
2. Definitions and reliability assessment of elementary ultrasound lesions in Giant Cell Arteritis: a study from the OMERACT Large Vessel Vasculitis Ultrasound Working Group
    a. Participation in Delphi to design the definitions
    b. Rating the encountered lesions for importance
    c. Scoring of 150 images on two separate occasions
    d. Co-authorship including final approval of manuscript
3. Assessing Vasculitis in Giant Cell Arteritis by Ultrasound: Results of OMERACT Patient-based Reliability Exercises
    a. Scribe in preliminary exercise to document ultrasound lesions in live exercise
    b. Survey of ultrasonographers to understand the artefactual influences in the preliminary exercise
    c. Analysis of survey data to inform the structure of the full exercise
    d. Co-authorship including final approval of manuscript

I am indebted to Mr Colin Jones, Dr Stavros Chrysidis, Dr Valentin Schafer and Professor Wolfgang Schmidt for the works presented in this section.

Validating a diagnostic Giant Cell Arteritis ultrasonography service against temporal artery biopsy and long-term clinical outcomes (99)

Authors

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Background

European League Against Rheumatism (EULAR) recommendations for the management of large-vessel vasculitis stated that a TAB should be attempted in all cases of suspected GCA to help make a definitive diagnosis (3). This recommendation has just been updated to state that imaging technologies have similar diagnostic value if assessors are proficient in these techniques (5). An artery demonstrating inflammatory changes can be considered specific for GCA in the appropriate clinical context (190). A negative biopsy does not rule out GCA and arguably may not affect the diagnostic process (191). Recently, the sensitivity of TAB has been shown to be about 40% (44, 192). This suggests that there are many cases diagnosed by either the American College of Rheumatology classification criteria or clinical judgement. However, we also know that these two methods are not infallible. The use of classification criteria for diagnosing vasculitis functions poorly (107). Currently, no modality serves as a gold standard for diagnosing GCA.

Barrier et al. used continuous wave Doppler pencil probe ultrasonography to guide the site of TAB in 1982 (92). The first description of a hypoechoic halo around the perfused lumen in a small series of patients with GCA was in 1995, and the authors predicted that ultrasonography might replace TAB as the primary diagnostic test (93, 193). In 2018, the EULAR recommended an imaging test like ultrasonography prior to TAB (6). A large meta-analysis of published literature has reported the sensitivity and specificity of the hypoechoic halo to be 68% and 81% when compared with TAB (194). But sensitivity and specificity of ultrasonography vs. TAB are meaningless because TAB is not a gold standard. To validate ultrasonography, we might need a

different approach like measuring agreement with a test like Cohen's kappa. Cohen's kappa is a robust way of analysing degree of agreement between two tests. Subsequent analysis of disagreement might reveal which test judged appropriately. When disagreements are observed, longitudinal follow-up might give us the best clue to the actual diagnosis, allowing us to make a better decision about the veracity of the test results rather than the blunt tools of 'sensitivity' and 'specificity'.

Ultrasonography for GCA is an operator-dependent tool without availability of formal certification. It is therefore paramount that a new service finds a way of validating itself against established parameters of diagnosing GCA. De Miguel et al. have published their experience of teaching this technique via lectures, assessment of examination videos of 30 cases and some hands-on training (195). In a clinical trial comparing ultrasonography vs. TAB, the training programme for recruiting sonographers comprised examining 10 controls under supervision and 1 'hot' case with definite disease. A video of the ultrasonography findings of the 'hot' case was reviewed by an expert (44). There are no data on the number of actual cases that an individual would need to complete prior to exhibiting competence for commencing a service.

To answer the question of how best to validate an ultrasonography service, we present our experience of cases where both ultrasonography and TAB were performed. We have performed notes review at 100 weeks to determine physician-verified 100-week diagnosis. We have made a four-way comparison between ultrasonography, TAB, baseline diagnosis and 100-week diagnosis using statistical methods to measure agreement rather than sensitivity and specificity.

Methods

Patients

From March 2013, we started a trial period of a diagnostic ultrasonography of temporal and axillary arteries in addition to TAB to validate our service. We have

included patients who had an ultrasonography within 7 days and TAB within 28 days of commencing high-dose prednisolone. Patients were informed that the ultrasonography was performed for service validation and not for influencing their care which would be reliant on the TAB result and the decision of the supervising clinician. Ethical approval was not sought because this was a service validation exercise.

Techniques

All ultrasonography examinations were performed by me on a Toshiba Viamo ultrasound machine with a linear transducer (4–14 MHz) (Toshiba, Tokyo, Japan) using tissue harmonic imaging mode. All patients had an examination of temporal and axillary arteries according to a previously published protocol (44).

TAB was performed under local anaesthesia by an ophthalmic surgeon. A 3-cm segment of the artery was sent to pathology in formalin.

Definitions of results

The ultrasonography was defined as positive in the presence of non-compressible vessel wall oedema (the 'halo' sign) in longitudinal and transverse views, stenosis, or obstruction (94). TAB was defined as positive in the presence of intramural inflammatory infiltrate. Clinical decisions were recorded as GCA if clinicians chose to treat patients with the hospital-approved Norwich regimen for prednisolone (196).

Statistics

A quadruple comparison was made between ultrasonography, TAB, baseline diagnosis and a 100-week diagnosis using Cohen's kappa. All tests were done on an online statistics package available on http://vassarstats.net/ (accessed March 18, 2019). Cohen's kappa of <0 would denote no agreement, 0–0.2 as slight, 0.2–0.4 as fair, 0.4–0.6 as moderate, 0.6–0.8 as substantial and 0.8–0.1 as near-perfect agreement.

Results

Twenty-five cases met our inclusion criteria (Table 4). The mean (Standard Deviation (SD)) time from commencing prednisolone to performing the ultrasonography was 2.5 (2.6) days. The mean (SD) time to TAB was 13.9 (10.1) days. In case 3 and case 9, the TAB was done before the ultrasonography. They were included because the results of the TAB were not available at the time of the ultrasonography. The CRP had been checked in 23/25 patients prior to commencing prednisolone. The mean (SD) CRP was 70.9 (67.9) mg/L. Fourteen ultrasonography scans were positive and 8 TAB were positive. Twenty cases were clinically treated as GCA at baseline. At 100 weeks, 16 cases were still thought to have had GCA (Table 4 and Table 5). There was no instance of a case diagnosed as not having GCA at baseline and was thought to have GCA at 100 weeks.

Table 4 Description of 25 cases

Case ID	Pred to US (days)	Pred to TAB (days)	US result	TAB result	CRP (mg/L)	Baseline clinical	100-week clinical	Other comments
1	4	7	+	+	118	GCA	GCA	
2	0	10	+	−	168	GCA	GCA	CT aorta—thickened aorta
3	1	− 5	+	−	22	GCA	GCA	PET scan positive
4	2	9	−	−	37	Not GCA	Not GCA	
5	6	15	−	−	21	Not GCA	Not GCA	
6	3	12	−	−	NA	GCA	GCA	The ESR was 82 at baseline.
7	1	20	−	+	182	GCA	GCA	
8	2	16	−	−	<1	Not GCA	Not GCA	
9	0	− 20	+	−	4	GCA	GCA	

10	6	13	−	−	NA	GCA	Not GCA	The ESR was 97 at baseline. Diagnosed with RA when prednisolone dropped to 6 mg od
11	0	13	+	−	223	GCA	GCA	Ultrasound proven relapse
12	5	20	+	+	25	GCA	GCA	
13	0	11	+	+	113	GCA	GCA	
14	2	15	−	−	106	GCA	Not GCA	CRP never settled; type 2 DM, ESRD requiring haemodialysis
15	0	18	−	−	6	GCA	Not GCA	Diagnosed with breast cancer
16	6	27	−	−	6	GCA	Not GCA	Diagnosed with prostate cancer
17	2	24	+	−	25	GCA	GCA	
18	5	28	–	−	7	Not GCA	Not GCA	
19	0	9	+	−	73	GCA	GCA	Ultrasound proven relapse
20	0	19	+	+	100	GCA	GCA	
21	3	10	+	−	172	GCA	GCA	
22	6	20	–	−	7	Not GCA	Not GCA	
23	0	22	+	+	29	GCA	GCA	
24	8	22	+	+	116	GCA	GCA	
25	0	10	+	+	71	GCA	GCA	

+ denotes positive result; − denotes negative result

Pred, prednisolone; US, Ultrasonography; CT, computed tomography; PET, positron emission tomography; RA, rheumatoid arthritis; NA, not available; ESRD, end-stage renal disease

Table 5 Matrix for 25 patients denoting positive and negative results by two diagnostic modalities and clinical judgement

	Positive TAB	Negative TAB	Total
Positive ultrasonography	7	7	14
Negative ultrasonography	1	10	11
Total	8	17	25
	Clinical GCA	Clinical not GCA	
Positive ultrasonography	14	0	14
Negative ultrasonography	6	5	11
Total	20	5	25
Positive TAB	8	0	8
Negative TAB	12	5	17
Total	20	5	25
	100-week GCA	100-week not GCA	
Positive ultrasonography	14	0	14
Negative ultrasonography	2	9	11
Total	16	9	25
Positive TAB	8	0	8
Negative TAB	8	9	17
Total	16	9	25

Cohen's kappa

The kappa (95% CI) for agreement between ultrasonography and TAB was 0.4 (0.1, 0.7); between ultrasonography and baseline diagnosis was 0.5 (0.2, 0.8) and between TAB and baseline diagnosis was 0.2 (0.0, 0.4) (Table 6).

Table 6 Matrix of kappa scores and 95% confidence intervals between two diagnostic modalities and clinical judgement

Versus	**US**	**TAB**	**Baseline clinical**
TAB	0.4 (0.1,0.7)		
Baseline clinical	0.5 (0.2, 0.8)	0.2 (0.0, 0.4)	
100-week clinical	0.8 (0.6, 1.0)	0.4 (0.1, 0.7)	0.6 (0.3, 0.9)

100-week review

Four cases (ID 10, 14, 15, 16) thought to have GCA were found to have a better explanation for their presentation by 100 weeks. All 4 had negative ultrasonography and negative TAB. Case 10 had not had a CRP check prior to commencing prednisolone. When the prednisolone dose reached 6 mg/day, he presented with small joint symmetrical synovitis and was diagnosed as having rheumatoid arthritis. Case 14 had a baseline CRP of 106 mg/L which failed to normalise even with high-dose prednisolone (Figure 2). At 100-week review, we thought that the initial presentation of headache might simply have been related to him suffering with end-stage renal disease for which he was haemodialysis dependent. Case 15 had a baseline CRP of 6 mg/L and developed breast cancer. Case 16 had a baseline CRP of 6 mg/L and developed prostate cancer. It was determined in retrospect that their initial manifestations were probably related to cancer. Kappa (95% CI) for ultrasonography vs. 100-week diagnosis was 0.8 (0.6, 1.0); for TAB vs. 100-week diagnosis, clinical decision was 0.4 (0.1, 0.7) and for agreement between baseline diagnosis and 100-week diagnosis was 0.6 (0.3, 0.9).

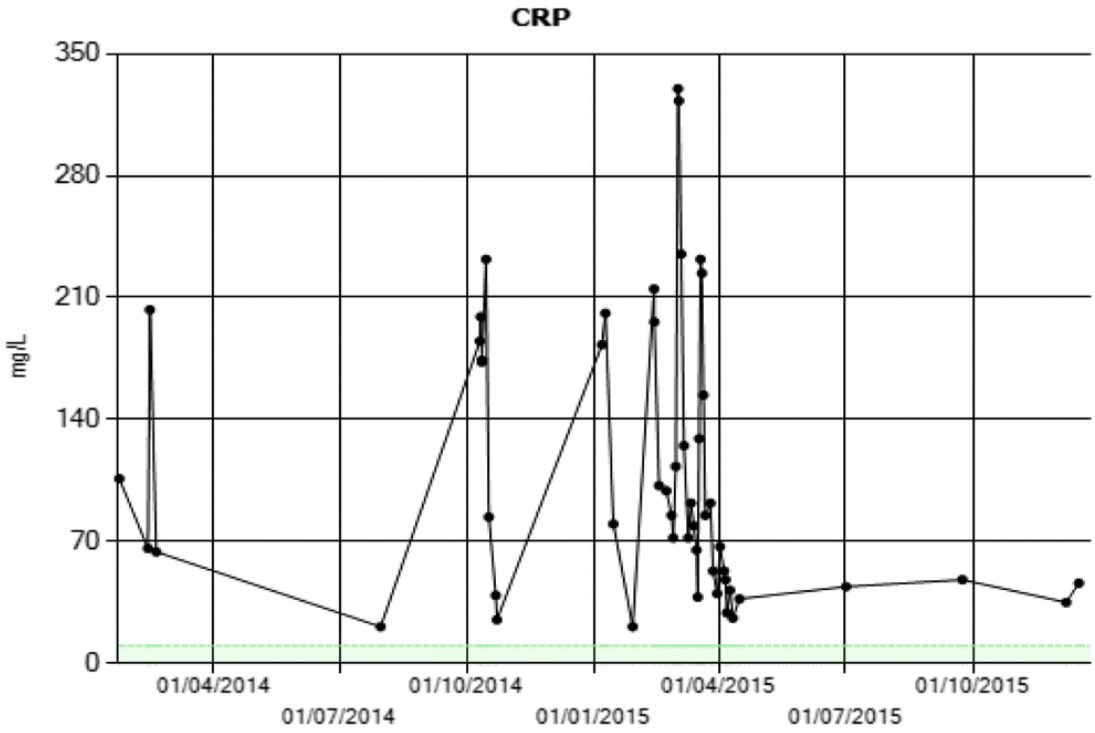

Figure 2 C-reactive protein results of patient 14 determined at 100 weeks to not have had GCA

Discrepancy analysis

There were 7 cases where ultrasonography was positive, but the TAB had been negative. In 2 of them, additional evidence emerged from other imaging modalities. Case 2 had a CT demonstrating aortic thickening (baseline CRP was 168 mg/L). Case 3 had a PET demonstrating large-vessel vasculitis (baseline CRP was 22 mg/L). Two additional cases (11 and 19) had further ultrasonography evidence of relapse needing introduction of methotrexate (Baseline CRPs were 223 mg/L and 73 mg/L, respectively). Three cases finished their 100-week regimen and were discharged from rheumatology with a final clinical diagnosis of GCA.

Case 7 had a definite false negative ultrasonography with positive TAB. Her CRP was 182 mg/L at baseline, and she had undergone an ultrasonography examination 1 day after commencing prednisolone. The TAB was done 20 days after commencing prednisolone.

Discussion

Our study has several strengths. All the ultrasound examinations were performed by a single clinician. All the patients were assessed within 7 days. Luqmani et al. showed that agreement between ultrasonography and TAB was optimal when ultrasonography was done within 7 days of commencing prednisolone (44). All TABs were done by an ophthalmologist within 28 days of commencing prednisolone. Jakobsson et al. showed TAB performed up to 28 days after initiation of glucocorticoid therapy yielded clinically useful information (197). We performed a more relevant statistical analysis between ultrasonography, TAB, and clinical diagnosis. We performed a review of notes at 100 weeks to determine final diagnosis, gaining a greater insight into the performance of ultrasonography and TAB.

We did not perform this exercise to validate ultrasonography for diagnosis of GCA. That has been done by several academics before us. We have shown that ultrasonography in our centre is a robust diagnostic tool. The kappa of 0.4 of ultrasonography against TAB would suggest a slight-fair performing diagnostic modality. But when we look at this in the context of the relationship of TAB with clinical judgement and long-term follow-up, ultrasonography performs superiorly to TAB and has substantial to near-perfect agreement with physician-verified diagnosis at 100 weeks. Our findings are like those of Luqmani et al. in a much larger study of 381 patients where the kappa between ultrasonography and TAB was 0.35 (44). The 4 over-turned diagnoses at the 100-week review meant that ultrasonography had the best kappa even compared with baseline diagnosis (Table 6).

There were 5 cases (ID 6, 10, 14, 15, 16) where GCA was diagnosed on clinical grounds with negative US and negative TAB. Of those, only case 6 was still thought to have GCA at 100-week review. Rheumatoid arthritis and cancers were alternative diagnoses considered for 3 of these patients. Cancer can often present with constitutional symptoms mimicking GCA in the elderly population. Hedges et al.

followed up 91 patients with a negative TAB and found that 21% of those patients had a final diagnosis of cancer vs. 3% of those with a positive TAB (198). We suggest that a diagnosis of GCA be made with extreme caution in cases with negative ultrasonography and TAB and a search for a malignancy be standard protocol in the investigation of these cases. Case 7 is the single case in this series where the ultrasonography was false negative. But the TAB was positive in this situation, suggesting a definite role for TAB in diagnosis of GCA, but perhaps after ultrasonography. This is like one of the conclusions arrived by Luqmani et al. (44).

Our study has limitations. It is a small study but the similarity of our results with a much larger clinical trial (44) suggests that our sample was representative. There is a risk of selection bias, but negative US did not stop clinicians from diagnosing GCA suggesting that we did not change clinician behaviour during this exercise.

One of the questions that we wanted to answer was the sample size necessary for accreditation. We propose that a series of 25 unique US examinations with auditing against TAB and long-term clinical follow-up would be sufficient. Luqmani et al. performed their follow-up examination at 6 months, and we did it at 100 weeks because we were not constrained by clinical trial environment. The Norfolk and Norwich University Hospital, UK, now offers regular ultrasonography for diagnosis followed by TAB in ultrasonography-negative patients if CRP is elevated or there are other strong clinical features of GCA.

Supportive work

Definitions and reliability assessment of elementary ultrasound lesions in Giant Cell Arteritis: a study from the OMERACT Large Vessel Vasculitis Ultrasound Working Group (94)

Introduction

GCA is the most common primary systemic vasculitis, occurring predominantly in Caucasian populations (199). GCA mainly involves large and medium-sized arteries, predominantly branches of the external carotid arteries such as the temporal arteries, and the aorta and its large branches such as the subclavian and axillary arteries. TAB has been regarded as the gold standard for decades; however, biopsy is invasive, and it lacks sensitivity, particularly in extracranial GCA (44). Imaging techniques including ultrasonography, MR imaging and PET-CT are increasingly being used in diagnosis of GCA and may in future replace biopsy in many cases (178, 200). Notably, ultrasonography is less invasive, reveals a higher sensitivity, particularly in extracranial disease, and results become available faster (201). Early diagnosis and treatment of patients with GCA are important since patients may develop irreversible ischaemic complications, including vision loss and stroke. The implementation of fast-track clinics that involve ultrasonography as a point-of-care test for patients with suspected GCA has led to a decrease of permanent vision loss (175, 176). A recently published multicentre study showed that a diagnostic algorithm including ultrasonography is cost-effective compared with a conventional strategy focusing on biopsy only (44).

GCA is characterised by inflammatory infiltration of the artery wall resulting in the so-called ‘halo’ sign, first described in 1995, which is a hypoechoic (dark) thickening of the vessel wall as visualised by ultrasonography (93). In contrast to the healthy artery, the inflammatory wall thickening is not compressible upon application of pressure with the ultrasonography probe. This feature has recently been termed the ‘compression’ sign (184).

Several studies have been conducted thus far to investigate the accuracy, construct, and criterion validity of ultrasonography in the diagnosis of GCA, and four meta-analyses of these studies have been published until now (183, 202-204). Despite the growing body of evidence supporting the utility of ultrasonography in GCA, standardised definitions of the elementary normal and abnormal appearance and their reliability are lacking. Therefore, an Outcome Measures in Rheumatology (OMERACT) Large Vessel Vasculitis Ultrasonography Working Group was formed to agree on the ultrasonography lesions suggestive of GCA as well as to test the reliability of these definitions.

The first aim of this study was to retrieve currently available definitions of ultrasonography key elementary lesions describing vasculitis in temporal and extracranial large arteries by a systematic literature review. Second, we intended to produce consensus-based definitions of normal and GCA characteristic appearances of temporal and extracranial large arteries as detected by ultrasonography, using a Delphi process among international experts. This Delphi process included definitions of the ultrasonography appearance of (1) normal, (2) arteriosclerotic and (3) vasculitic temporal and axillary arteries and (4) a consensus on which anatomical structures and findings should be considered when performing ultrasonography in suspected GCA. The third aim was to test the interobserver and intraobserver reliabilities of the definitions of each elementary ultrasonography lesion in GCA using a web-based exercise.

Methods

Study design

The study design followed the stipulated OMERACT methodology in accordance with previous studies of the OMERACT ultrasonography working group for defining disease characteristic lesions and testing reliability of ultrasonography in other rheumatic diseases (205-207). The OMERACT Large Vessel Vasculitis

Ultrasonography Working Group was formed at the Annual American College of Rheumatology meeting Boston, Massachusetts, USA, in 2014.

Systematic Literature Review to identify previously applied ultrasonography definitions of Large Vessel Vasculitis

According to the OMERACT standard operating procedures, a systematic literature review was conducted to identify definitions of normal and abnormal ultrasonography appearance of large arteries applied in previous studies. Details on the key question, search, data synthesis and quality assessment are provided in the online supplementary material. In brief, two authors searched the PubMed, EMBASE and the Cochrane Library databases using Medical Subject Headings terms, full text, and truncated words from the inception dates (1946, 1974 and 1993, respectively) to 23 November 2014. The following inclusion criteria were applied: (1) number of patients enrolled ≥20 patients and (2a) full research articles of prospective or retrospective studies on diagnostic accuracy of ultrasonography in suspected large vessel vasculitis (i.e., cranial and extracranial GCA, Takayasu arteritis and idiopathic aortitis as these exhibit similar ultrasonography pathologies) using an appropriate reference standard (i.e., clinical diagnosis, published criteria and/or positive TAB) or (2b) cross-sectional studies assessing large vessel vasculitis by ultrasonography in patients with established GCA, PMR or Takayasu arteritis. Data were extracted using a predefined template. The Quality Assessment of Diagnostic Accuracy Studies-2 and Quality in Prognosis Studies tools were used to assess quality of diagnostic accuracy and prognostic studies, respectively (208, 209).

Delphi consensus on definitions of Large Vessel Vasculitis elementary ultrasonography appearances

The group decided to focus the Delphi exercise on ultrasonography key lesions for GCA only, because of the paucity of ultrasonography data in Takayasu arteritis and idiopathic aortitis.

Based on the results from the systematic literature review, the steering committee developed a WORD™-based written questionnaire that included 25 statements. Of these 25 statements, 3 addressed the definitions of the appearances of normal and arteriosclerotic temporal and extracranial large arteries; 15 statements addressed 5 definitions of the 'halo' sign, stenosis (temporal and extracranial large arteries), occlusion, 'compression' sign (temporal arteries) and vessel wall pulsation (temporal arteries) and 7 statements addressed the requirements for diagnosis of vasculitis by ultrasonography.

Twenty-five physicians experienced in ultrasonography and/or large vessel vasculitis were invited by email to participate. They were from 14 countries (Austria, Czech Republic, Denmark, France, Germany, Italy, Norway, Poland, Portugal, Slovenia, Spain, The Netherlands, UK, and USA). The group consisted of 22 rheumatologists, 1 internist and 2 physicians in the last year of rheumatology training. Nine, six, four, two and four participants have performed >300, 101–300, 51–100, 21–50 and <20 diagnostic GCA ultrasonography examinations, respectively. Sixteen were currently offering a diagnostic GCA ultrasonography clinic. The participants were asked to rate each definition using a level of agreement or disagreement for each statement according to a 1–5 Likert scale with 1=strongly disagree, 2=disagree, 3=neither agree nor disagree, 4=agree and 5=strongly agree. A Likert score of 4 or 5 was considered as agreement. Only when statements achieved a score of >75%, a consensus was considered for appropriately defining the category. Statements satisfying these requirements were used for the definition of the most important ultrasonography elementary appearances for the diagnosis of vasculitis. Those statements with already achieved agreement, but suggestions for an improved wording in the first Delphi round were rephrased according to the experts' comments and reappraised in the second round. Statements with a <75% agreement in the first round were not further taken to the second round.

The questionnaire also included a rating of the importance of the different ultrasonography elementary appearances for the diagnosis of cranial and

extracranial large vessel vasculitis using a Likert scale as mentioned above. Up to two reminders were sent out to the experts if they had not responded within the given time limit. The answers of the first Delphi round were summarised with the percentage of agreement to each statement. For the second Delphi round, all comments of the panellists were anonymised and re-sent together with a questionnaire revised by the steering committee to those experts who had responded in the first round. At a face-to-face meeting of the expert panel (‘round 3´), held at the 2015 San Francisco American College of Rheumatology Meeting, the wording of one definition was slightly revised.

Interobserver and Intraobserver web-based reliability exercise

All members of the OMERACT Large Vessel Vasculitis Ultrasonography Working Group were asked to submit 16 representative still images and 20 representative videos: eight still images and eight videos represented normal anatomical segments (superficial temporal artery, frontal branch, parietal branch, and axillary arteries) in longitudinal and transverse planes; and the eight other still images and eight videos represented the same segments exhibiting the ‘halo’ sign. Four additional videos showed a positive and a negative ‘compression’ sign of the temporal artery branches in longitudinal and transverse views, respectively. All pathological images and videos originated from patients with active disease who met the expanded American College of Rheumatology classification criteria of GCA, and in whom diagnosis was confirmed either by TAB or on a clinical basis, including ultrasonography and follow-up (210). The images and videos were collected by a facilitator of the group who constructed an electronic database using REDCap (Research Electronic Data Capture; Vanderbilt University, Nashville, Tennessee, USA) hosted by a server from the Italian Society for Rheumatology (211).

From 550 submitted images and videos, 150 images and videos were selected by the facilitator for the web-based reliability exercise: 20 videos of axillary arteries, 20 still images of axillary arteries, 45 videos of temporal arteries, 45 still images of temporal

arteries and 20 videos of the 'compression' sign applied to temporal arteries. The distribution between longitudinal/transverse views and normal/pathological vessels was as follows: temporal artery still images and videos: transverse 56, longitudinal 54, pathological 57 and normal 53. Axillary artery still images and videos: transverse 18, longitudinal 22, pathological 19 and normal 21. A link with the web-based exercise was sent to the same physicians who participated in the Delphi process, asking them to apply the definitions agreed in the Delphi exercise to decide whether each still image or video was suggestive of vasculitis according to the definitions. Two weeks after the first evaluation, the participants received the same images and videos in a different order for evaluating the intra-rater agreement.

All images and videos were anonymised for patients' data, the centre where the image was obtained, ultrasonography machine settings/producer and intima-media thickness measurements. Images and videos from patients were only submitted from countries without restrictions for patient image transfer.

Statistical analysis

In the systematic literature review and in the Delphi process, only descriptive statistics were used. Intraobserver and interobserver reliabilities were calculated using the kappa coefficient (κ). Intraobserver reliability was assessed by Cohen's κ, and Interobserver reliability was studied by calculating the mean κ on all pairs (i.e., Light's κ) (212). Kappa coefficients were interpreted according to Landis and Koch with κ values of 0–0.2 considered poor, 0.2–0.4 fair, 0.4–0.6 moderate, 0.6–0.8 good and 0.8–1 excellent (213). The percentage of observed agreement (i.e., the percentage of observations that obtained the same score) and prevalence of the observed lesions were also calculated. Analyses were performed using R Statistical Software (Foundation for Statistical Computing, Vienna, Austria).

Results

Systematic Literature Review on definitions of key elementary ultrasonography lesions describing vasculitis

Out of 2960 articles screened, 39 studies were finally included. Some of these studies addressed more than one key objective (and are reported in the following as if they were separate articles). Twenty-four articles focused on diagnostic accuracy of ultrasonography in GCA (96, 97, 182, 184, 214-233), studies investigated the value of US for the prediction of GCA outcome (98, 234, 235), 13 studies reported the possible role of ultrasonography for monitoring disease activity (96-98, 217, 218, 220, 224, 225, 227, 228, 234-236) and 14 cross-sectional studies assessed large vessel vasculitis by ultrasonography in patients with GCA, PMR and Takayasu arteritis (178, 220, 225, 236-246). All diagnostic accuracy studies evaluated the role of ultrasonography for the diagnosis of cranial GCA, two of them also included patients with extra cranial GCA (225, 232). In seven reports, arterial involvement of patients with PMR was addressed (97, 217, 224, 237-240), and two cross-sectional studies assessed by ultrasonography the involvement of large vessels in patients with Takayasu arteritis (245, 246). No diagnostic accuracy study was identified for Takayasu arteritis and isolated idiopathic aortitis.

Most ultrasonography studies in patients with GCA and PMR tested the 'halo' sign (n=36) (96-98, 178, 182, 184, 214-232, 234-244) as a key elementary lesion defining vasculitis. Other ultrasonography signs of vasculitis reported (mostly in combination with the 'halo' sign) were stenosis (n=21) (96, 97, 178, 184, 214, 215, 220, 222, 224-226, 229, 234, 236-243), occlusion (n=18) (97, 178, 184, 220-222, 224, 226, 229, 234, 236-243), the 'compression' sign (n=2) (184, 233) and a conspicuous vessel wall pulsation by M-mode (n=1) (221). Cut-off values of the intima-media thickness for the definition of the 'halo' sign were provided in nine studies (178, 217, 226, 227, 231, 237, 240, 241, 244), ranging from 0.3 to 1 mm for temporal arteries and from 1.3 to 2 mm for extracranial large arteries. For Takayasu arteritis, the term 'Macaroni

'sign has been used in two studies describing the same pathology as the 'halo' sign (245, 246). Stenosis, occlusion, and arterial dilatation have also been addressed as ultrasonography key elementary signs in patients with Takayasu arteritis (245, 246).

No separate definitions for the distinction between acute and chronic vasculitic lesions have been published, neither for GCA nor for Takayasu arteritis.

Delphi exercise

Twenty-four of the 25 invited participants responded to the first Delphi questionnaire (96% response rate). All 24 participants also responded to the second round of the Delphi questionnaire (100% response rate).

In round 1, a consensus was achieved on nine definitions on normal temporal and extracranial large arteries, arteriosclerosis, 'halo' sign, stenosis of temporal and extracranial large arteries, occlusion, 'compression' sign (temporal arteries) and ultrasonography assessment of the 'compression' sign (temporal arteries) (Table 7). A definition of the 'halo' sign not including the measurement of the intima-media thickness was preferred by the group, because of the high variance of proposed cut-off values for temporal and extracranial large arteries found in the systematic literature review and the lack of validated data at that time (178, 217, 226, 227, 231, 237, 240, 241, 244).

Table 7 Statements on definitions (n=8) and conduct (n=1) of ultrasound (US) elementary appearances in large vessel vasculitis agreed upon through a Delphi survey

Domain	Definition	Agreement (%)	Delphi round
Ultrasonography appearance of			
normal temporal arteries	Pulsating, compressible artery with anechoic lumen surrounded by mid-echoic to hyperechoic* tissue. Using ultrasonography equipment with high resolution, the intima-media complex presenting as a homogenous, hypoechoic, or anechoic echo structure	95.7	1

	delineated by two parallel hyperechoic margins (‘double line pattern’) may be visible.		
normal extracranial large arteries	Pulsating, hardly compressible artery with anechoic lumen; the intima-media complex presents as a homogenous, hypoechoic, or anechoic echo structure delineated by two parallel hyperechoic margins (‘double line pattern’), which is surrounded by mid-echoic to hyperechoic tissue.	100	1
arteriosclerotic arteries	Heterogeneous and in part hyperechoic, irregularly delineated, and eccentric vessel wall alteration.	95.8	2
‘halo’ sign	Homogenous, hypoechoic wall thickening, well delineated towards the luminal side, visible both in longitudinal and transverse planes, most commonly concentric in transverse scans.	91.3	2
stenosis in temporal arteries	A stenosis is characterised by aliasing and persistent diastolic flow by colour Doppler ultrasonography. The maximum systolic flow velocity determined within the stenosis by pulsed wave-Doppler US is ≥2x higher than the flow velocity proximal or distal to the stenosis.	95.8 100	2 3
stenosis in extracranial large arteries	Typical vasculitic vessel wall thickening with characteristic Doppler curves showing turbulence and increased systolic and diastolic blood flow velocities.	75	1
occlusion	Absence of colour Doppler signals in a visible artery filled with hypoechoic material, even with low pulse repetition frequency and high colour gain.	87.5	1
‘compression’ sign of temporal arteries	The thickened arterial wall remains visible upon compression; the hypoechogenic vasculitic vessel wall thickening contrasts with the mid-echogenic to hyperechogenic surrounding tissue.	78.3	1
Ultrasonography assessment of			
‘compression’ sign of temporal arteries	The compression sign should be assessed by applying pressure via the transducer until the lumen of the temporal artery occludes and no arterial pulsation remains visible.	91.3	1

*The term ‘midechoic’ is equivalent to the term ‘isoechoic’.

In round 2, three definitions (arteriosclerosis, 'halo' sign and stenosis of temporal arteries) were redefined, voted, and agreed upon. The statements on vessel wall pulsation (definition and assessment) and the assessment of the 'halo' sign by measurement of vessel wall thickness did not reach the threshold for consensus. At the OMERACT Large Vessel Vasculitis ultrasonography face-to-face group meeting ('round 3'), the second part of the definition on 'stenosis in temporal arteries´ was rephrased from '… before or behind the stenosis' to '… proximal or distal to the stenosis'. The final definitions for normal and pathological cranial and extracranial vessels are described in Table 7.

The 'halo' sign and 'compression' signs were deemed to be the most important ultrasonography signs for cranial and extracranial GCA with 100% and 83.3% agreement, respectively. Of the panellists, 95.8 % thought that the 'halo' sign needs to be present to meet the minimum requirement for vasculitis.

Web-based exercise on still images and videos

Eighteen members from 13 different countries had submitted images and videos including five different ultrasonography brands (Hitachi, Esaote, GE, Siemens, and Philips) using linear transducers with maximum grey scale frequencies of 15, 18 or 22 MHz. Twenty-five group members participated in the web-based exercise in round 1, and 25/25 participants (100%) performed the exercise in round 2.

The reliability of the 25 participants was excellent with mean inter-rater agreements for all still images and videos of 91–99% and mean Light's κ values of 0.83–0.98 for inter-rater reliability (Table 8) depending on the lesions and sites assessed. Also, the examined intra-rater reliability with a mean agreement of 91–99% and a mean Cohen's kappa values of range 0.83–0.98 (Table 9) was excellent. The interobserver and intraobserver reliabilities performed all with κ >0.8 irrespective of the view (longitudinal or transverse, still images or videos) or anatomical segments.

Table 8 Interobserver agreements for the 'halo' and 'compression' signs in temporal and axillary arteries

Section	Lesion (mean prevalence, %) *	Agreement (mean, %)	Agreement (range)	Light's κ (mean)	Light's κ (range)
'halo' (all images & videos)	51.4	94	82–100	0.89	0.65–1
'halo' (all images)	54	98	89–100	0.95	0.78–1
'halo' (all videos)	49.3	92	77–100	0.84	0.54–1
'halo' temporal arteries (images & videos)	53.2	94	78–100	0.87	0.58–1
'halo' temporal arteries (images)	57.5	97	84–100	0.94	0.69–1
'halo' temporal arteries (videos)	50	91	74–100	0.83	0.49–1
'halo' axillary arteries (images & videos)	46	97	80–100	0.93	0.58–1
'halo' axillary arteries (images)	45	99	90–100	0.98	0.80–1
'halo' axillary arteries (videos)	47	94	70–100	0.88	0.34–1
'compression' sign (videos)	53.6	92	70–100	0.83	0.34–1

*Calculated as pathological lesions out of 100 presented images and/or videos.

Table 9 Intraobserver agreements for the halo' and 'compression' signs in temporal and axillary arteries

Section	Lesion (mean prevalence, %)	Agreement (mean, %)	Agreement (range)	Cohen's κ (mean)	Cohen's κ (range)
'halo' (all images & videos)	51.4	95	83–99	0.89	0.66–0.99
'halo' (images)	54	98	89–100	0.96	0.79–1
'halo' (videos)	49.4	92	79–100	0.84	0.56–1

'halo' temporal arteries (images & videos)	53.3	94	83–99	0.88	0.66–0.98
'halo' temporal arteries (images)	57.9	97	89–100	0.94	0.78–1
'halo' temporal arteries (videos)	50.1	91	78–100	0.83	0.57–1
'halo' axillary arteries (images & videos)	46	96	78–100	0.93	0.53–1
'halo' axillary arteries (images)	45	99	90–100	0.98	0.80–1
'halo' axillary arteries (videos)	47.1	94	65–100	0.87	0.21–1
'compression' sign (videos)	53.3	91	75–100	0.83	0.48–1

Discussion

Many previous studies have investigated ultrasonography as a diagnostic tool for GCA using different definitions for normal and abnormal findings. This study now provides expert consensus-based definitions for ultrasonography in large vessel vasculitis that can be applied in future studies. The consensus-based definitions revealed excellent interobserver and intraobserver reliabilities when tested on images and videos of patients.

Although we included all types of large vessel vasculitis as possible search terms in the systematic literature review, the Delphi as well as reliability exercise was focused on GCA only, as the systematic literature review revealed insufficient data to provide a solid basis for the consensus process. It is, however, the clinical experience of the experts that ultrasonography abnormalities in patients with Takayasu look similar. Future ultrasonography studies in Takayasu arteritis and idiopathic aortitis are necessary to gather more data on ultrasonography key lesions also in these large vessel vasculitis entities.

The OMERACT Group agreed that ‘halo’ sign and ‘compression’ sign should be regarded as the primary elementary ultrasonography signs of cranial and/or extracranial GCA without including stenosis or occlusion. The ‘halo’ sign has been applied in most published studies (96-98, 178, 182, 184, 214-232, 234-244). The ‘compression’ sign was only addressed by two studies from one research group so far (184, 233). However, it has shown good diagnostic performance and is feasible in daily practice. It is a method to better visualise the ‘halo’ sign. In early studies, the presence of stenosis helped to increase the sensitivity of temporal artery ultrasonography (97, 202). On the other hand, many sonographers feel that stenosis may reduce the specificity of the examination (44). Furthermore, due to far higher resolution of modern ultrasonography equipment, a ‘halo’ sign can now usually be visualised in stenotic vessel areas, and temporal artery occlusions in GCA usually occur together with the non-compressible ‘halo’ sign’ (201).

It was also agreed not to include the measurement of intima media thickness for the definition of the ‘halo’ sign, as at the time of the Delphi process only proposals for cut-off values but no studies for validating cut-off values were available. Several previous studies had proposed a wide range of cut-off values for the diameter of a halo sign, for example, 0.3–1 mm for temporal arteries and 1.3–2 mm for extracranial large arteries (178, 217, 226, 227, 231, 237, 240, 241, 244). A study investigating patients with newly diagnosed active GCA and healthy controls has been recently performed by members of the group for calculating intima-media thickness cut-off values in normal temporal and axillary arteries (247). The role of intima-media thickness measurements for diagnosis and monitoring is yet uncertain and needs to be addressed by future studies.

The interobserver and intraobserver agreements of the web-based exercise were excellent. Images and videos were submitted by participating experts as in previous OMERACT-related ultrasonography exercises (205-207, 248). Images and videos for the present web-based exercise were taken from patients with newly diagnosed active GCA since ultrasonography signs in patients with established disease resolve

rapidly with treatment (228). Reliability data for 12 sonographers reading videos from the international multicentre TAB vs ultrasonography study have now been published (44). Videos from that study were randomly chosen from all stored videos of the study, irrespective of their quality, whereas the quality of images and videos in the OMERACT study may have been better as the members submitted material which they deemed representative. Sonographers of the TAB vs. ultrasonography study were less experienced than sonographers of the present OMERACT study. Kappa values for the intraobserver reliability in the TAB vs. ultrasonography study were 0.69–0.81. Interobserver reliability was only provided as Intraclass Correlation Coefficients (ICC). Notably, the reliability of 14 pathologists reading TAB specimens was similar when compared with the 12 sonographers (Intraclass coefficient 0.61 vs 0.62).

We asked the experts to submit images from GCA cases and controls which include patients with arteriosclerosis. Few of the control cases indeed had arteriosclerotic changes; however, we did not specifically question in our rating to distinguish between arteriosclerosis and non-arteriosclerotic controls. We were therefore unable to conduct a separate analysis in this regard. We did not score images and videos with stenosis or occlusions.

In conclusion, an international expert consensus was reached using OMERACT methodology for the definitions of normal ultrasonography appearance and abnormalities seen in the temporal and axillary arteries in GCA. This OMERACT exercise (along with the previously reported TAB vs. ultrasonography study) shows that images and videos of ultrasonography scans of inflamed temporal and axillary arteries can reliably document the characteristic and diagnostic abnormalities in patients with suspected GCA. Our study supports the use of ultrasonography abnormalities, including both images and videos, as an inclusion criterion for future GCA trials. Confidence is increasing in the use of ultrasonography in mainstream clinical practice, and it may be incorporated into future guidelines for GCA diagnosis.

The next step in the OMERACT validation process is the interobserver and intraobserver reliability test of these definitions for normal and vasculitic arteries in patient-based exercises.

Assessing Vasculitis in Giant Cell Arteritis by Ultrasound: Results of OMERACT Patient-based Reliability Exercises (95)

Early and accurate diagnosis of GCA is imperative. Failure to accurately diagnose and expeditiously treat GCA may lead to vision loss and other severe ischemic complications, whereas misdiagnosis of non-GCA pathology as GCA leads to inappropriate glucocorticoid use and toxicity. TAB has been the diagnostic test of choice. However, TAB is invasive, and results are not immediately available. Hence it is increasingly being replaced by imaging, which includes ultrasonography, MR imaging, CT, and FDG-PET (201). FDG-PET and CT facilitate the examination of extracranial arteries to confirm the diagnosis of extracranial GCA and exclude alternative serious pathology. MR imaging and particularly ultrasonography can additionally visualize temporal arteries and other superficial cranial arteries.

Ultrasonography is widely available in rheumatology practice. It is patient-friendly, reproducible, and repeatable. Modern ultrasonography transducers achieve image resolution of 0.1 mm for superficial arteries, which is higher than that of other imaging techniques (201). Ultrasonography displays a noncompressible, hypoechoic, most commonly concentric arterial wall thickening ("halo sign") in acute GCA (97, 184). Alongside medical history and clinical examination it can be used in fast-track clinics offering appointments for patients within 24 hours, to rapidly confirm or exclude the diagnosis of suspected GCA. Two studies have shown a decrease of permanent irreversible vision loss after inauguration of fast-track clinics (175, 176).

Ultrasonography in all patients with suspected GCA is cost-effective compared to biopsy plus clinical judgment without imaging (44). It has a higher sensitivity than TAB regarding the clinical diagnosis, particularly in patients with extracranial GCA (44, 178). Several studies have investigated the accuracy, and construct and criterion validity of ultrasonography in the diagnosis of GCA, including 3 metanalyses (183, 202, 203). There is a trend to higher sensitivities in newer studies because of better technology and increasing experience. A new metanalysis including studies until

February 2017 revealed a pooled sensitivity of 77% and a pooled specificity of 96% with a positive likelihood ratio of 19 and a negative likelihood ratio of 0.2 for the halo sign in temporal arteries compared to the clinical diagnosis of GCA (204).

Nevertheless, issues have been raised regarding the diagnostic performance and reliability of ultrasonography, thus challenging its overall usefulness in GCA. A recent phase III trial enrolled 37% of its patients based on cross- sectional imaging, although ultrasonography was not included (249). Another phase III trial (ClinicalTrials.gov identifier: NCT02531633) included ultrasonography as an eligible diagnostic modality. This trial was however prematurely terminated in October 2017 by the sponsor, based on the decision to discontinue development of sirukumab in autoimmune diseases. Recently published EULAR recommendations on imaging in large vessel vasculitis suggest ultrasonography as the first imaging modality particularly in patients with suspected predominantly cranial GCA (6).

An OMERACT ultrasonography subgroup on large vessel vasculitis was formed. A Delphi survey based on a systematic literature search arrived at ultrasonography definitions for normal temporal and axillary arteries, the halo sign, and the "compression sign." These definitions were tested in a web-based exercise on still images and videos of normal and vasculitic temporal and axillary arteries. The reliability was excellent, with interobserver agreement of 91–99% and mean κ values of 0.83–0.98 for both interobserver and intraobserver reliability (94).

The focus of our study, described herein, is the OMERACT validation process, which tested the inter- and intraobserver reliability of the definitions for both normal and vasculitic arteries. The real-time patient- based exercises required simultaneous data acquisition and interpretation.

Materials and Methods

Study design and setting

A preliminary 1-day meeting was held following the International Symposium on GCA, PMR and Large Vessel Vasculitis in Southend, UK, in March 2016 to test the feasibility and study setting for a patient-based exercise. Lessons learned were implemented in a definitive 3-day exercise in Berlin, Germany, in February 2017, modelled on previous OMERACT Ultrasonography Working Group studies for testing patient-based reliability of ultrasonography in rheumatic diseases (205, 250, 251). The methodology and reporting of the Berlin OMERACT reliability exercise adhered to the recommendations from the Enhancing the Quality and Transparency of Health Research Network (252) using the Guidelines for Reporting Reliability and Agreement Studies Statement (253).

US examination

At each meeting, 12 sonographers individually examined 6 study subjects. All sonographers were previously involved in the development of the consensus-based ultrasonography definitions. Each sonographer performed bilateral examinations of the superficial temporal artery, its frontal and parietal branches and of the axillary arteries (i.e., 8 artery segments per patient) in longitudinal and transverse scans applying a binary score for vasculitis ultrasonography lesions as defined by OMERACT (94). The subject was lying on an examination couch in supine position. The head was rotated slightly toward the examiner for examining the left temporal artery and away from the examiner for examining the right temporal artery. The probe was placed in the axilla for examining the axillary artery. After a predetermined time, sonographers rotated to the next station until every sonographer examined all patients / controls. The data were collected immediately after each examination to exclude communication between sonographers. Sonographers were blinded to the study subjects' diagnosis. They were not allowed to communicate with the patients about

signs or symptoms of the disease. None of the examined patients had visibly swollen temporal arteries. An identical examination sequence was repeated later the same day to assess intrareader reliability.

US equipment and settings

Esaote MyLab Twice/Class systems equipped with 6–18 MHz linear array transducers were used in the exercises. In the Berlin meeting, 2 additional Esaote MyLab 8 machines were used. The following settings were applied for the examination of the temporal artery (axillary artery): B-mode frequency 18 MHz (14 MHz), image depth 1.5 cm (3 cm), 1 focus point at 0.5 cm (1.5 cm) below skin surface, colour Doppler frequency 9 MHz (6 MHz), and pulse repetition frequency 2.5 KHz (3.5 KHz). Sonographers were advised not to change these predefined settings except for adjusting image depth and focus point position for the examination of the axillary arteries, if necessary.

Preliminary meeting

The sonographers received no training on US machines and settings before the exercise. Thirteen minutes were allocated for scanning and scoring the findings for the first round and 10 min for the second round. The limit was set after a discussion about daily clinical practice conditions, where these time frames seemed to be adequate and realistic.

The examined study subjects were chosen by the convenors, who did not participate in the reliability exercise. WAS, being unblinded to the history and diagnosis of all study subjects and having performed >5000 scans in suspected GCA over 23 years, examined all study subjects in addition to the other sonographers (independent sonographer) to decide whether arterial segments were exhibiting clear or ambivalent pathology and to store reference images and videos. The examined study subjects were 63–76 years old (mean age 68 years). Four of them were females. Four study subjects had GCA consistent with the revised inclusion criteria of the SIRRESTA

trial (NCT02531633). These criteria require age ≥50 years, erythrocyte sedimentation rate ≥50 mm/h, and/or CRP ≥ 2.45 mg/dl (24.5 mg/l), unequivocal cranial symptoms of GCA and/or PMR, and evidence of large vessel vasculitis by cross-sectional imaging including ultrasonography if diagnosis is not confirmed histologically. Further, the diagnosis had remained unchanged until the exercise. By the time of the exercise, patients were receiving glucocorticoid therapy for 5 weeks, 2 years, 2 years, and 6 years. One of the 2 controls had an uncommon finding of arteriosclerosis of both axillary arteries.

All sonographers were rheumatologists except one who was in his last year of rheumatology training. Prior to the exercise, 7 sonographers had performed >300 scans of temporal and axillary arteries before, 2 had performed 101–300 scans, 2 had performed 51–100 scans, and 1 had performed <20 scans. Five sonographers used US machine types in their institutions similar in manufacturer and price level to the ones used in the exercise.

Full meeting

The meeting included 6 hours of practical ultrasonography training on healthy individuals and patients with GCA, different from those who participated in the exercise, using the machines and settings used in the exercise. In the exercise, 20 min were allocated for scanning and scoring the findings for the first round and 15 min for the second round.

The examined study subjects were chosen and examined by the convenor, who did not participate in the reliability exercise. Subjects' age ranged from 56 to 80 years (mean 68 years). Four of them were females. Four study subjects had GCA fulfilling the above-mentioned inclusion criteria. They had been receiving glucocorticoid therapy for 4, 7, and 8 months. The fourth patient had a persistent halo sign of temporal arteries for 4 years despite discontinuation of glucocorticoid therapy. Two controls never had any signs or symptoms of GCA.

Eight of the 12 sonographers had participated in the preliminary exercise. All sonographers were rheumatologists. Eleven sonographers had performed >300 scans of temporal and axillary arteries before. Two of them had indicated an experience of 101–300 scans at the time of the preliminary meeting. One sonographer had performed 51–100 scans at the time of each meeting. Six sonographers used ultrasonography machines in their institutions similar in manufacturer and price level to the ones used in the exercise.

Ethics committee approval was obtained from the Berlin Medical Association (Berliner Ärztekammer, Eth-04-17). All patients provided written informed consent prior to participation in our study.

Definitions

The definitions obtained by the Delphi exercise and applied at the Web-based reliability exercise (94) were also used in the patient-based reliability exercises:

Normal temporal artery: Pulsating, compressible artery with anechoic lumen surrounded by mid- to hyperechoic tissue. Using ultrasonography equipment with high resolution, the intima-media complex presents as a homogeneous, hypo-, or anechoic echo structure delineated by 2 parallel hyperechoic margins (double-line pattern) may be visible.

Normal axillary artery: Pulsating, hardly compressible artery with anechoic lumen; the intima-media complex presents as a homogeneous, hypoechoic, or anechoic echo structure delineated by 2 parallel hyperechoic margins (double-line pattern), which is surrounded by mid- to hyperechoic tissue.

Halo sign: Homogeneous, hypoechoic wall thickening, well delineated toward the luminal side, visible both in longitudinal and transverse planes, most commonly concentric in transverse scans.

Compression sign: The thickened arterial wall remains visible upon compression; the hypoechogenic vasculitic vessel wall thickening contrasts with the mid-echogenic to hyperechogenic surrounding tissue.

Figures explaining these definitions can be found in the article describing the Delphi process in more detail (94) and in another review article (254).

Statistical analysis

All sonographers (n=12) evaluated all study subjects (n = 6) in 2 rounds, in a total of 8 anatomical positions (superficial temporal artery, parietal branch, frontal branch, and axillary artery), taking both sides of the body (right, left) into account. Intra- and interobserver reliabilities were calculated using the kappa coefficient (κ). Intraobserver reliability was assessed by Cohen's κ. Interobserver reliability was studied by calculating the mean κ on all pairs (i.e., Light's κ) (212). Kappa coefficients and the corresponding 95% CI were interpreted according to Landis and Koch: κ values of 0–0.2 were considered poor, 0.2–0.4 fair, 0.4–0.6 moderate, 0.6–0.8 good, and 0.8–1 excellent (213). The percentage of observed agreement (i.e., percentage of observations that obtained the same score), prevalence of the observed lesions, and prevalence-adjusted bias-adjusted κ were also calculated (255, 256). Analyses were performed using R Statistical Software (Foundation for Statistical Computing).

Results

Preliminary meeting

The mean interobserver agreement for the overall diagnosis of GCA was 0.73 in round 1 and 0.83 in round 2. It was 0.79 in round 1 and 0.77 in round 2 for identifying vasculitis in the respective anatomical segments. The mean intraobserver agreements were 0.82 (0.50–1) for the overall diagnosis of GCA and 0.84 (range 0.58–1) for identifying vasculitis in the respective anatomical segments.

The mean interobserver reliabilities were fair to moderate for the overall diagnosis of GCA (Light's κ 0.29–0.51) and poor to fair for identifying vasculitis in the respective anatomical segments (Light's κ 0.02–0.46). Mean intraobserver reliabilities were moderate (Cohen's κ 0.32–0.64).

The independent sonographer rated 21 of 36 temporal artery segments (58%) as ambivalent because of minor pathology, such as very small halo size of about <0.5 mm and incomplete compressibility in some subsegments because of chronic changes in longstanding disease (Figure 3). He considered 4 of 12 axillary arteries (33%) ambivalent including both axillary arteries of 1 control with unusually pronounced arteriosclerosis showing heterogeneous and in part hyperechoic, irregularly delineated, eccentric vessel wall alteration with a diameter of up to 1.7 mm. Only 3 experienced sonographers (>300 scans) considered the findings in these patients non-GCA in both rounds. There were 65% of sonographers who felt that unfamiliarity with the equipment might have hampered their results of false-positive or negative diagnosis and of intrareader reliability.

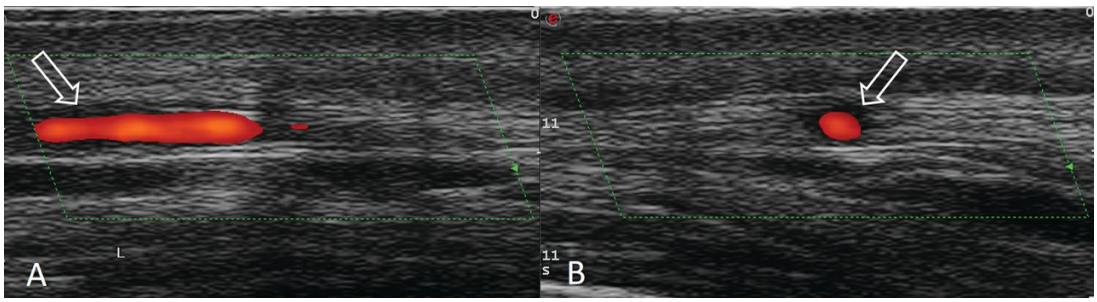

Figure 3 Small segmental, only slightly hypoechoic halo of a temporal artery branch in a patient of the full exercise with longstanding GCA. A. Longitudinal view. B. Transverse view. GCA: giant cell arteritis.

Full meeting

The mean interobserver agreement for the overall diagnosis of GCA was 0.88 in round 1 and 0.93 in round 2. It was 0.78 (range 0.75–0.83) in round 1 and 0.82 (range 0.79–0.86) in round 2 for identifying vasculitis in the respective anatomical segments. The mean intraobserver agreements were 0.96 (range 0.83–1) for the overall

diagnosis of GCA and 0.89 (range 0.58–1) for identifying vasculitis in the respective anatomical segments.

The interobserver reliability was good to excellent. The mean Light's κ was 0.76 in round 1 and 0.86 in round 2 for the overall diagnosis of GCA. The mean prevalence-adjusted bias-adjusted κ was 0.77 and 0.86 in rounds 1 and 2, respectively. For identifying vasculitis in the respective anatomical segments, the reliability was moderate for the temporal arteries (mean κ 0.46–0.53, mean prevalence-adjusted bias-adjusted κ 0.49–0.66) in round 1, moderate to good in round 2 (mean κ 0.5–0.71, mean prevalence-adjusted bias-adjusted κ 0.58–0.72), and moderate for the axillary arteries in both rounds (mean κ 0.64–0.66). The intrareader reliability was excellent for the diagnosis of GCA (Cohen's κ 0.91, prevalence-adjusted bias-adjusted κ 0.92) and good (Cohen's κ 0.71–0.80, prevalence-adjusted bias-adjusted κ 0.73–0.81) for the respective anatomical segments.

The independent sonographer rated 14 of 36 temporal artery segments (39%) and none of the 12 axillary arteries as ambivalent due to minor pathology because of chronic changes in longstanding disease. All sonographers agreed in both rounds that the controls had no GCA. Agreement was also 100% in both rounds for the diagnosis of GCA in 3 patients with GCA. Disagreement occurred only when 5/12 and 3/12 sonographers missed the diagnosis of GCA in rounds 1 and 2, respectively, in 1 obese patient with bilateral axillary artery vasculitis, very small residual artery lumen, pronounced collateral flow, and normal temporal arteries (Figure 4).

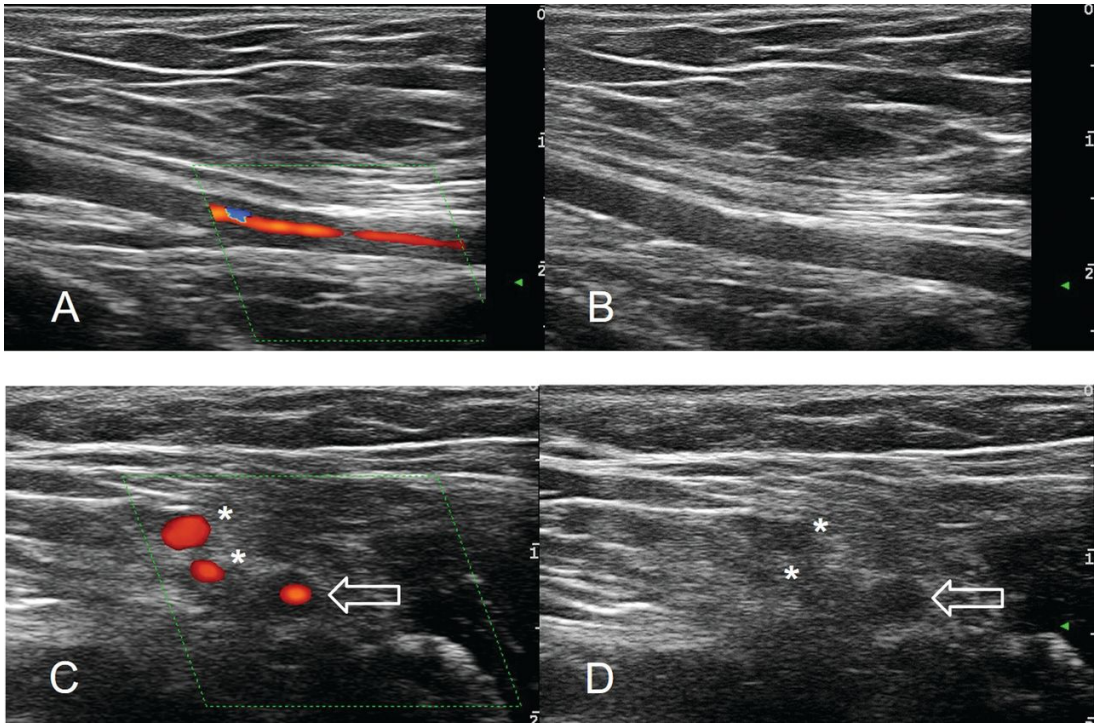

Figure 4 Halo sign of an axillary artery of a patient with GCA in the full exercise in longitudinal (A, B) and transverse (C, D) views. It is only visible when applying colour Doppler (A, C). In the transverse views, collateral vessels without halo sign (*) appear larger than the lumen of the affected axillary (arrows). GCA: giant cell arteritis.

In both exercises, reliabilities did not significantly differ whether halo sign or compression sign was evaluated. The detailed results are shown in Table 10, Table 11 and Table 12.

Table 10 Interobserver reliability and agreement in the full exercise (Round 1)

Variables	**Mean Prevalence, %**	**Mean Agreement**	**Mean κ**	**Mean PABAK**
Ultrasonography positive for GCA	61.1	0.88	0.76	0.77
Halo sign				
Temporal arteries, all segments	31.3	0.77	0.47	0.55
Superficial temporal artery	34.7	0.78	0.49	0.55
Frontal branch	31.2	0.77	0.46	0.54
Parietal branch	27.8	0.78	0.46	0.56

Axillary arteries	52.4	0.83	0.66	0.66
Compression sign				
Temporal arteries, all segments	32.6	0.78	0.49	0.55
Superficial temporal artery	35.4	0.78	0.51	0.57
Frontal branch	33.3	0.75	0.44	0.49
Parietal branch	29.2	0.80	0.53	0.60

PABAK: Prevalence-adjusted bias-adjusted κ

Table 11 Interobserver reliability and agreement in the full exercise (Round 2)

Variables	**Mean Prevalence, %**	**Mean Agreement**	**Mean κ**	**Mean PABAK**
Ultrasonography positive for GCA	62.5	0.93	0.86	0.86
Halo sign				
Temporal arteries, all segments	33.3	0.82	0.60	0.65
Superficial temporal artery	41.0	0.86	0.71	0.72
Frontal branch	31.3	0.79	0.50	0.58
Parietal branch	27.8	0.82	0.54	0.65
Axillary arteries	52.8	0.81	0.64	0.63
Compression sign				
Temporal arteries, all segments	33.8	0.83	0.60	0.65
Superficial temporal artery	38.2	0.83	0.63	0.65
Frontal branch	34.0	0.81	0.57	0.62
Parietal branch	29.2	0.84	0.60	0.68

PABAK: Prevalence-adjusted bias-adjusted κ

Table 12 Intraobserver reliability and agreement in the full exercise.

Variables	**Mean Prevalence, %**	**Mean Agreement**	**Mean κ**	**Mean PABAK**

Ultrasonography positive for GCA	61.8	0.96	0.91	0.92
Halo sign				
Temporal arteries, all segments	32.3	0.88	0.71	0.76
Superficial temporal artery	37.9	0.87	0.71	0.73
Frontal branch	31.2	0.89	0.73	0.77
Parietal branch	27.8	0.89	0.71	0.78
Axillary arteries	52.4	0.90	0.80	0.81
Compression sign				
Temporal arteries, all segments	33.2	0.89	0.73	0.78
Superficial temporal artery	36.8	0.89	0.75	0.77
Frontal branch	33.7	0.88	0.74	0.75
Parietal branch	29.2	0.89	0.72	0.77

PABAK: Prevalence-adjusted bias-adjusted κ

Discussion

The inter- and intraobserver reliabilities for performing ultrasonography of temporal and axillary arteries in patients with GCA and controls were good to excellent for the diagnosis of GCA with experienced sonographers who were familiar with the ultrasonography equipment.

Better reliabilities attained in the full exercise compared to the preliminary exercise could be explained by the following:

1. Lack of sonographer training on the ultrasonography equipment and its settings in the preliminary exercise. Only 42% of sonographers in the preliminary exercise and 50% in the full exercise were using similar equipment in their institutions. Even if a sonographer is familiar with a certain type of machine, experience with

the settings is important as these may considerably influence the appearance of the ultrasonography images.

2. Only 58% of sonographers in the preliminary exercise had performed >300 examinations in suspected GCA compared to 92% in the full exercise. The European Federation of Societies for Ultrasound in Medicine and Biology minimum training requirements for rheumatologists performing musculoskeletal ultrasonography demand a minimum of 300 ultrasonography examinations for achieving level I competency (257). Our current study suggests that this requirement may also apply for temporal and axillary artery ultrasonography in suspected GCA.
3. More time was provided for each examination in the full exercise because 67% of sonographers of the preliminary exercise said they felt that time restrictions had hampered the results. An examination time of 15–20 min appears to be optimal for examining temporal and axillary arteries in suspected GCA.
4. The time frame when performing ultrasonography is important for image interpretation. In patients with untreated GCA, the pathology is much more pronounced than in patients with longstanding, treated disease. The real-time patient-based reliability exercises, according to an OMERACT algorithm, are faced with this shortcoming, because it is impossible to obtain patients with untreated GCA for these exercises. The disease was more longstanding, and pathologies were subtler in the preliminary exercise, with 52% of examined anatomical segments showing ambivalent findings compared to 29% in the full exercise. The sensitivity of temporal artery ultrasonography decreases rapidly with glucocorticoid therapy. In 1 study, the sensitivity compared to the final clinical diagnosis dropped from 88% in patients who had been untreated or who had received glucocorticoid therapy for not longer than 1 day, to 50% in patients who had been treated for 2 days or longer (228). Another study, however, found that a residual halo sign may persist for 8 weeks in half of the patients (98). In axillary arteries, ultrasonography visible pathology may remain longer, for months and years, but it also decreases over time (178). Nevertheless, as halo

size decreases and halo echogenicity increases with treatment, it is more difficult to differentiate normal from abnormal findings in treated established GCA. This is probably also the case for histology because giant cells do not persist longer than 6 months (258). Arteriosclerosis may be a potential confounder in the mainly elderly GCA population. It is, however, far less common in the temporal and axillary arteries than in the carotid and femoral arteries.

Few studies have yet assessed real-time patient-based reliabilities for ultrasonography in suspected GCA. As for other indications and other imaging methods, reliability was higher when investigated for only 2 sonographers from the same institution. Agreement of 2 sonographers examining temporal arteries for halo sign, stenosis, and occlusions was 95% for the diagnosis of GCA in 1 study (97). In another study, 2 sonographers evaluating the compression sign of temporal arteries disagreed only in 1 of 60 patients (233). A single study with multiple sonographers from Spain found excellent reliability with a κ value of 0.85 for interobserver reliability and of 0.95 for intraobserver reliability after a training workshop (195). The reliability in our study may be lower probably because of a tighter protocol.

Our study has limitations. The reliability may depend on the severity of the pathologic findings. Because all patients were receiving glucocorticoid therapy, reliability may have been impaired by ambivalent pathology. The repetition of the examination sequence on the same day may have led to overestimation of intraobserver reliability. Although similar ultrasonography equipment was used, even machines of the same type may exhibit different image features. Our study was performed with current high-quality modern 6–18 MHz probes. Probes for examining temporal arteries should provide frequencies of ≥15 MHz (259). Probes with frequencies >20 MHz will further increase resolution and allow reliable measurement of the intima-media complex of temporal arteries (247). Very few of the sonographers participating in our study are using these probes. Further, intima-media complex measurement of axillary arteries could have a role in future ultrasonography protocols in suspected GCA.

These exercises following the OMERACT Ultrasonography Group guidelines show that the OMERACT-derived definitions of halo and compression signs of temporal and axillary arteries are applicable in recent-onset GCA with excellent inter- and intraobserver reliabilities for the diagnosis of GCA if sonographers are experienced, are provided sufficient time for examination, and are familiar with the US equipment, high frequency probes > 15 MHz, and settings.

Chapter 3 Assessment

There are no validated biomarkers for the assessment of primary systemic vasculitis (112). In their absence there has been a concerted effort to create clinical tools that accurately assess outcomes of interest. For any disease, the ultimate outcome is 'cure'. This has been difficult to achieve in most autoimmune rheumatic diseases. The focus has therefore been on 'remission'. If 'remission' is defined as absence of disease activity, 'relapse' could be defined as a return of disease activity. For both concepts to work, it must be possible to tangibly quantify 'disease activity'. By 2006, BVAS (109), BDCA (121), VAI (122) and BVAS/WG (123) were clinical tools that were being used in clinical trials of primary systemic vasculitis to quantify disease activity. They all had major limitations. BVAS was cumbersome and had to be modified before it could be used in any clinical trial (260). BVAS v2 was used without undergoing any formal validation. BDCA and BVAS/WG were disease specific tools for Behçet's disease and GPA respectively, that underwent very limited validation (Table 2 and Table 3). VAI was validated across a breadth of vasculitis syndromes but was only had convergent validity assessed against PGA (Table 3). None of these clinical tools passed the OMERACT filter (131), which is what the international community had come to expect of outcome measures. There was need for a new activity measure that had convergent validity against clinical and biological parameters, was reliable, sensitive to change and feasible to perform so that it could enter daily clinical practice. We validated the BVAS v3 in a UK cohort across a breadth of vasculitis syndromes with convergent validity against the BVAS v2, treatment decisions, CRP, PGA and VAI; excellent inter and intraobserver reliability and sensitivity to change (110). I submitted an extended analysis of this work for a higher degree at the University of Oxford (130). This work needed validation in a second international cohort.

With the recognition that remission induction for primary systemic vasculitis needed a combination high dose glucocorticoid therapy and cytotoxic chemotherapy came

the appreciation of iatrogenic effects of the drugs (261-263). These drugs caused ‘damage’, irreversible scars which were sometimes as bad as the disease that they were meant to be treating. At the same time, the disease itself could continue causing damage (137). To ensure that clinical assessment could differentiate ‘damage’ from ‘activity’, the VDI was formed and validated for use alongside BVAS (136). The purpose of recognising damage was purely to differentiate it from active disease to allow for improved clinical decision-making (136). Over time, it was recognised as an independent risk factor for survival (137, 264). Was ‘damage’ something to be catalogued, used for differentiating from ‘activity’, or a prognostic marker? In addition to these questions, academics from the USA were using VDI with different rules to those used in its formal validation. They used a different timescale for defining ‘damage’ (6 months vs 3 months in the original VDI validation). There was also a difference of opinion on whether items of damage should be attributable to vasculitis. The original concept was of identifying damage as distinct from activity, but when using VDI was considered for use in clinical trials, there was concern that indexing items that may not be related to vasculitis or treatment may make data difficult to interpret. There was need for homogeneity on how VDI was to be used, the need for a different instrument, and a clear vision on why we needed to record ‘damage’.

‘Activity’ and ‘Damage’ are two sides of a coin that clinicians are concerned about. There had been recognition that what matters to clinicians may not necessarily be patient-focussed (152, 155, 265). BVAS v3 and VDI, for example, did not consider activities of daily living, employment, fatigue, disability, pain, mental health etc. There was recognition that we needed relevant patient-focussed outcome measures (266). Inducing ‘remission’ as measured by clinical tools did not necessarily equate to improvements in QOL (157). That raises the question of whether we can classify patients as ever being in ‘Remission’ if they are still feeling unwell, unable to work, have high levels of pain and fatigue (168). Presently, there are no validated QOL or patient-reported outcome measures for primary systemic vasculitides.

I present three papers here that have helped improve assessment of vasculitis. The main work constitutes one paper each on 'activity' and 'damage'. A consensus position paper on the future of damage assessment is presented as supportive work. My role in the three papers is as under –

1. A cross-sectional study of the BVAS v3 in systemic vasculitis
    a. Recruitment of cases at two sites
    b. Design of database for data capture
    c. Analysis
    d. Completing paper cases for feasibility
    e. Editing manuscript
2. Measurement of damage in systemic vasculitis: a comparison of the Vasculitis Damage Index with the Combined Damage Assessment Index
    a. Construct of CDA
    b. Recruitment of cases at two sites
    c. Design of database for data capture
    d. Writing paper cases for training
    e. Analysis
    f. Editing manuscript
3. The future of damage assessment in vasculitis
    a. Discussions over 3 days at OMERACT 8
    b. Defining domains of assessment for damage
    c. Editing the manuscript

I am indebted to Dr Ravi Suppiah, Professor Raashid Luqmani, Dr Philip Seo and Professor Peter Merkel for the work presented here.

A cross-sectional study of the Birmingham Vasculitis Activity Score version 3 in systemic vasculitis (124)

Authors

Ravi Suppiah, Chetan Mukhtyar, Oliver Flossmann, Federico Alberici, Bo Baslund, Rajbir Batra, Denise Brown, Julia Holle, Zdenka Hruskova, David Jayne, Andrew Judge, Mark Little, Alessandra Palmisano, Coen Stegeman, Vladimir Tesar, Augusto Vaglio, Kerstin Westman, Raashid Luqmani

Introduction

The vasculitides are a group of complex heterogeneous disorders where multiple organ systems can be involved. The common feature between these diseases is inflammation of blood vessels; usually categorized by the predominant calibre of the vessels involved. Most of the vasculitides can be fatal or organ threatening and require glucocorticoid therapy alone or in combination with more potent immunosuppression.

Disease activity is a well-recognized concept for inflammatory diseases where high disease activity suggests the need to escalate treatment and low disease states indicate that the disease is under control with current therapy. This differs from the concept of damage in vasculitis, which represents chronic scarring that is not responsive to further therapy (136). Unfortunately, in systemic vasculitis there is no single biomarker that can reliably inform us about disease activity. Inflammatory markers such as CRP are non-specific and may be raised for multiple other reasons or may be low due to recent steroid treatment. Other assessments such as rising ANCA titres (267), PET scanning (268-270) and MR imaging have all been proposed as methods of measuring activity but none have yet proved to satisfactorily perform this function (271, 272). Instead, the current best method of determining disease activity is to use a comprehensive clinical tool that can capture the multi-organ nature of vasculitis (109).

The importance of accurately quantifying disease activity is to allow physicians to make informed decisions about how to manage potentially toxic therapies. The current most widely used generic tool to quantify disease activity in systemic vasculitis is the BVAS (109, 110, 260). The original version was developed by consensus expert opinion in 1994 and consisted of 59 items grouped into nine organ systems (109). The BVAS v2 (260) was subsequently modified for use in the European Vasculitis Study Group (EUVAS) trials and more recently to the current version: BVAS v3 (110). The main difference between BVAS v3 and BVAS v2 is that the persistent boxes for each variable were replaced by a single box for the whole form, which is only ticked if all the items are due to persistent disease. There was a reduction in the number of items from 64 to 56 by merging or omission, but the overall maximum score was maintained. The weighting of items that was decided by expert consensus in the original version has remained relatively unchanged between the three versions.

The BVAS v3 has undergone initial validation in a cohort of 313 patients with mixed primary and secondary vasculitis from the UK (110). The objective of this study was to revalidate the BVAS v3 in a different cohort of patients from Europe.

Patients and Methods

Two hundred and thirty-eight consecutive patients (both inpatients and outpatients) with new or existing diagnoses of vasculitis were recruited from 11 centres in 7 European countries: UK (55), Netherlands (51), Denmark (49), Germany (47), Italy (25), Czech Republic (6) and Sweden (5). Local medical ethics requirements were met by each participating site. Only UK sites required formal ethics approval. Continental European sites did not require formal ethical approval as this was an observational study and did not involve any specific intervention. Participants gave their written informed consent before participating in the study. Basic demographics, type of vasculitis and duration of disease were recorded Table 13. All patients were assessed for disease activity and disease damage.

Table 13 Baseline demographics of the revalidation cohort

Diagnosis	*n* (%)	F	M	Median age (range), years	Median disease duration (range), months
GPA (renal)	98 (41.2)	39 (40)	59 (60)	56 (17–85)	38 (1–362)
GPA (non-renal)[a]	51 (21.4)	26 (51)	24 (47)	53 (19–75)	68 (1–269)
EGPA[a]	23 (9.7)	12 (52)	10 (43)	68 (45–82)	20 (2–252)
MPA	22 (9.2)	10 (45)	12 (55)	56 (17–81)	38 (2–219)
Other[b]	13 (5.5)	10 (77)	3 (23)	62 (29–84)	34 (0–228)
Mixed essential cryoglobulinemia	9 (3.8)	7 (78)	1 (11)	56 (27–77)	49 (8–420)
IgA vasculitis	7 (2.9)	4 (57)	3 (43)	23 (19–78)	18 (2–336)
Takayasu arteritis	6 (2.5)	6 (100)	0 (0)	32 (21–62)	98.5 (36–145)
Behçet's disease	5 (2.1)	3 (60)	2 (40)	39 (21–66)	120 (24–480)
Leucocytoclastic skin vasculitis	2 (0.8)	1 (50)	1 (50)	55 (25–84)	41.5 (5–78)
PAN (Hep B negative)	2 (0.8)	1 (50)	1 (50)	57 (37–78)	160 (114–206)

[a] Gender was missing for one patient. [b] Other vasculitis comprised: AAV not fitting any specific diagnosis; CNS vasculitis; drug-induced vasculitis; Goodpasture's disease; systemic rheumatoid vasculitis; not further specified; SLE vasculitis; GCA; hypocomplementaemic urticarial vasculitis.

Disease activity was measured using the BVAS v3, Vasculitis Activity Index (VAI) (122), Physician Global Assessment (PGA) on a 100-mm visual analogue scale, treatment decision (Table 14) and CRP. The VAI is an alternative validated measure of disease activity, which incorporates a subjective score for nine organ systems based on

perceived severity of involvement (each organ scored 0-4), and then the overall score divided by the number of organ systems scored (122). The BVAS v3 was tested against alternative measures of disease activity to assess convergent validity. Convergent validity tests the extent to which assessments that should theoretically be related to each other are in fact related. To demonstrate that BVAS v3 does not measure damage, we tested it against the VDI, which is a validated measure of damage in systemic vasculitis. Interobserver reliability (reproducibility) of BVAS v3 was examined in patients independently assessed by two observers on the same day (n = 20).

Table 14 Treatment decision categories and definitions

Category	Treatment decision	Definition
6	Major escalation	Commencing any immunosuppressive agent, glucocorticoid, or plasmapheresis, without stopping or reducing the dose of any other treatment OR Increasing the dose of glucocorticoid and immunosuppressive agent
5	Continue at major level	No change to a therapeutic regimen that includes cyclophosphamide or biologic therapy
4	Minor escalation	Increasing the dose of immunosuppressive agent or glucocorticoid
3	Continue at minor level	No change to a therapeutic regimen that excludes cyclophosphamide and biologic therapy
2	Reduction at major level start at minor level	Reduction or stopping of one or more drugs that includes cyclophosphamide or biologic therapy AND Commencing another drug
1	Reduction of therapy	Reduction or stopping of one or more drugs without increasing or commencing any other drug
0	No therapy	No therapy

Statistical analysis

R version 2.9.1 was used for the statistical analysis. The BVAS v3 scores were not normally distributed, so we used a non-parametric approach to measure its correlation with the VAI, treatment decision, CRP, and Physicians global assessment. In instances where more than one observation was available in a single patient, measurements from the patient's first visit were used for correlation.

Spearman's rank correlation coefficient (ρ) was calculated by independently ranking the two scores, then calculating the Pearson correlation between the ranks rather than the original measurements. The CIs for ρ were calculated using Fisher's transformation.

We used the ICC to calculate interobserver reliability for the overall BVAS v3 score. This method estimates the average correlation between all possible orderings of pairs and was calculated using a one-way analysis of variance. To assess reliability between observers for each of the categories in the BVAS v3 score, a linear-weighted κ-statistic was calculated, in which observed and expected proportions of agreement are modified to include partial agreements by assigning a weight of between 0 (complete disagreement) and 1 (complete agreement) to each category.

Results

The demographics of the cohort are shown in Table 13. GPA (63%), EGPA (9%) and MPA (9%) were the most common diagnoses. The remaining patients suffered from a mixture of other primary and secondary vasculitides. The BVAS v3 score ranged from 0 to 39 (maximum possible score 63) with the largest range seen in patients with GPA. There were 115 patients who were in remission (BVAS v3 score of 0) and 123 patients with active disease (BVAS v3 score ≥ 1). Table 15 compares the range scores for each diagnosis between this cohort and the original validation cohort described in the original validation cohort.

Table 15 Comparison of the range of diagnosis and BVAS (v. 3) scores between the current study and the original validation cohort

	Current study, patients from Europe (n = 238)		Original validation cohort, patients from the UK (n = 313)	
Diagnosis	n (%)	BVAS v3 median score (range)	n (%)	BVAS v3 median score (range)
GPA (general)	98 (41.18)	1 (0–36)	101 (32.27)	1 (0–37)
GPA (non-renal)	51 (21.43)	0 (0–39)	54 (17.25)	0.5 (0–25)
EGPA	23 (9.66)	0 (0–14)	28 (8.95)	0 (0–24)
MPA	22 (9.24)	2 (0–22)	15 (4.79)	2 (0–25)
Other[a]	13 (5.46)	0 (0–15)	46 (14.70)	4 (0–34)
Mixed essential cryoglobulinemia	9 (3.78)	5 (0–26)	6 (1.92)	6.5 (0–24)
IgA Vasculitis	7 (2.94)	1 (0–13)	10 (3.19)	3.5 (0–21)
Takayasu arteritis	6 (2.52)	0 (0–4)	9 (2.88)	0 (0–2)
Behçet's disease	5 (2.10)	6 (0–18)	25 (7.99)	2 (0–19)
Leucocytoclastic skin vasculitis	2 (0.84)	2.5 (2–3)	9 (2.88)	2 (0–6)
PAN (Hep B negative)	2 (0.84)	0.5 (0–1)	10 (3.19)	0 (0–6)

Other vasculitis comprised: AAV not fitting any specific diagnosis; CNS vasculitis; drug-induced vasculitis; Goodpasture's syndrome; systemic rheumatoid vasculitis; not further specified; SLE vasculitis; GCA; hypocomplementaemic urticarial vasculitis; granulomatous nephritis; polymyositis; systemic sclerosis-related vasculitis

Convergent validity

Of 238 patients, 234 (98%) had a treatment decision recorded. There was moderate correlation between BVAS v3 and treatment decision [ρ = 0.54 (95% CI 0.44, 0.62)] (Figure 5). Definitions for the treatment decisions are given in **Error! Reference source not found.**. Subgroup analysis of the 147 patients with GPA revealed a similar

correlation [ρ = 0.58 (95% CI 0.46, 0.68)]. Of the 238 patients, 217 (91%) had CRP levels recorded on the same day the BVAS v3 score was measured. There was a low correlation between BVAS v3 and CRP levels [ρ = 0.18 (95% CI 0.05, 0.30)] (Figure 5). BVAS v3 correlated strongly with the PGA [ρ = 0.85 (95% CI 0.81, 0.88)] and the VAI (ρ = 0.82, 95% CI 0.77, 0.85); n = 188 for both (Figure 5). The correlation remained strong when patients in remission (BVAS v3 = 0) were excluded from the analysis; BVAS v3 with PGA [ρ = 0.79 (95% CI 0.71, 0.85)] and the BVAS v3 with VAI (ρ = 0.75, 95% CI 0.66, 0.82).

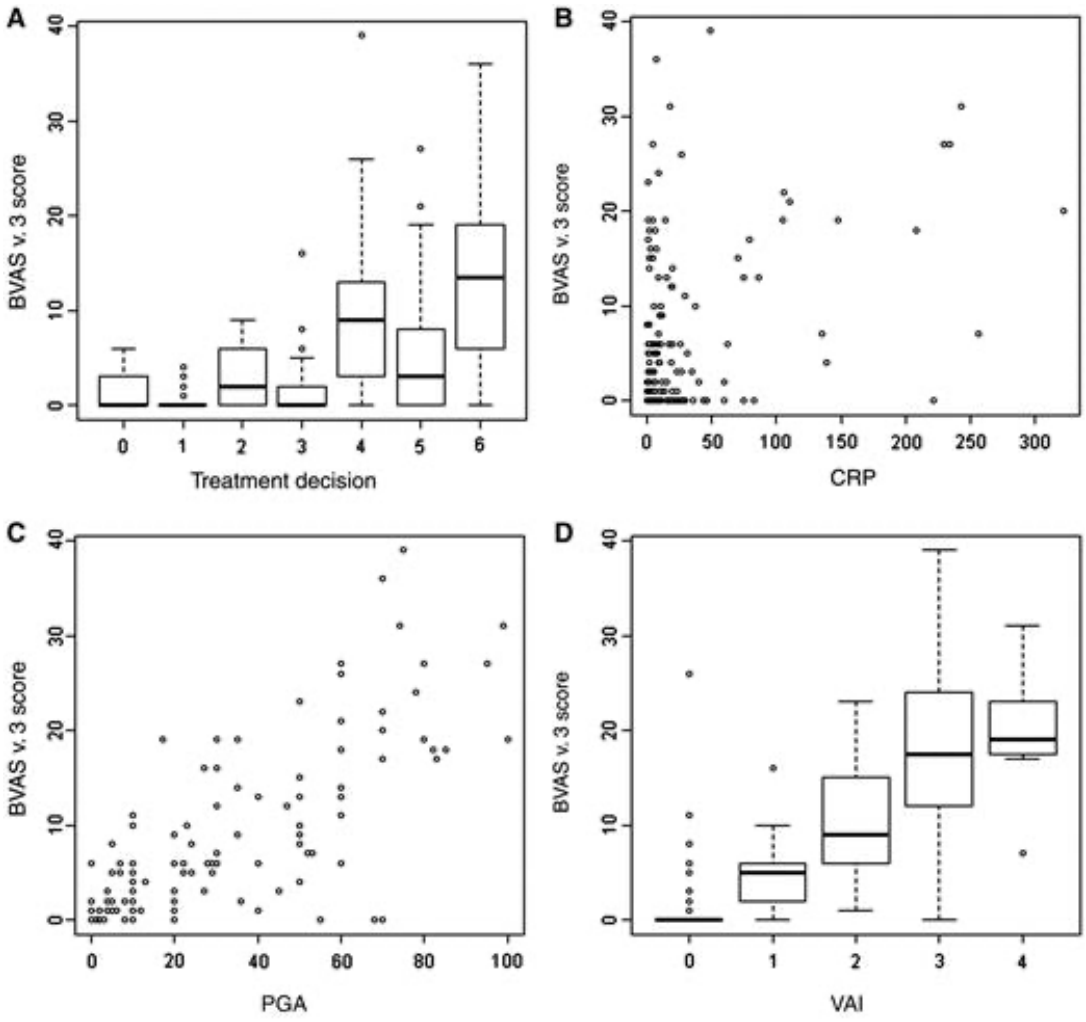

Figure 5 Comparison between potential measures of disease activity and the BVAS v3; (A) treatment decision, (B) CRP, (C) PGA and (D) VAI.

Divergent validity

There was no correlation between BVAS v3 and a concurrent measure of disease damage (the VDI) [ρ = −0.10 (95% CI −0.22, 0.03)].

Reliability

The interobserver reliability (n = 20) was very high with an ICC of 0.996 (95% CI 0.990, 0.998), for the total BVAS v3 score. The κ-statistics for the individual organ systems of BVAS v3 for interobserver reliability demonstrated perfect agreement [κ= 1.0 (95% CI 1.0, 1.0)] for cutaneous, mucous, ENT, chest, cardiovascular, abdominal, renal, and nervous systems. There was good agreement for general [κ = 0.71 (95% CI 0.29, 0.94)] and mucous membranes [κ = 0.88 (95% CI 0.00, 1.0)], although CIs were wide due to the small numbers. The κ-statistics for the cardiovascular and abdominal systems were not defined because all items were recorded as absent by both observers in all 20 patients.

Discussion

Quantifying vasculitis disease activity and extent of organ involvement assists clinical decision making. In the absence of a suitable biomarker that can quantify disease activity, a structured clinical tool like the BVAS v3 is necessary. The BVAS provides a standardized measure of disease activity in clinical trials, and provides a structured approach for these heterogeneous, multisystem disorders on which treatment decisions in clinical practice can be based.

This study reinforces the validity of the BVAS v3 and increases the generalizability of the tool. The original validation study included patients from the UK only (110), whereas this study includes patients from six other countries across Europe. The BVAS is a generic tool intended for all types of vasculitis, but has been used primarily in assessment of disease activity in AAV in clinical trial settings (273).

There is no gold standard for measuring disease activity in vasculitis, and hence our decision to compare multiple alternative methods. The BVAS v3 correlated well with the VAI and an informed PGA (performed after completing the BVAS v3), which both measured disease activity at the same time point. In addition, there was only a moderate correlation between BVAS v3 and treatment decision, which was expected. Treatment decision is dependent on what has happened to a patient's disease activity recently (i.e., serial BVAS scores) rather than at a single time point. For example, at disease onset, if a patient has haemoptysis and renal failure their disease would be very active and the BVAS score would be high. The treatment decision would be to start immunotherapy. If we then determined the patient's disease activity 4 weeks later, the haemoptysis and renal failure may have resolved, and therefore the BVAS score would be low. The treatment decision at that point would likely be to continue therapy at a major level because of the recent high disease activity and the knowledge that if treatment is reduced too soon the disease may flare. However, if the BVAS was repeated 6 months later and the score was still 0, the treatment decision would be likely to reduce therapy. Due to the cross-sectional nature of this study, we are unable to directly infer from our results that the BVAS v3 influences treatment decisions.

The feasibility of the tool has already been confirmed by earlier versions of the BVAS by their use in clinical trials involving over a thousand patients (the BVAS v3 is a condensed version of the previous versions) (110, 170, 274-277). All versions of the BVAS have high investigator acceptance. The BVAS v3 form takes <3 min to complete and requires minimal training, although training is important to achieve optimum reliability and reproducibility. A training manual, complete with practice cases and an online calculator are available on the EUVAS web site: http://www.vasculitis.org/.

Achieving remission (the total absence of disease), maintaining remission, and reducing the frequency of flares have been the primary outcome measures in most therapeutic trials in vasculitis in the past decade (110, 170, 274-277). These endpoints have almost always been defined in terms of the BVAS score, where

remission is a BVAS score of 0 and a flare is a rise in the BVAS score from 0. Experts in vasculitis, trial investigators and regulatory agencies have accepted the BVAS as the best available measure of disease activity, which reinforces the content and construct validity of the tool (169). In addition, the BVAS score at baseline has been shown to predict disease damage that occurs within the first 6 months (264), which in turn predicts mortality (137, 278).

This study has limitations. It is a cross-sectional study with few longitudinal data. The study design was not conducive to adequately assessing sensitivity to change. In the original validation study (110), this exercise was carried out in 39 patients for whom data were available at 0 and 3 months after introduction of treatment classified as major escalation. The treatment was expected to reduce disease activity in most patients. The BVAS v3 met that expectation in a clinically meaningful and a statistically significant way. This aspect of the BVAS v3 can be reassessed in future controlled clinical trials. A further limitation of the study is the small number of patients with large vessel vasculitis and non-AAV that were evaluated. We think that it is important to continue to evaluate patients with these other forms of vasculitis to add to the utility of the tool for those conditions and allow for cross-comparison between diseases. There is potential circularity in using the PGA as one of the reference standards to evaluate the BVAS v3. Investigators in this study both had expertise in vasculitis care and are involved with research in this area. Therefore, it is probable that the PGA was influenced by completion of the BVAS v3 form. We included the PGA in this study because it is a well-recognized comparator when developing or validating disease activity scores in other rheumatological diseases (278-280). To reduce this potential bias when validating the BVAS v3, we used several alternative methods of assessing disease activity such as the VAI, CRP and treatment decision.

In summary, this study adds support to the validity of the BVAS v3 and provides data that can be combined with other studies to continue to refine the tool. The current weighting of BVAS items is based on expert opinion (109, 110, 260). The next

evolution of the BVAS is likely to be in the form of improving the weighting of individual items based on available data sets (e.g., cross-sectional studies such as this and the previous validation study (110), as well as data from the long-term follow-up of the EUVAS trials (170, 275-277), and the Wegener's Granulomatosis Etanercept Trial (274). Mahr et al (281) have attempted to improve the scoring of an alternative version of the BVAS designed specifically for GPA (BVAS/WG) using the PGA as the reference standard. This method does not improve on expert opinion because it uses a subjective physician score as the reference to reweight items. We would advocate for objective endpoints to be used as the external anchors to determine new weighting. For example, variables known to influence rates of remission and relapse, renal survival, cardiovascular survival and mortality, or these events themselves could be used. We have previously published a systematic review exploring these factors (282).

Measurement of damage in systemic vasculitis: a comparison of the Vasculitis Damage Index with the Combined Damage Assessment Index (146)

Authors

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Introduction

The prognosis for a patient with systemic vasculitis has improved with treatment (170, 282-286). However, the long-term outlook is characterised by morbidity from recurrent flares, low- grade grumbling disease and/or accumulation of damage from previous disease activity or treatment (282, 287-289). Systematic recording and quantification of damage allows recording of the natural history of the disease, provides distinction from disease activity, and can be used as an outcome measure for clinical trials (145).

The VDI is a validated (136) method for measuring damage sustained from vasculitis or its treatment. It was developed by consensus by a group of vasculitis experts and is widely used in clinical trials (170, 274, 277, 290). However, the VDI may not adequately capture all damage caused by small and medium vessel vasculitis or treatment (145). A group of international experts in vasculitis from Europe and the USA constructed a new tool to measure damage called the Combined Damage Assessment Index (CDA) (Appendix 3). It is based on the VDI (145), and includes additional items of damage that were recorded in the Wegener's Granulomatosis Etanercept Trial but not captured by individual items on the VDI (145, 289).

The VDI comprises 64 items grouped into 11 categories. The CDA has 135 individual items in 17 categories and includes some bilaterality for items involving the eyes and

ears; 8 items assign gradation. The VDI and the CDA measure damage that has occurred since the onset of vasculitis; pre-existing comorbidity is not counted.

The OMERACT filter consists of the following criteria. (1) Truth: does it measure what it intends to measure? (2) Discrimination: does it discriminate from situations of interest? (3) Feasibility: can the measure be easily applied given the constraints of time, money, and interpretability? (131)

The objective of this study was to: (1) compare the performance of the CDA to the VDI in a cross-sectional study of patients with vasculitis, (2) begin to evaluate the CDA with respect to the OMERACT filter and (3) review the use of individual items in VDI and CDA.

Methods

Consecutive patients with new or existing diagnoses of vasculitis were recruited from 11 European centres. Local medical ethics requirements were met by each participating site. Participants gave their written informed consent before participating in the study.

Basic demographics, type of vasculitis, duration of disease, CRP and ANCA results were obtained on each patient. Patients were assessed for disease activity using the BVAS v3 (110) and disease damage using the VDI and CDA by an observer at each site (total of 11 observers). All forms were completed in English. For this study any damage scored had to be present following the onset of vasculitis and be present for at least 3 months. The total VDI score and the total CDA score are each represented by the cumulative number of items that are recorded, respectively. The VDI and CDA scores can stay the same or worsen over time but cannot improve. Each item in CDA or VDI contributes 1 point to the total score (266).

Convergent validity measures the extent to which assessments that are theoretically related to each other are actually related. In this case VDI and CDA should be closely

correlated. Convergent validity was assessed by comparing overall VDI and CDA scores as well as individual organ scores. To evaluate discrimination, we assessed the relationship between the damage assessment tools with the BVAS v3, CRP and ANCA result. In addition, interobserver and intraobserver reliability was investigated. A total of 28 (9.9%) patients were scored by 2 different observers at the same time point and 14 (4.9%) by the same observer at 2 different time points within 3 months of each other. This was the total number achieved during the study and not specifically chosen, but our expectation was that using trained observers would demonstrate good agreement based on previous experience with the VDI (136).

In addition to real patients, a VDI and CDA were completed on up to 20 different paper cases by an independent group of specialist doctors, fellows, and research nurses with an interest in vasculitis. The paper cases were used to assess feasibility only. The paper cases were designed on real cases seen by RL and CM but modified to encompass the range of items recorded in the VDI and CDA. The observers were provided with written instructions on how to complete the assessment. All observers who completed a CDA and a VDI on patients or paper cases were invited to complete a feasibility questionnaire for each of the damage assessment tools. The feasibility questionnaire was a series of 10 statements or questions that the respondents had to rate or answer on a 4-point Likert scale.

We identified unused items in VDI from the current study and combined data published on damage assessment in the Wegener's Granulomatosis Etanercept Trial (274) and from unpublished 5-year follow-up results from the EUVAS cohorts (170, 275-277) to provide a large sample of patients to determine the potential redundancy of VDI items.

Statistical analysis

Stata V.10, (StataCorp, College Station Texas, USA) was used for analysis. The distributions of the BVAS v3, VDI and CDA scores were not normally distributed, so

we used a nonparametric approach based on ranks to measure their correlation. Spearman's rank correlation coefficient was calculated by independently ranking the VDI and CDA scores, then calculating the Pearson correlation between the ranks rather than the original measurements. We used the ICC to calculate interobserver and intraobserver reliability for overall VDI and CDA scores. This method estimates the average correlation between all possible orderings of pairs and was calculated using a one-way analysis of variance. To assess interobserver reliability between observers for each of the categories in the VDA and CDA a linear-weighted κ statistic was calculated, in which observed and expected proportions of agreement are modified to include partial agreements by assigning a weight between 0 (complete disagreement) and 1 (complete agreement) to each category. The 17 subcategories of the CDA were collapsed into the same 11 categories of the VDI for this analysis.

Results

A total of 283 patients (51% women, 49% men) with vasculitis were evaluated. Disease duration ranged from 0 to 480 months. A summary of the range of diagnosis, VDI and CDA scores and disease duration is shown in

Table 16. GPA (58.4%) and MPA (11.0%) were the most common diagnoses. The remaining patients were a mixture of other primary and secondary vasculitis. The scores ranged from 0 to 12 for the VDI and 0 to 26 for the CDA, with the largest range seen in patients with GPA with renal involvement. Table 17 shows organ system involvement as recorded by each of the damage tools. Of the 192 patients with a disease duration of at least 12 months, 170 (89%) had some damage recorded on the VDI compared to 176 (92%) on the CDA (as determined by a score >0 on each tool, respectively).

Table 16 Diagnoses, disease duration, disease damage and disease activity scores in patients with vasculitis

Diagnosis	n (%)	Median disease duration in months (range)	VDI Median (range)	CDA Median (range)	BVAS v3 median score (range)
GPA (with renal involvement)	104 (36.8)	36 (0–396)	2 (0–12)	4 (0–26)	1 (0-36)
GPA (without renal involvement)	61 (21.6)	60 (1–300)	3 (0–8)	4 (0–21)	1 (0-39)
MPA	31 (11.0)	18.5 (0–252)	2 (0–7)	3 (0–12)	0 (0-25)
EGPA	24 (8.5)	38 (2–240)	3 (0–12)	3 (0–15)	2 (0-22)
Other vasculitis*	17 (6.0)	20.5 (0–228)	1 (0–9)	2 (0–16)	2 (0-17)
IgA vasculitis	11 (3.9)	39 (2–360)	1 (0–5)	1 (0–11)	2 (0-15)
Mixed essential cryoglobulinemia	11 (3.9)	49 (3–420)	2 (0–6)	4.5 (0–10)	6.5 (0-26)
Behçet's disease	9 (3.2)	60 (7–480)	3 (0–7)	5 (1–8)	4 (0-18)
Takayasu arteritis	7 (2.5)	109 (36–264)	3 (0–4)	4 (0–7)	0 (0-4)
Isolated skin vasculitis	4 (1.4)	20.5 (4–78)	0 (0–4)	0.5 (0–9)	3.5 (2-5)
PAN (not HBV associated)	2 (0.7)	160 (114–206)	0.5 (0–1)	1 (0–2)	0.5 (0-1)
Systemic rheumatoid vasculitis	2 (0.7)	40 (32–48)	1.5 (1–2)	2 (2–2)	1 (1-1)

**Other vasculitis comprised of: AAV not fitting any specific diagnosis (four patients); unspecified small vessel vasculitis (three patients); CNS vasculitis (three patients); not further specified (two patients); SLE vasculitis (one patient); GCA (one patient); hypocomplementemic urticarial vasculitis (one patient), drug-induced vasculitis (one patient), Anti-GBM disease (one patient).*

Table 17 Frequency of organ system damage as determined by VDI and CDA and the correlation between the total score for each organ system between the two disease damage tools in patients with vasculitis

Score	Frequency of organ damage as determined by VDI, n (%)	Median VDI (range)	Frequency of organ damage as determined by CDA, n (%)	Median CDA (range)	Spearman's ρ for total score in each organ system (95% CI)

Total score	213 (76.6)	2 (0–12)	212 (76.3)	3 (0–26)	0.90 (0.87 to 0.92)
Musculoskeletal	46 (16.6)	0 (0–3)	45 (16.2)	0 (0–4)	0.86 (0.83 to 0.89)
Skin/mucous membranes*	20 (7.2)	0 (0–3)	76 (27.3)	0 (0–4)	0.47 (0.38 to 0.56)
Ocular	46 (16.6)	0 (0–3)	52 (18.7)	0 (0–6)	0.94 (0.93 to 0.96)
ENT†	110 (39.6)	0 (0–5)	108 (38.9)	0 (0–13)	0.89 (0.86 to 0.91)
Pulmonary	42 (15.1)	0 (0–3)	43 (15.5)	0 (0–3)	0.94 (0.92 to 0.95)
Cardiovascular	50 (18.0)	0 (0–3)	67 (24.1)	0 (0–5)	0.77 (0.72 to 0.82)
Peripheral vascular disease	13 (4.7)	0 (0–3)	92 (33.1)	0 (0–4)	0.81 (0.77 to 0.85)
Gastrointestinal	1 (0.4)	0 (0–1)	30 (10.8)	0 (0–1)	0.71 (0.64 to 0.76)
Renal	61 (21.9)	0 (0–3)	4 (1.4)	0 (0–7)	0.89 (0.86 to 0.91)
Neuropsychiatric‡	74 (26.6)	0 (0–2)	69 (24.8)	0 (0–4)	0.75 (0.70 to 0.80)
Endocrine	NA	NA	30 (10.8)	0 (0-2)	
Haematology / Oncology	NA	NA	4 (1.4)	0 (0-1)	
Other¶	59 (21.2)	0 (0-2)	69 (24.8)	0 (0-2)	

The p value for all Spearman's correlations is less than 0.001.

**The main reason for discrepancy is the inclusion of skin bruising and scaring on the CDA; items not present on the VDI. When these two items were removed from the analysis the Spearman's ρ was 0.70 (95% CI 0.64 to 0.76).*

†ENT is composed of four separate categories on the CDA: ears, nose, sinuses, and subglottic stenosis.

‡More than 80% of this organ system involvement was accounted for by peripheral neuropathy. §Haematology and oncology items are captured under 'other' in the VDI.

¶Weight gain >10 lbs/4.4 kg was the main item captured under 'other' on the CDA (14.8%). Weight gain is not present as an individual item on the VDI.

Convergent validity

Measurements taken in an individual patient on the same date for VDI and CDA scores were paired together. In instances where more than one paired observation was available in a single patient (i.e., patients assessed twice to calculate interobserver or intraobserver reliability), one of the paired observations was randomly chosen. For the total VDI and CDA scores there was a high positive correlation (ρ=0.90, p<0.001); a graphical representation of this is shown in Figure 6. There was a high positive correlation between the organ system scores, except for 'skin/mucous membrane', where there was a moderate correlation (ρ=0.47, p<0.001). When the two skin-related items found in CDA but not VDI, 'easy bruising' (15.8% of patients) and 'cutaneous scarring' (9.0%) in the CDA, were removed from the analysis, the correlation was 0.70 (p<0.001). A complete list of the correlations between the organ systems between the VDI and CDA is provided in Table 17.

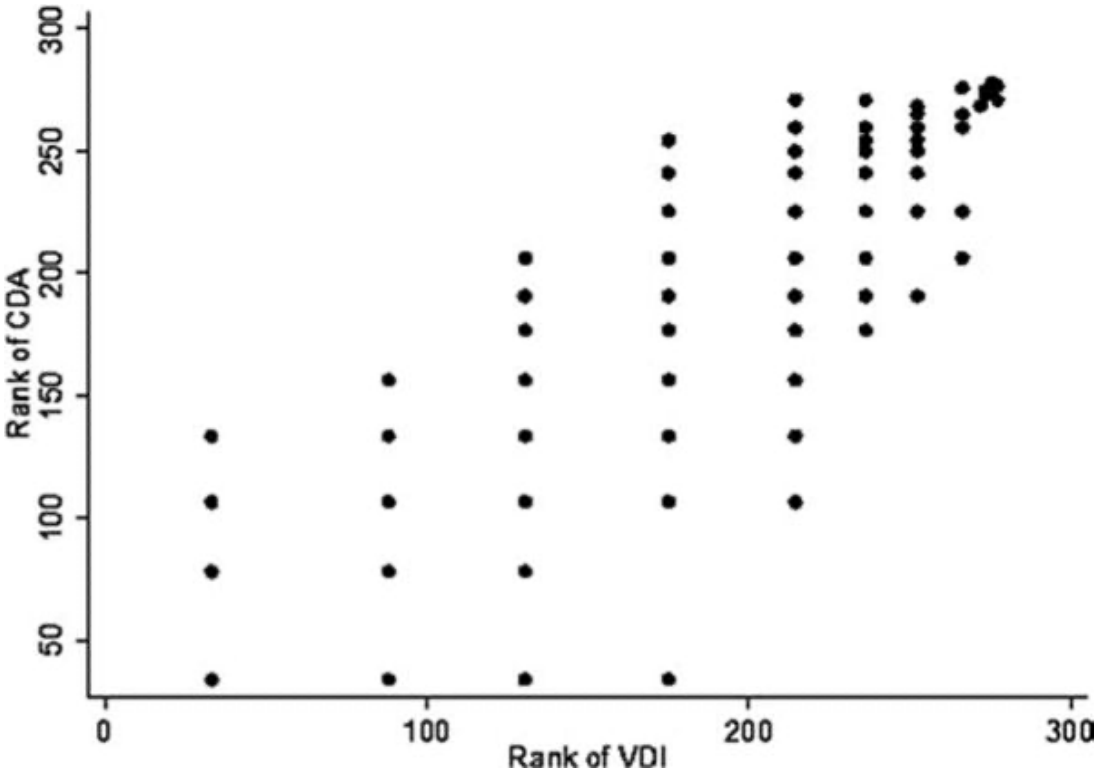

Figure 6 Scatterplot showing ranked VDI versus CDA. Patients with the same score were assigned average rank.

Discrimination

The correlation (Spearman's ρ) with BVAS v3 was −0.17 (95% CI −0.28 to −0.05) and −0.19 (95% CI −0.30 to −0.07); CRP −0.09 (95% CI −0.21 to 0.04) and −0.12 (95% CI −0.24 to 0.01); ANCA −0.26 (95% CI −0.45 to −0.06) and −0.32 (95% CI −0.49 to −0.12), for VDI and CDA, respectively. This shows that there was no correlation between the two measures of disease damage with measures of disease activity or items considered unrelated to disease damage.

Reliability

The interobserver reliability using the ICC was 0.94 (95% CI 0.89 to 0.98) for the VDI and 0.78 (95% CI 0.63 to 0.93) for the CDA. The interobserver reliability was better for patients with short compared with long disease duration: ICC was 0.99 (95% CI 0.97 to 1.00) and 0.87 (95% CI 0.74 to 0.99) for disease duration ≤3 years versus 0.90 (95% CI 0.79 to 1.0) and 0.67 (95% CI 0.33 to 1.0) for disease duration >3 years on the VDI and CDA, respectively. Observations for intraobserver reliability were restricted to patients who were reassessed by the same observer within 3 months (14 patients for the VDI, 15 patients the CDA). The intraobserver reliability was 0.92 (95% CI 0.83 to 1.00) for the VDI and 0.87 (95% CI 0.75 to 1.00) for the CDA. There were not enough patients to determine intraobserver reliability stratified by disease duration. The κ statistics for the individual systems for interobserver and intraobserver reliability (Table 18) demonstrated fair to good agreement, although CIs were wide due to small numbers (only 3/28 patients had any items recorded in the musculoskeletal system). No individual musculoskeletal item could account for the wide CIs.

Table 18 Interobserver and intraobserver reliability of measurement of damage in vasculitis for each organ system

Organ system	Interobserver reliability	Intraobserver reliability

	κ (95% CI)		κ (95% CI)	
	VDI (n=28)	CDA (n=28)	VDI (n=14)	CDA (n=15)
Musculoskeletal	0.65 (0.02, 1.00)	0.65 (0.02, 1)	–	–
Skin / mucous membrane	0.78 (0.59, 1)	0.59 (0.32, 0.83)	1.00 (1, 1)	0.41 (0, 0.65)
Ocular	1	1	1 (1, 1)	1 (1, 1)
ENT	0.77 (0.46, 1)	0.59 (0.23, 0.84)	0.79 (0.46, 1)	0.78 (0.50, 0.96)
Pulmonary	1	0.78 (0.37, 1)	1 (1, 1)	0.76 (0.32, 1)
Cardiovascular	0.83 (0.60, 1)	0.63 (0.42, 0.84)	1 (1, 1)	0.77 (−0.07, 1)
Peripheral vascular	1	0.31 (−0.82, 1)	–	–
Gastrointestinal	–	–	–	–
Renal	0.80 (0.19, 1)	0.70 (0.40, 0.88)	0.82 (0.45, 1)	0.45 (0, 0.88)
Neuropsychiatric	0.52 (0.11, 0.92)	0.46 (0, 0.92)	0.76 (0.32, 1)	0.58 (0.07, 1)

- No patients had damage in this organ system

The use of individual items

Table 19 shows the 10 most used items for each of the damage assessment tools. The items mainly comprised upper respiratory tract, renal, auditory features, and peripheral neuropathy (in keeping with GPA being the most common diagnosis). Items frequently used in the CDA, but not captured by the VDI were easy skin bruising (15.8%), weight gain >10 lbs/4.4 kg (14.8%) and cutaneous scarring (9.0%). Due to the increased number of options for recording damage on the CDA this has resulted in discrepancy in scoring items on the CDA compared to the VDI. For example, the proportion of patients with glomerular filtration rate <50% is different between the two assessment tools, primarily because there are other options on the CDA for recording renal impairment.

Table 19 The 10 most used individual items of damage in vasculitis

VDI	**%**	**CDA**	**%**
Nasal blockage/crusting	22.3	Chronic rhinitis/crusting	26.6
Peripheral neuropathy	21.9	Hypertension[*]	21.6
Hearing loss	19.1	Sensory neuropathy[†]	21.6

Hypertension	16.6	Proteinuria <3 g/24 h	17.6
Proteinuria	16.6	Easy bruising	15.8
GFR<50%	15.1	Weight gain >10 lbs/4 kg	14.8
Osteoporosis	11.9	Conductive hearing loss	13.7
Chronic sinusitis	11.5	GFR<50%	13.3
Nasal bridge collapse	9.7	Chronic kidney disease	12.6
Cataract	9.0	Osteoporosis	12.6

**This includes patients with prehypertension, or stage 1 or stage 2 hypertension.*

†Includes patients with mild, moderate, or severe sensory neuropathy.

A total of 13 items of damage were not used in the VDI; 11 additional items were used less than 1% of the time. In comparison, the CDA had 23 items of damage, 4 gradations of severity and 2 items attributing causality that were not used. There were an additional 45 items that were used less than 1% of the time. Table 20 shows a list of the least used items in both damage tools.

Table 20 Least used items in the VDI and CDA in patients with vasculitis

Items not used	**Items used <1%**
VDI:	
Second episode fresh loss of pulses in one limb[*†]	Deforming/erosive arthritis[*]
Second cerebrovascular accident[*]	Cardiomyopathy
Blindness other eye	Claudication
Chronic peritonitis[*†]	Gut infarction/resection
Major psychosis[*†]	Major tissue loss[†]
Mesenteric insufficiency/pancreatitis[*]	Marrow failure
Minor tissue loss	Myocardial infarction[*]
Oesophageal stricture/upper GI surgery[*†]	Pleural fibrosis
Osteomyelitis[†]	Pulmonary infarction
Pericarditis ≥3 months/pericardiectomy[*†]	Seizures[*†]
Pulmonary hypertension[†]	Transverse myelitis[*]
Subsequent major tissue loss[*†]	
Subsequent myocardial infarction[*†]	

CDA:	
Auricular cartilage deformity left	Auricular cartilage deformity right
Cervical cancer	Bladder cancer
Cholesteatoma left	Continuous oxygen dependency
Cholesteatoma right	Gangrene with permanent tissue loss
Chronic peritonitis	Gut infarction/resection
Haematopoietic malignancy	Hepatic fibrosis
Mesenteric insufficiency/pancreatitis	Impaired fasting glucose
Myelodysplastic syndrome	Optic nerve oedema left
Oesophageal stricture/surgery	Pericarditis or pericardiectomy
Optic nerve oedema right	Pleural fibrosis
Osteomyelitis	Pseudotumour left eye
Percutaneous coronary intervention	Pseudotumour right eye
Pulmonary hypertension	Pulmonary infarction
Refractory cytopenia	Retinal artery occlusion left
Retinal artery occlusion right	Retinal changes left
Retinal vein occlusion right	Retinal vein occlusion left
Scleral perforation left	Scleral thinning left
Scleral perforation right	Scleral thinning right
Second cerebrovascular accident	Second episode of absent pulses in one limb
Subsequent major tissue loss	Tissue loss (includes major and minor)
Third degree AV block	
Transverse myelitis	
Vena caval filter	

For VDI, items used <1%. For CDA, items used <0.05%

**Items not used in the Wegener's Granulomatosis Etanercept Trial cohort, n=180 patients*

†*Items not used in the long-term follow-up (5-year VDI) of the EUVAS cohorts, n=339 patients*

Redundant items on the VDI

Combining our study population with the Wegener's Granulomatosis Etanercept Trial cohort and patients with 5 years of follow-up in the EUVAS cohorts represent a total of 804 patients. The following seven items of damage were not used in the VDI in this

combined population: second episode of fresh loss of pulses in one limb, chronic peritonitis, major psychosis, oesophageal stricture/upper gastrointestinal surgery, pericarditis ≥3 months/pericardiectomy, subsequent major tissue loss and subsequent myocardial infarction.

Feasibility

In all, 12 observers completed the feasibility questionnaire (including 7/11 observers who scored the VDI and CDA in real patients and 5 who completed paper cases only). The five observers who completed the paper cases only were new users to both tools. Completion time was 5–10 min (range: <5–10 min) for VDI compared to 10–15 min (<5–20 min) for CDA. Experienced users completed both assessments in <5 min. In all, 10 observers (83%) reported that the VDI and CDA were useful to record the natural history of vasculitis. All observers stated that the CDA covered the full spectrum of damage attributable to vasculitis compared to 7/12 (58%) for the VDI. In all, 8 (67%) observers said that the VDI was a practical tool for clinical use compared to 5/12 (42%) for the CDA; however, only 7/12 (58%) and 3/12 (25%), respectively, would use it in clinical practice. Nine (75%) observers found the VDI easy to complete compared to five (42%) for the CDA. All observers stated that the VDI was a useful tool to measure outcomes in clinical trials whereas two disagreed with this statement for the CDA. Overall preference for the tools was mixed; 8/12 (67%) favoured the VDI. The CDA was preferred by some experienced observers, especially by those individuals who could complete both tools in a similar timeframe.

Discussion

Damage assessment represents the permanent cumulative burden of disease morbidity from vasculitis or its treatment. It records the disease course, identifies the manifestations that do not warrant further immunosuppressive treatment and serves as an outcome measure in clinical trials (266). Both tools evaluated in this study serve this function well but have contrasting benefits and drawbacks.

The level of damage detected is consistent with previous reports; 89% of patients with at least 12 months of disease duration had ≥1 item of damage captured by VDI and 92% by CDA. This compares to 89% in the Wegener's Granulomatosis Etanercept Trial (289). A Norwegian study of GPA showed 100% of patients having damage by the end of follow-up (mean 4.7 years) (264); and a UK series with systemic vasculitis demonstrated 96% with a VDI score of ≥1 by the end of follow-up (mean 6.1 years) (137). The median disease duration of 39 months in this study may have been too short to detect some items of damage such as malignancy which was recorded in only 1.4% of patients. However, the relationship between vasculitis and malignancy is complex (291-294).

The advantages of the VDI are that it is simple to complete, has very good reliability and is a widely accepted outcome measure in clinical trials (170, 277, 289), with proven prognostic value. A score ≥1 at diagnosis predicts increased mortality and future organ damage (264). The VDI was preferred by most observers in this study, mainly due to its relative simplicity, especially by less experienced users, which is of key importance if it is to be used infrequently in clinical practice. However, the main application of the VDI is in clinical trials, where it functions as a generic damage assessment tool for all types of vasculitis, thereby enabling widespread use, which facilitates familiarity, accuracy, and completion speed.

The CDA is intended for use in clinical trials of AAV. The CDA is more comprehensive than the VDI and may be more sensitive in detecting damage. In addition, the ranges of scores are larger and may be better at detecting change, although this was not tested in the current study. The CDA takes longer to complete than the VDI in less experienced observers, but the difference was minimal among experienced investigators. In a clinical trial setting where more investment in training is available and there is less time pressure, the increased level of data capture by the CDA may be more desirable. There is disagreement among experts as to whether or not we should move towards disease-specific assessment tools in vasculitis clinical trials (i.e., whether specific forms should be used for specific types of vasculitis, or if VDI could

apply to types of vasculitis) (145, 295). The benefit of increased sensitivity of a disease-specific tool such as the CDA must be balanced against more limited application (i.e., confined to use only in AAV). In addition, if multiple tools are developed for different forms of vasculitis, it reduces the ability for comparison between broadly similar conditions. Ultimately it may be useful to discuss a damage form that has a generic component and a specific component.

Gradations of severity and weighting of items are not adequately captured by existing damage tools. Intuitively, some forms of damage or gradations of severity may have more impact on a patient's QOL or prognosis than others. The future weights applied to individual items on the CDA or VDI should improve the correlation between mortality and QOL (266). Efforts are underway to address this (296). In addition, there are redundant items in both tools; the seven unused items on the VDI (from Wegener's Granulomatosis Etanercept Trial and EUVAS trials) could be omitted from any future damage tools that are specific for AAV to simplify the forms. Even if these items are removed from the main form, they will be retained in the glossary under 'other items' so these less common items can be recorded and contribute to the index. However, unused items such as cardiomyopathy or loss of pulses may be important for some diseases (e.g., Takayasu arteritis) therefore should be retained in generic damage assessment tools.

There are limitations in this study. Study observers were already familiar with the VDI from previous clinical or trial experience whereas for most investigators, this study was the first time they used the CDA. This may explain the lower interobserver and intraobserver reliability of the CDA. Further training and more experience with the CDA could improve its reliability and acceptability. The current study is cross-sectional, and therefore cannot demonstrate changes to the CDA over time. Grading severity of individual items and allowing resolution of items may influence its correlation with QOL indices and mortality. The classification of patients with less well-defined forms of disease is difficult and there may be overlap between the

categories listed in Table 16. This is the real-life setting and therefore inclusion of these heterogeneous patients allows for the generalisability of our results.

In summary, this is the first study to test the CDA as a measure of damage in vasculitis. We have started evaluating the CDA with respect to the OMERACT filter, but more experience, especially in a longitudinal setting is required. The VDI remains the standard for damage assessment in vasculitis, and this study further validates its use. If there is move toward disease-specific damage assessment, then future revisions including a weighting system are likely to serve as outcome measures for trials in AAV.

Supportive work

The future of damage assessment in vasculitis (145)

Although clinical trials of vasculitis frequently focus on disease activity, for the individual patient the most concerning issue may be damage (i.e., the disease sequelae that are unlikely to respond to immunosuppressive agents). International interest has led to a new initiative that will re-examine the way damage in vasculitis is assessed. In 2004, an international group of investigators with an interest in vasculitis began re-examining all aspects of outcome measures in vasculitis. The 2004 OMERACT 7 Vasculitis Special Interest Group led to development of a consensus regarding the status of outcome measures in vasculitis and set in motion an agenda directed to replacing existing measures with data-driven revisions or new methods of disease assessment (136). The Vasculitis Clinical Research Consortium OMERACT Working Group continued to meet and work toward these goals. The OMERACT 8 Vasculitis Workshop provided a forum to refine a research agenda for vasculitis outcomes measurement, with a particular focus on damage assessment.

The OMERACT initiative is a collaborative project of the Vasculitis Clinical Research Consortium and the EUVAS and is supported by grants from the US National Institutes of Health and EULAR. Our report introduces the concept of damage assessment in vasculitis, gives the results of the OMERACT 8 Vasculitis Workshop, and outlines the agenda for an international project to redefine the assessment of damage in vasculitis.

Background

After a disease flare is successfully controlled, patients continue to experience the consequences of the damage that result from disease flare, persistent low-level ("grumbling") disease, and the toxic effects of therapy. Distinguishing activity from damage is crucial to identify aspects of disease that will not respond to

immunosuppressive therapy, and to prevent unnecessary use of cytotoxic medications.

Although the concept of damage seems intuitive, it must be strictly defined to ensure reproducibility among clinicians from diverse backgrounds and with different levels of experience. The aim of a damage index is to catalogue the forms of damage that occur because of vasculitis, so that they can be consistently identified and recorded as a measure of the cumulative burden of disease.

The VDI comprises 64 items of damage (grouped into 11 organ-based systems) that a group of experts agreed was representative of the forms of damage incurred by patients with systemic vasculitis (Appendix 2) (295). Damage was defined in the VDI by the following characteristics:

- Irreversibility: By definition, the VDI items of damage are irreversible.
- Time element: By definition, a finding must be present continuously for at least 3 months before it can be an item of damage.
- Attribution: The VDI records all forms of damage that have occurred since the onset of vasculitis, regardless of cause.
- Grading and weighting: Individual items of damage are not scaled according to severity; all items of damage contribute equally to the overall VDI score.

Increasing use of formalized damage assessment in clinical trials of vasculitis has led to a growing need to improve the evaluation of damage in vasculitis and to re-examine the principles on which damage assessment is based. This process is a natural part of the cycle of revision and improvement that occurs with all outcome measures. This re-examination will strengthen our understanding of this fundamental concept, improve our ability to track patient outcomes and response, and provide stronger outcome tools for use in clinical trials.

In 2004, investigators with expertise in the assessment of vasculitis assembled at OMERACT 7 to discuss the status of outcome measures in vasculitis (295). As a

starting point, the group concentrated on AAV, i.e., GPA and MPA, which have recently been the focus of important clinical trials in the US and in Europe (274, 276, 277). This meeting was the start of a new initiative to reexplore the definition of damage to improve existing instruments for the assessment of vasculitis, and to achieve broader consensus within the vasculitis research community for outcome assessment in clinical trials.

As a result of meetings in preparation for OMERACT 8, we recognized that there was significant intellectual overlap between American efforts to develop an index of damage specific for AAV and a European project to refine the VDI. Because of this overlap, and the strong desire to avoid the creation of multiple overlapping outcome measures, we elected to combine these efforts toward creating a CDA that will lead to the development of an improved instrument that will eventually be used to assess many forms of small and medium-vessel vasculitis.

Objectives and Hypotheses

The purpose of a damage index for vasculitis is 3-fold:

- To provide a clear distinction between disease activity and disease damage
- To record the natural history of disease (whether treated or untreated)
- To serve as an outcome measure for clinical trials

The application of a damage index at a predetermined time following disease onset or relapse (probably 1 year) may be a valuable endpoint for clinical trials and may serve as a method for comparing the efficacy of competing therapies. Such an endpoint could be defined by the number of patients who exceed a threshold damage index at time X or by the rate of accumulation of damage after Y months of therapy. Since many patients in clinical trials may have already suffered significant amounts of damage at the time of enrolment, it may also be important to specify the level of baseline damage.

We propose to re-examine the assessment of damage in vasculitis in 4 phases:

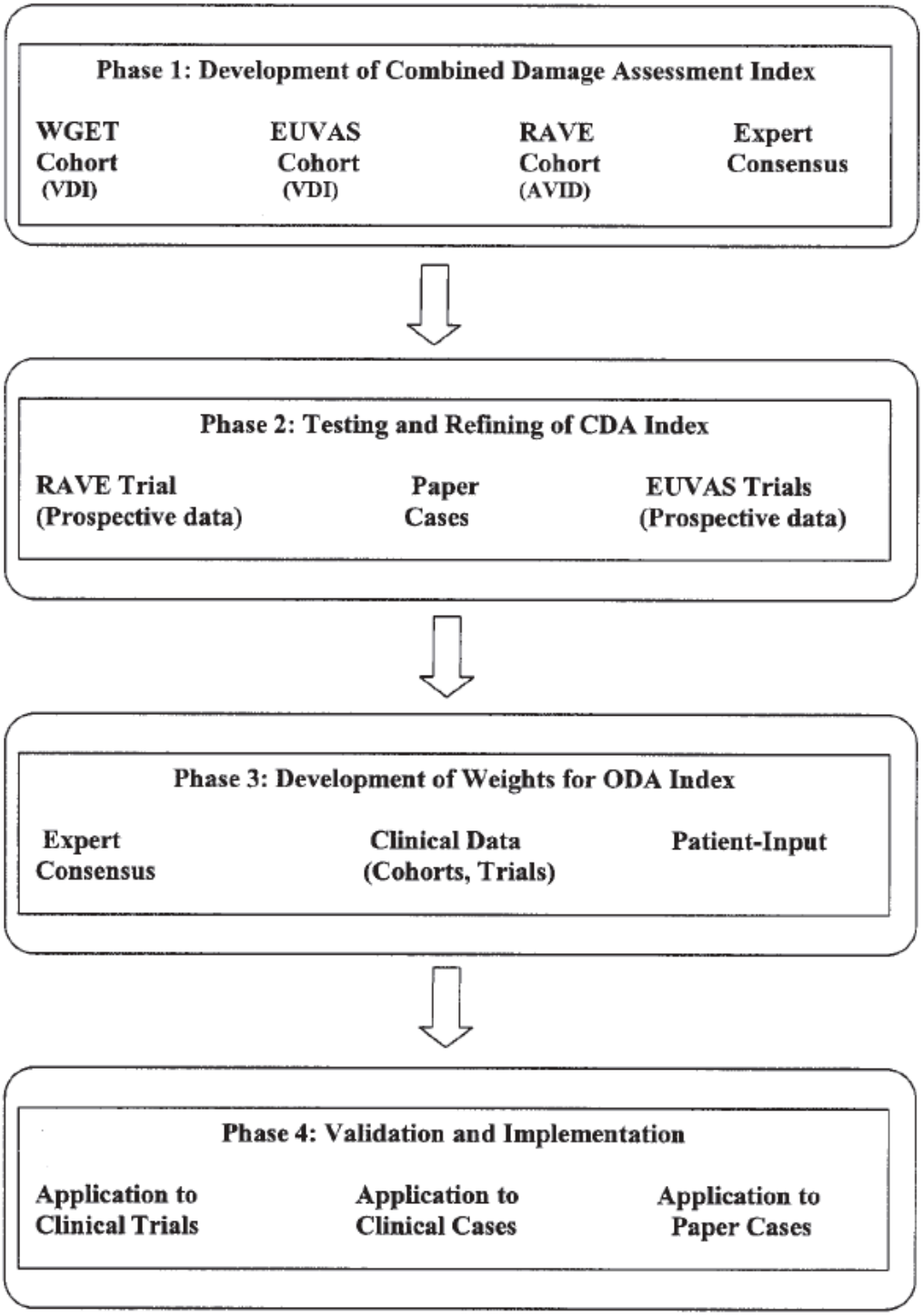

Figure 7 The process of the Vasculitis Clinical Research Consortium-OMERACT damage assessment initiative

- Phase 1: Development of the CDA

- Phase 2: Testing and refining the CDA
- Phase 3: Development of a weighting schema
- Phase 4: Validation of the CDA

Phase 1: Development of the CDA

Because the VDI was designed to assess damage for all the vasculitides, there has been concern that it might not adequately record all forms of damage incurred by patients with these diseases. For example, the VDI does not distinguish among conductive, sensorineural, and mixed causes of hearing loss, making it difficult to collect reliable data regarding aetiology. Further, data for gradations within specific manifestations, such as the severity or degree of proteinuria, renal insufficiency, muscle atrophy, pulmonary impairment, or hypertension, cannot be systematically recorded by the VDI.

This concern led to a project to develop a new damage assessment instrument that would focus specifically on the AAV. A draft version of a new instrument for damage assessment in AAV was created in 2005 with contributions from vasculitis investigators in the US and the European Union. This new instrument, named the AAV Index of Damage, was specifically designed for AAV because of the primacy of these diseases internationally in vasculitis research.

At the OMERACT 7 conference, we re-examined the basic elements used to define damage, and created the following guidelines for the AAV Index of Damage:

- Irreversibility: Unlike the VDI, the AAV Index of Damage allows items of damage to be reassessed (and unscored) as necessary.
- Time element: Three months was deemed insufficient time to differentiate between the consequences of irreversible damage and reversible disease flare. Therefore, in AAV Index of Damage, the time element has been increased to 6 months.

- Attribution: In the VDI, attribution of the cause of a damage item is not taken into consideration. The variability in scoring introduced by this rule was felt to be greater than the variability resulting from relying on the clinical judgment of investigators. For that reason, in AVID only items of damage felt to be secondary to some combination of the underlying vasculitis or its therapy are scored.
- Classification: For purposes of analysis, items of damage are divided into 3 categories: items of damage attributed to the vasculitis; items of damage attributed to the consequences of treatment; and items of damage for which the attribution is unclear.
- Grading and weighting: In the VDI, scoring of damage is binary (i.e., either an item is present, or it is not). AAV Index of Damage expands the range of damage that can be recorded by grading items of damage such as renal insufficiency and hypertension according to widely recognized standards. Moreover, there must also be some acknowledgment in a damage index that certain items of damage (e.g., renal failure) have a greater effect on the quantity and quality of life than others (e.g., cataracts).

As this work on AAV Index of Damage was taking place, a EUVAS-based initiative began to re-examine some of the fundamental concepts underlying damage assessment in vasculitis, including a critical look at the performance of the VDI as applied to patients with AAV. When the VDI was developed, the original intent was to return to it at some future point to appraise its performance. EUVAS proposed to accomplish this by conducting a retrospective long-term outcome study of over 500 patients enrolled in EUVAS trials.

During OMERACT 8 discussions, we realized that there is significant overlap between the AVID project and European efforts to revise the VDI. We now propose to develop a CDA that would promote our overall goal of creating a standardized approach to disease assessment more broadly applicable to the small- and medium-vessel vasculitides. A proposed list of items of damage for this CDA appears in Table 21. Development of the CDA will be data-driven, taking advantage of the data acquired

by the application of the VDI and AAV Index of Damage to large cohorts of patients with GPA and MPA enrolled in clinical trials in the US and in Europe, as well as a new patient-derived outcomes project.

Table 21 Draft proposal of the Combined Damage Assessment Index

Musculoskeletal
Osteoporosis/vertebral collapse
Bone fracture
• Due to renal dystrophy
• Due to osteoporosis
• Due to both
Muscle atrophy due to glucocorticoid therapy
• Normal strength, atrophy on examination
• Weak on examination, normal ADL
• Weak and has difficulty with ADL
Avascular necrosis
Deforming/erosive arthritis
Osteomyelitis
Skin/Mucous membranes
Alopecia
Mouth ulcers
Cutaneous scarring
Cutaneous ulcers
Striae
Gangrene with permanent tissue loss
Easy bruising
Ocular
Proptosis
Pseudotumor
Scleral thinning
Scleral perforation
Optic nerve oedema
Optic nerve atrophy
Retinal changes

	Retinal artery occlusion
	Retinal vein occlusion
	Low vision
	Diplopia
	Blindness
	Blindness in 2nd eye
	Cataracts
	Glaucoma
	Orbital wall destruction
Ear	
	Sensorineural hearing loss
	Conductive hearing loss
	Tympanic membrane perforation or scarring
	Tinnitus
	Eustachian tube dysfunction
	Auricular cartilage deformity
	Cholesteatoma
Nose	
	Chronic rhinitis/crusting
	Nasolacrimal duct obstruction
	Nasal bridge collapse/saddle nose
	Nasal septal perforation
	Anosmia
	Ageusia
Sinuses	
	Chronic sinusitis
	Neo-ossification of sinuses
Subglottic stenosis	
	No intervention required
	Intervention required
Pulmonary	
	Irreversible loss of lung function
	Fixed large airway obstruction
	Pulmonary hypertension
	Pulmonary fibrosis
	Pulmonary embolism

Pulmonary infarction

Vena caval filter

Continuous oxygen dependency

Chronic asthma

Pleural fibrosis

Chronic breathlessness

Cardiac

Hypertension

Angina

Myocardial infarction

Percutaneous coronary intervention

Coronary artery bypass graft

Left ventricular dysfunction

- NYHA Class I/II
- NYHA Class III/IV

Third-degree AV block

Valvular disease

Pericarditis or pericardiectomy

Vascular disease

Absent pulses in 1 limb

2nd episode of absent pulses in 1 limb

Major vessel stenosis

Claudication > 3 months

Minor tissue loss

Major tissue loss

Subsequent major tissue loss

Deep venous thrombosis

Complicated venous thrombosis

Carotid artery disease

Renal artery stenosis

Arterial thrombosis/occlusion

Gastrointestinal

Gut infarction/resection

Hepatic fibrosis

Mesenteric insufficiency/pancreatitis

Oesophageal stricture/surgery

Chronic peritonitis

Renal

Estimated/measured GFR<50%

Chronic kidney disease

End stage renal disease

Dialysis

Renal transplant

Proteinuria

- < 3 g/24 h
- >3 g/24 h

Neurologic

Seizures

Transverse myelitis

Sensory polyneuropathy

- Mild
- Moderate
- Severe

Motor neuropathy (mononeuritis)

Neuropathic pain

Cerebrovascular accident

2nd Cerebrovascular accident

Cranial nerve lesion

Psychiatric

Cognitive impairment

Anxiety disorder due to vasculitis

Mood disorder due to vasculitis

Major psychosis

Endocrine

Diabetes insipidus

Premature ovarian failure

Azoospermia

Impaired fasting glucose

Diabetes mellitus

Haematology/Oncology

Bladder cancer

	Cervical cancer
	Hematopoietic malignancy
	Solid tumour malignancy
	Refractory cytopenia
	Myelodysplastic syndrome
Other	
	Weight gain > 10 lbs/4.4 kg
	Fibromyalgia
	Drug-induced cystitis
	• With microscopic haematuria • With gross haematuria • Requiring transfusion • Requiring cystectomy
	Damage requiring surgical intervention
	Medications to manage side effects of immunosuppressive agents

The Wegener's Granulomatosis Etanercept Trial Cohort

The Wegener's Granulomatosis Etanercept Trial was a multicentre, double-blinded trial that randomized 180 patients with active GPA to receive adjunctive treatment with etanercept (or placebo) in addition to standard of care therapies (297). The addition of tumour necrosis factor blockade did not alter disease outcomes (274), thus providing the opportunity to examine the spectrum of damage accrued by a well characterized cohort of patients with AAV.

In the Wegener's Granulomatosis Etanercept Trial, the VDI was applied at the time of enrolment and then every 6 months until trial closeout, and it revealed the broad spectrum of damage experienced by patients with GPA (289). The most frequently scored item was hearing loss, reported by 26% of patients in the cohort. Proteinuria (>0.5 g/24 h) was observed in 18.9% of patients in the cohort. Nasal blockade/chronic discharge, nasal bridge collapse/septal perforation, and renal insufficiency were each scored on 32 patients (17.8%). Significant muscle atrophy or weakness, osteoporosis, cataracts, chronic sinusitis, subglottic stenosis, pulmonary fibrosis, chronic

breathlessness, impaired lung function, hypertension, end stage renal disease, gonadal failure, and diabetes were all reported in 5%–10% of patients.

Study of damage in the Wegener's Granulomatosis Etanercept Trial cohort highlights some ways the VDI could be refined to be potentially more responsive to damage specific to the small- and medium-vessel vasculitides. Investigators in the Wegener's Granulomatosis Etanercept Trial recorded 38 additional items of damage that were not captured by the set VDI items (by means of a blank "other" field open to completion at each VDI assessment). These items included psychiatric conditions (i.e., anxiety and depression); the direct consequences of disease (i.e., tympanic membrane scarring, lung nodules, nasolacrimal duct obstruction, proptosis, and scleral scarring or thinning); the consequences of therapy (i.e., weight gain and striae); and fibromyalgia. Subsequent studies based on the Wegener's Granulomatosis Etanercept Trial cohort also revealed a previously unsuspected relationship between GPA and both solid tumour malignancy (298) and venous thromboembolic disease (299). Analysis of the Wegener's Granulomatosis Etanercept Trial data indicated that 26% of the items listed in the VDI were not scored by any patient in the Wegener's Granulomatosis Etanercept Trial cohort; most of these items described the consequences of large-vessel vasculitis, which are rare events among patients with GPA. Additionally, several Wegener's Granulomatosis Etanercept Trial investigators were frustrated by the lack of gradation in the VDI, which prevents recording different degrees of damage.

The mean follow-up period of patients in the Wegener's Granulomatosis Etanercept Trial cohort was 1.8 years (274). Longer follow-up is likely to lead to greater understanding of the accrual of damage among patients with vasculitis over time. For that reason, we are conducting a prospective survey of the patients in the Wegener's Granulomatosis Etanercept Trial cohort that will collect data on the accrual of damage that had occurred since the end of the trial (September 2002). In addition to the items listed in the VDI and AAV Index of Damage, we will also collect information on the additional items of damage identified by the Wegener's Granulomatosis

Etanercept Trial investigators (including the incidence of malignancy), which may provide a fuller picture of damage accrual, and will serve to inform revisions to a future version of a damage instrument. By deliberate intent, the long-term follow-up data collection for Wegener's Granulomatosis Etanercept Trial will include a substantial portion of the questions planned for use by EUVAS in the long-term EUVAS trial cohort study, outlined next.

The European Vasculitis Study Group Cohort

We are also in the process of conducting a retrospective long-term outcome study of the first 567 patients recruited to EUVAS trials (to determine patient survival and morbidity (300)). All 567 patients were newly diagnosed with AAV at the time of trial entry and were evaluated using the VDI during the trials. All participating investigators in 68 centres were sent questionnaires to collect data on patient survival, renal function and survival, immunosuppressive therapy, relapses, malignancy, and cardiovascular morbidity as well as fractures and serious infections. In addition, the investigators are asked to complete a VDI for the 5-year timepoint. We will be examining the utility of VDI in the setting of small-vessel systemic vasculitis. In this study, we will use the VDI data in the EUVAS longitudinal database for each patient at the time of trial enrolment and at Year 1 and Year 5.

Because we are collecting the same data in the long-term follow-up studies of the Wegener's Granulomatosis Etanercept Trial and EUVAS cohorts, the data can be combined for increased power. The Wegener's Granulomatosis Etanercept Trial and EUVAS cohorts will allow us to analyse each VDI item as follows:

- Items of damage as scored by the VDI are not reversible. The long-term follow-up dataset will provide an opportunity to check the consistency of this convention.
- The VDI allows the clinician to record additional "other" items of damage that are not explicitly stated in the form.

- Examining the frequency of use of these additional items will guide the choice of new items for inclusion in a revised damage index.
- We will consider discarding items that are not used, rewording the definitions of items that have caused confusion, and combining items that provide overlapping information.
- For each patient, external validation will be recorded by an assessment of a series of endpoints that will include documented measures of disease severity such as relapse, severe organ failure, end stage renal disease, and specific comorbidities. These external measures may be useful in the development of a new damage assessment index.

The Rituximab in AAV Trial Cohort

The Rituximab in AAV trial is a multicentre, randomized, double-blind, placebo-controlled trial designed to compare the efficacy of rituximab versus cyclophosphamide for the induction of sustained remission. The trial began enrolment in December 2004 and has a total goal of 200 subjects. Both AAV Index of Damage and the VDI are applied to every patient in the Rituximab in AAV trial at the time of enrolment and every 6 months thereafter. This trial will provide us with another opportunity to examine the effect of damage and include the new elements and approaches in the AAV Index of Damage draft instrument. For example, the presence of certain items of damage, such as the presence of chronic kidney disease, may have prognostic value as an early indicator of patients who are at higher risk for poor outcomes (such as faster accumulation of damage, higher cumulative levels of damage, diminished QOL, or mortality). Data from the Rituximab in AAV trial will be useful to determine the correlation between the total damage scores from AAV Index of Damage and the VDI, and their correlation with several factors, including cumulative BVAS/WG activity scores (123), initial PGA, cumulative glucocorticoid exposure, cumulative cyclophosphamide exposure, adverse events, serious adverse events, and mortality. This information will heavily influence refinement of the CDA in the following ways:

- Re-examination of specific items of damage: AAV Index of Damage is the result of expert consensus, which was used to identify specific items of damage thought to be relevant to the assessment of GPA and MPA, but not explicitly captured by the VDI. It is not clear, however, if the inclusion of a larger number of items of damage will lead to an improvement in our ability to fulfil the requirements of the OMERACT filter, particularly regarding truth (i.e., does the new instrument effectively capture all forms of damage) and discrimination (i.e., is the AAV Index of Damage better able to detect different levels of damage). The application of the new instrument to a large population of patients evaluated by multiple investigators will allow us to identify other items of damage that are not captured by the draft instrument. This will also allow us to judge both the relevance and the utility of specific items of damage that appear in both instruments. Items of damage that are not used in RAVE (or are scored inconsistently) will be reviewed and potentially removed, modified, or combined with other items of damage to streamline the instrument.
- Attribution of specific items of damage: Damage may be attributed either to the recurrent flares of vasculitis or to the medications used for its treatment. The use of a summation damage index score, however, implies that all forms of damage are roughly equivalent, regardless of aetiology. Examining damage according to aetiology, despite the inherent difficulties and pitfalls, may improve our ability to apply these concepts to clinical trials. Identification of specific items of damage that result from disease activity, for example, will help highlight the limitations of current therapeutic strategies. Items of damage that result from drug toxicity, on the other hand, may be more amenable to prevention.

The Rituximab in AAV trial dataset will provide an additional dataset for validation of prognostic data derived from the analyses in the long-term Wegener's Granulomatosis Etanercept Trial and EUVAS cohorts, each of which could be viewed as a "derivation" set for predictive variables for damage.

Patient-Reported Outcomes of Damage

At OMERACT 8 it was concluded that patient-reported outcome assessment is lacking in vasculitis clinical trials. The Vasculitis Clinical Research Consortium-EUVAS-OMERACT group is therefore launching a separate research project involving patient-derived outcomes. This project, which will be conducted in several phases, will start by collecting data from patients with vasculitis during the 2006 Vasculitis Foundation Symposium, a meeting that attracts hundreds of patients with vasculitis from several countries. Through focus groups and questionnaires, we will gain important input from patients on both the range of damage items to consider for the CDA and the items' relative importance.

Development of Draft Combined Damage Assessment

Based on the results of the activities outlined above, a draft of the CDA form will be created. It is anticipated that the CDA will include many items from the original VDI, additional items from AAV Index of Damage, some form and style from AAV Index of Damage (e.g., ability to document bilateral involvement), more gradations of severity, and new items based on data from trials and patient input. Wherever possible, the revisions/drafting will be based on data analysis rather than expert opinion.

Phase 2: Testing and Refining the CDA

The CDA will be vetted by means of a series of projects involving investigators in both the US and Europe, including paper-case exercises and application to clinical trials, and will include comparisons between the CDA and the VDI. These projects will allow us to assess the ability of the CDA to satisfy the 3 elements of the OMERACT filter (truth, discrimination, and feasibility).

Paper-Case Exercise

The purpose of the paper-case exercise is to test the reliability and feasibility of the CDA draft and to compare the CDA to the VDI. Fifteen investigators from 15 centres in the US and Europe with expertise in the evaluation of patients with AAV will be asked to select 2 patients with GPA or MPA from their clinic populations who have had disease for over 1 year: 1 patient who is alive and has had disease for over 1 year, and 1 patient who died due to the vasculitis or its therapy. The clinical course and significant events of the 2 patients will be excerpted. Investigators will be provided with sample cases to use as a template and cases will be reviewed to ensure that a uniform format is used.

Two investigators from each of the 15 centres will score the 30 paper cases, using electronic forms on the VCRC website. All investigators will be asked to repeat the exercise in 6 months using the same 30 cases. This exercise will address the 3 components of the OMERACT filter:

Truth

Face validity and content validity of the indices for detecting damage will be examined. Convergent validity will be demonstrated by comparing the performance of the new instrument to that of the VDI. We predict that there will be a high correlation between the 2 instruments.

Discrimination

The concept of damage assessment was first developed to serve as a surrogate marker for mortality in clinical trials. Damage index scores have been shown to correlate with mortality in both vasculitis (264) and systemic lupus erythematosus (301). This exercise will permit calculation of odds ratios of mortality based on arbitrary cut-offs (e.g., CDA and VDI index scores from 1 to 5) to compare the strength of the associations. This exercise will also allow us to compare the sensitivity of these

damage indices in detecting the presence of damage. We predict that the range of CDA scores will be larger, and the mean CDA score will be significantly higher, than the VDI scores for the same patients, reflecting a potentially greater ability to detect damage in these patients. Intraobserver reliability will be demonstrated by comparing the damage scores assigned by investigators at 2 different timepoints (i.e., test-retest); discrepancies between the 2 scores may help identify items of damage that are not clearly defined. Interobserver reliability will be demonstrated by the calculation of ICC.

Feasibility

Because CDA is significantly more detailed than other damage assessment instruments, demonstrating the practicability of the new instrument will be important. We expect that the use of the electronic forms developed by the Vasculitis Clinical Research Consortium will facilitate data collection and make CDA no more onerous than the VDI.

Application of CDA to Clinical Trials

The AAV Index of Damage, as it is being used in the Rituximab in AAV trial, includes most of the elements of the draft CDA that are applicable to GPA and MPA. The data on AAV Index of Damage in Rituximab in AAV Trial will therefore provide significant insight into the performance of the full CDA in these diseases. In future clinical trials sponsored by the Vasculitis Clinical Research Consortium and EUVAS, we will use both the CDA and the VDI to compare the ability of these instruments to fulfil the criteria described by the OMERACT filter.

Phase 3: Development of a Weighting Schema

Although the VDI is primarily an outcome measure, the total VDI score has been used as a prognostic measure. Indeed, each item in the VDI was selected as representing a poor outcome, either directly or indirectly. Intuitively, however, not all forms of

damage are equal. Hence, it is not clear if a total damage index score is truly meaningful. By default, all items in the VDI are equally weighted. Although the total VDI score has been shown to be predictive of poor outcome (302), it is possible that the meaning of the scores is obscured by the lack of an appropriate weighting system. One would suspect that certain forms of damage are more important than others; proving this and quantifying the differences are challenging.

Crucial to the development of a weighting schema is deciding what the damage index score is trying to represent. A damage index is, at best, a surrogate measure of a real outcome, such as burden of disease, pain, disability, or death. The index's ability to represent a "true" assessment of the burden its validity; the intent of weighting, therefore, would be to bring the index closer to an accurate representation of the "truth." The validity of a weighted index could be determined by comparing it to the unweighted index in terms of the strength of correlation with several endpoints, including mortality, long-term disability, the SF-36, PGA, and comorbid conditions of interest. This would be the start of an iterative process that may require multiple attempts to yield an appropriate set of weights.

How to best achieve a meaningful system of weights for the CDA is not clear. There are a few nonexclusive approaches to this important question, each of which has inherent advantages and disadvantages, as follows.

Data-Driven Approach Based on Predictive Power in Longitudinal Cohorts

We could select defined outcomes such as death, work disability, dialysis dependence, oxygen dependence, malignancy, cardiovascular events, need for new medications because of damage, need for surgical intervention because of damage, other organ failure, or other critical defined events. These could serve as the hard outcome measures against which a weighting schema could be tested. We could use logistic regression modelling of the data accumulated by EUVAS to determine odds ratios for individual items of damage (either at baseline or at 1 year) based on their

relationship with each outcome of interest. This method would result in a set of weightings for CDA items that predict risk of future untoward events. The additional availability of similar longitudinal data from the Wegener's Granulomatosis Etanercept Trial cohort would provide either more initial power for prediction rules or a validation data set. The advantage of this approach is that it would make use of the wealth of information already accumulated by trials regarding the long-term outcomes of patients with AAV. The disadvantage is that given the number of variables involved, it could potentially take even more data to determine an odds ratio for each item of damage for each outcome of interest; further, a purely mathematical approach has the potential to yield conclusions that lack face validity. Finally, this approach requires expert consensus for the selection of the outcomes on which this analysis would be based.

Expert Consensus on Relative Ranks

Because the damage index is an artificial construct, there is not a true "gold standard" that can be used to judge the validity of a given set of weights. The judgment of those with expertise in the diseases of interest (including physicians, nurses, physician assistants, and other care providers) may be as close as we can come to having an authoritative estimate of the true impact of individual forms of damage on patients. Using this approach, individual forms of damage would be rated by experts from a scale of 1 to 5 (where "1" means the item of damage exerts minimal impact; and "5" means that the item of damage exerts a serious impact on quality of life or mortality); these ratings could be used to develop the basis of a weighting schema. The advantage of using expert consensus is that the resulting index has inherent face validity, which would increase its acceptance by the community; the disadvantage is that using expert consensus runs the risk of calcifying old, unproven prejudices into dogma (although these conclusions will be subjected to testing and retesting during this process).

Patient Assessments

The goal of damage assessment is to measure the influence of the disease on patients. While physicians may have expertise and knowledge of poor medical outcomes and have a generally good sense of the concerns of patients, unless patients are directly involved in the process of determining the effect of the disease, any measure will risk missing crucial information. Therefore, it seems logical to seek patient input regarding the effect of individual items of damage, in addition to the weighting exercises noted above. As outlined earlier, the OMERACT group is launching a separate research project involving patient-derived outcomes. Input from patients with vasculitis will be important to ensure that the full spectrum of damage is measured, and to develop a meaningful system of weights for a new damage assessment instrument.

Phase 4: Validation of the CDA

Although the CDA is envisioned primarily to be an outcome measure, the face and construct validity of the damage index is partially derived from the sense that it can predict poor outcome. If damage is to be used as an endpoint for clinical trials, it is important to demonstrate that a damage index is sufficiently sensitive to detect the accumulation of new damage in individual patients over time and that these data are useful. It is also important to demonstrate the correlation of damage index results with other disease outcomes. The prognostic significance of the CDA score can be explored in future therapeutic trials in systemic vasculitis by determining the ability of the new score at 0, 6, 12, or 18 or more months after enrolment and to predict a poor outcome (e.g., mortality, end stage renal failure, functional score, malignancy, or cardiovascular events).

Paper-Case Validation Exercise

Thirty investigators with expertise in the assessment of AAV will be asked to apply the final form of the CDA to the 30 paper cases described in Phase 2. This will help

determine content validity, face validity, and feasibility of the CDA for patient assessment, and will provide us with the opportunity to determine whether the weighted index has a stronger correlation with mortality than the unweighted index. Intraobserver reliability will be tested via test-retest exercise and interobserver reliability by comparing scores among investigators.

Clinic-Based Validation Exercise

Prior to, or in parallel with, full implementation of the CDA to a new trial, we plan to perform a clinic-based exercise that will provide further support of the practicability and validity of the new index, demonstrate the ability of the new index to detect damage at a given timepoint, and measure the change in damage over time. Thirty investigators will be asked to apply the VDI and CDA to 10 consecutive patients with either GPA or MPA at 2 visits, 1 year apart. At both timepoints, investigators will be asked to record a PGA of damage using a 10-point Likert scale and to collect other key outcome measures such as activity scores, QOL measurements, and vital status.

Like the paper-case exercise, this exercise will allow us to demonstrate the ability of the CDA to represent truth, by allowing us to explore both face and content validity of the new instrument using patients well known to the individual investigators. This will also provide an opportunity to record and to analyse forms of damage noted by investigators, but not specifically recorded by either instrument. Unlike the paper cases, this exercise will allow us to address the issue of discrimination, by examining the ability of the 2 instruments to detect changes in levels of damage in individual patients over time. This exercise will also allow us to examine the feasibility of the CDA instrument in a setting that more closely mimics a clinical trial.

Following this exercise, the CDA will be applied to a set of patients with other forms of small-vessel systemic vasculitis (including the EGPA, Behçet's disease, cryoglobulinaemic vasculitis, PAN, IgA vasculitis, and secondary vasculitis). We expect that the scores will be significantly different between the different forms of

vasculitis and do not intend to compare scores across diseases. However, this exercise will help to define the range of scores expected in patients with different forms of vasculitis, and to validate the use of the combined index in other forms of small- and medium-vessel vasculitis.

Responsiveness will be measured by examining individual items from the CDA assessed at 2 timepoints. Once the CDA has been tested in patients, we can explore the prognostic significance of the CDA score. In future therapeutic trials in systemic vasculitis, the CDA score will be employed to record damage. The ability of the new score at various timepoints to predict a poor outcome (e.g., mortality, end stage renal failure, functional score, malignancy, cardiovascular events) will be determined prospectively. For each patient in whom the CDA is measured, external validation will be recorded by assessment of a series of endpoints that will include externally documented measures of disease severity such as relapse, severe organ failure, end stage renal disease, or development of specific comorbidities (including malignancy, development of fracture or diabetes, cerebral and coronary artery disease, venous thrombosis, infection requiring hospital admission, and death). These external measures will provide additional evidence of content and construct validity and will allow us to compare the performance of the weighted and unweighted versions of the CDA.

Future Directions

The OMERACT initiative in vasculitis requires a re-exploration of some fundamental concepts underlying the measurement of damage in vasculitis. Several issues have not yet been resolved and remain open for further discussion. These issues include the following:

1. Need for a disease-specific instrument: The vasculitides consist of a broad spectrum of disorders with heterogeneous manifestations. It is reasonable to ask whether one instrument is sufficient to assess damage for all forms of vasculitis.

At minimum, the large vessel vasculitides probably require a separate damage assessment instrument, distinct from the CDA. Many of these diseases share common features, and it may be possible to develop a core damage index module (based on these common forms of damage) that could be supplemented by disease-specific modules.

2. Attribution: Excluding items of damage based on attribution may limit our ability to identify causal relationships that have not yet been recognized; the systematic inclusion of coincidental forms of damage, however, may make the total damage index scores less meaningful.
3. Gradation: Damage is not always a binary event. Many forms of damage may occur in degrees, which can be difficult to identify in a damage assessment instrument. Moreover, it is difficult to determine how important it is to record this level of detail, and, if the extra level of complexity is worth the additional information accrued.
4. Ideal number of items of damage: It is possible that a short version with the most prognostically significant items will emerge in addition to the complete index, which might be more useful for tracking the natural history of treated vasculitis.
5. Intended use of damage assessment instruments: Damage indices have been developed primarily for use in clinical trials. How these instruments might be used in routine clinical practice by clinicians who are not expert in the assessment of vasculitis has not been explored.
6. Acceptability of damage assessment in drug development. Since many clinical trials of new agents will be industry sponsored, it would be useful to solicit feedback from attendees from the US Food and Drug Administration, the European Medicines Agency, and industry during the development of these new instruments.

Ultimately, the goal of this initiative will be to develop a new index of vasculitis for the assessment of patients, potentially both in clinical trials and in clinical practice. This project will take advantage of the cumulative knowledge gained in recent years

from clinical trials of GPA and MPA to further our understanding of the concept of damage as it applies to vasculitis, and to improve our ability to assess a patient's response to therapy.

International consensus is crucial to the Vasculitis Clinical Research Consortium-EUVAS OMERACT initiative. We agree that clinical investigation would be hampered by the existence of multiple disparate approaches to the assessment of disease activity and damage in vasculitis. Unless clinical trials are judged using similar criteria, it will be impossible to determine the optimal approach to these diseases. The projects outlined above have an enormous potential for synergy and will undoubtedly benefit from the pooling of data and resources, including the complementary expertise of investigators in the United States and Europe. Our patients are best served by the development of a uniform approach to the assessment of vasculitis; our ability to work together toward this common goal will be an important measure of our success.

Chapter 4 Outcomes

Outcomes in medicine are a quantification of the presence or absence of morbidity or mortality related to disease (Figure 8). A healthy person may become unwell with a disease, and either get better or worse. The hard endpoints of 'cure' or 'death' are punctuated by 'remission' and 'organ failure' respectively. 'Cure' is not a realistic outcome in most autoimmune rheumatic diseases, especially not in primary systemic vasculitis (168). Prior to the discovery of glucocorticoid therapy, death was a common outcome. Early clinical trials therefore focussed on 'Survival' as the main outcome of interest (303, 304). With better understanding of the use of chemotherapeutic agents like cyclophosphamide, survival became a steadily achievable outcome. But the use of agents which had hitherto been used to treat cancer produced significant toxicity. There was recognition that agents that were used to induce remission, could not be safely continued to maintain remission. The outcomes of interest, therefore, followed the path of outcomes in cancer. The vasculitis community became interested in drugs that induced 'Remission' (288) and those that prevented 'Relapse' (305). These outcomes are not as hard as 'Survival' and have been defined variably making it difficult to compare them across clinical trials (168). Over time, the definitions of 'Remission' have become more stringent and have been qualified by the absence of need for pharmacotherapy (306). Along with these outcomes, there has been growing recognition for therapies that prevent end-organ damage, specifically the eyes (154) and the kidneys (170).

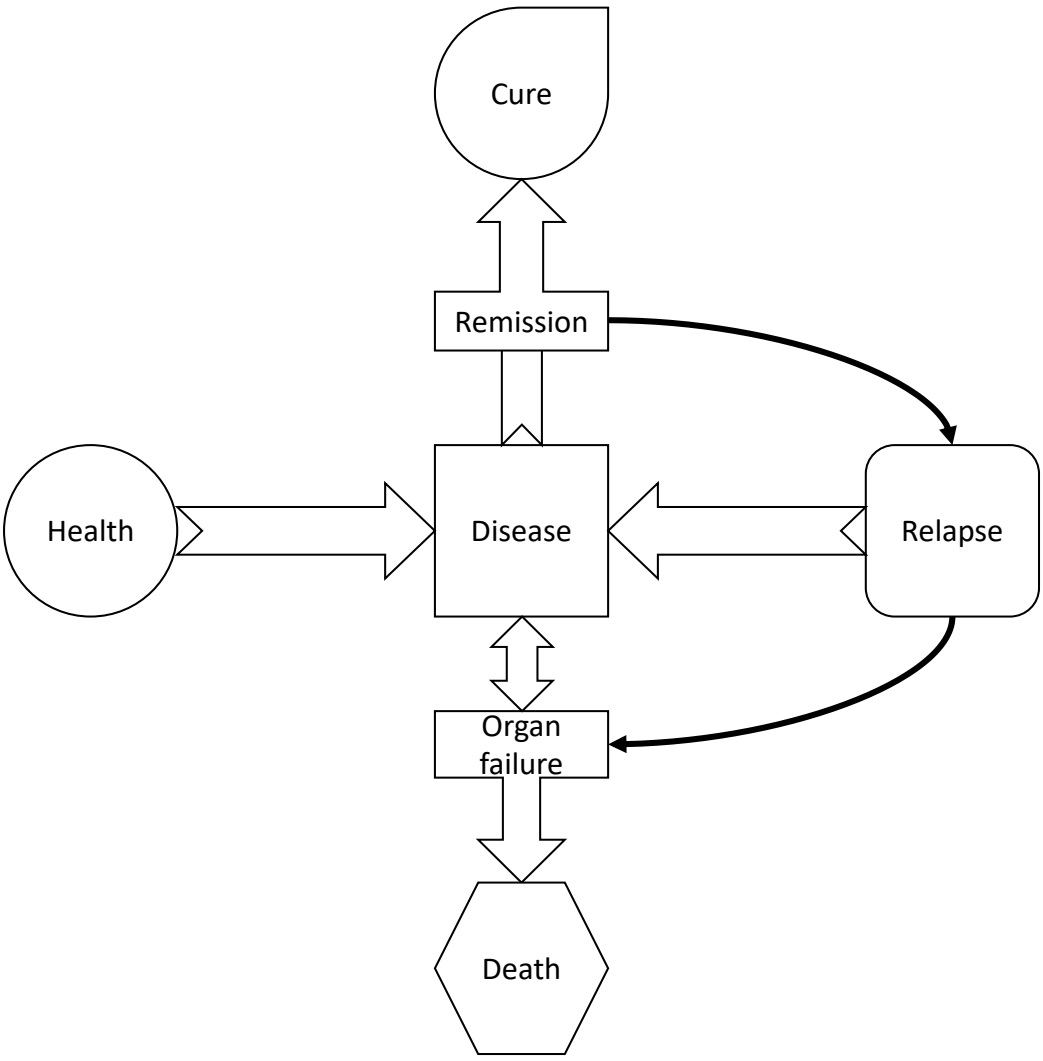

Figure 8 An organogram of measurable outcomes of disease

With the focus on improving measurable outcomes to justify the use of potent immunomodulatory treatments, QOL improvement was not on the radar till recently. QOL is a nebulous entity and is affected by several subjective variables including but not limited to expectation of the person suffering with vasculitis. We know that primary systemic vasculitis causes 'damage' as discussed in Chapter 3. We know that this can happen early in the course of disease (137) and can affect QOL irrespective of whether remission can be induced (155). There is a specific tool for measuring QOL in Behçet's disease (307), but the most widely used tool for measuring QOL in primary

systemic vasculitis has been the SF-36 which has been used in GCA (154), GPA (155), Behçet's disease (161) and Takayasu arteritis (158).

I present two papers where we have studied outcomes in primary systemic vasculitis. The first paper was a systematic review of literature to study 'Remission', 'Relapse', 'Survival' and 'Renal survival' in AAV. The second paper is a study of QOL as measured by SF-36 in AAV. My work in the two paper is as under

1. Outcomes from studies of Antineutrophil cytoplasm antibody associated vasculitis: a systematic review by the European League Against Rheumatism systemic vasculitis task force
    a. Search of the medical subject heading library of the National Library of Medicine to identify terms of interest.
    b. Construction of search strings
    c. Grading the quality of evidence of every identified abstract
    d. Writing the manuscript as the first author
2. Health-related quality of life in patients with newly diagnosed antineutrophil cytoplasmic antibody-associated vasculitis
    a. Building a database of baseline and longitudinal data of 4 clinical trials including creating analytical relationships between domains of interest.
    b. Scoring the SF-36 forms of every individual in the 4 clinical trials
    c. Comparing the data against UK normative data to create Z-scores
    d. Co-writing the first draft of the manuscript as second author

I am indebted to Professor Raashid Luqmani, Dr Michael Walsh and Professor David Jayne for the work presented here.

Outcomes from studies of Antineutrophil cytoplasm antibody associated vasculitis: a systematic review by the European League Against Rheumatism systemic vasculitis task force (282)

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Introduction

Outcome measures in primary small vessel vasculitis help to describe the natural history of treated disease. Cyclophosphamide and glucocorticoid therapy have reduced mortality in AAV, although cure remains uncommon (308). The 5-year survival of treated AAV is over 70% (309-312), but relapse and low grade persistent disease result in poor quality survival (311, 313-315). There is an increased focus on preserving target organ function (264, 309, 316).

Terms used to describe and quantify different disease states have been inconsistent. Methodological agreement is important to enable inter-study comparison and enable uniform management in future studies.

We undertook a systematic literature review to define disease specific outcomes in primary systemic vasculitis, and the factors affecting them. We concentrated on remission, relapse, renal survival, and mortality. This systematic review forms the basis of recently published recommendations for conducting clinical studies in vasculitis (169).

Methods

Search methods

We identified the following medical subject headings in the indexing database of Medline through PubMed to construct our search: “Antibodies, Antineutrophil cytoplasmic”, “Vasculitis”, “Granulomatosis with Polyangiitis”, “Eosinophilic granulomatosis with polyangiitis”, “Epidemiologic Study Characteristics”, “Evaluation Studies” and “Study characteristics”. “Microscopic polyangiitis” is not a medical subject heading term, therefore it was used as a free text phrase to be used in “all fields”. The search identified 832 citations, excluding case reports. These were limited by the terms “Adult” and “Abstracts” to 502 results, but there were no limits by time or language. A search of the Cochrane library did not produce any additional papers. No manual searching of papers was performed.

Selection criteria

From 502 papers identified, 44 were selected using the following criteria:

- >20 patients per cohort/arm of a study.
- Disease specific sub analysis in heterogeneous cohorts (one paper did not meet this criterion but was included because the cohort had 94% homogeneity). 12 Papers were ignored if the patient population was defined by their serological status only, without a specific diagnosis.
- Relevant outcome data.
- Multivariate analysis for risk factors affecting the outcomes.
- Elimination of duplicate data.

Data analysis

Patients were classified as GPA, MPA and EGPA as described in the articles. The identified risk factors for outcomes have been awarded a level of evidence according

to EULAR standardised operating procedures (317). We discussed the variability in terminology, outcomes and risk factors affecting the outcomes.

Results

Methodological quality of the studies

A total of 44 papers met the selection criteria; 25 were retrospective studies. Of the 19 prospective studies, 6 were randomised controlled trials (274, 276, 277, 318-320). Three of these trials had heterogeneous cohorts (276, 277, 320), and only one had disease specific analysis (320)

Granulomatosis with Polyangiitis

Remission

The remission rate for GPA (Table 22) ranges from 30% to 93% depending on the definition of remission and remission induction therapy (276, 308, 309, 318, 321-325). The definition of remission varied from "commencement of clinical improvement", to "complete absence of disease manifestations for at least 6 months". In most studies, the time to achieve remission (where stated) is less than 6 months. The heterogeneity of remission induction therapy and the definition of remission make this data difficult to interpret.

Table 22 Rates of remission from studies of GPA with definitions of remission and the remission induction therapy

Author	Study	Size (N)	Remission rate (%)	Time to remission	Remission induction therapy	Definition of remission
Hoffman et al 1992 (308)	P	133	75	NA	CYC (2 mg/kg/day) + Pred (1 mg/kg/day, tapered after 2–4 weeks)	Complete absence of disease

Reinhold-Keller et al 1994 (321)	P	43	30	NA	CYC (mean 667 mg/m^2/month) + iv Pred 100 mg +/– oral Pred	Complete absence of disease for 6 months
Sneller et al 1995 (322)	P	42	71	4.2 months (median)	MTX (20–25 mg/week) + Pred 1 mg/kg/day	Complete absence of disease
Guillevin et al 1997 (318)	P	27	89	6 months	CYC (0.7 g/m^2 thrice weekly) + Pred 1 mg/kg/day	Clinical improvement
		23	78	6 months	CYC (2 mg/kg) + Pred 1 mg/kg/day	
Aasarod et al 2000 (309)	R	108	81	4 months (median)	Heterogeneous	Complete absence of disease
Reinhold-Keller et al 2000 (323)	P	155	54	NA	Heterogeneous	Complete absence of disease for 3 months
Bolley et al 2000 (324)	R	38	68	NA	Heterogeneous	Undefined
Koldingsnes and Nossent 2003 (325)	R	52	85	NA	Heterogeneous	Complete absence of disease
De Groot et al 2005 (276)	P	49	90	3 months (median)	MTX (20–25 mg/week) + Pred 1 mg/kg/day	BVAS 1=0 and BVAS 2<2
		46	93	2 months (median)	CYC 2 mg/kg/day + Pred 1 mg/kg/day	

**There were six patients with MPA in this cohort, divided between the two arms; iv, intravenous; CYC, cyclophosphamide; MTX, methotrexate; Pred, prednisolone; P, prospective; R, Retrospective*

Factors affecting remission

Two main factors affected remission. Firstly, in a retrospective study, severe disease as defined by a BVAS of >23, was associated with an increased likelihood of achieving remission independent of treatment intensity; relative hazard 2.94, 95% CI 1.48 to 5.85, level of evidence = 3 (325). This finding may reflect increased responsiveness of severe disease to immunosuppression. Patients with higher activity have poorer survival (287, 326). It is possible to have life threatening disease, responsive to treatment. Subsequent studies have not re-examined this relationship.

Secondly, in a retrospective cohort, each 1-point increase in the VDI increased treatment resistance; OR 1.53 (95% CI 1.03 to 2.27), level of evidence = 3 (325). Damage occurred early in disease (137), and its presence may have influenced the definition of remission in this study, but it is likely that damage makes disease less responsive to therapy.

Relapse

Relapse was common in GPA (Table 23). The rate (18–40% at 24 months) and time to first relapse (15 to 29 months) varied (274, 277, 290, 308, 318, 319, 322, 325, 327-331). This variability may be spurious (due to differing definitions of relapse) or genuinely due to differing remission maintenance therapies or the presence or absence of risk factors for relapse (Table 24).

Table 23 Incidence of relapse in GPA with definition of relapse and the remission maintenance regimen

Author	Study	Size (N)	Relapse rate	Time to relapse	Maintenance regimen	Definition of relapse
Hoffman et al 1992 (308)	P	98	56% at 60 months	NA	Heterogeneous	Undefined

Sneller et al 1995 (322)	P	30	36% at 29 months	29 months	MTX 20–25 mg/week + tapering Pred	Reappearance of disease
Reinhold-Keller et al 1996 (327)	P	24	42% at 13 months	NA	TMP + SMX (2×960 mg/day)	Undefined
		21	29% at 23 months	NA	None	
Stegeman et al 1996* (319)	P	41	18% at 24 months	NA	TMP/SMX (2×960 mg/day) + standard therapy	Reappearance of disease
		40	40% at 24 months	NA	Placebo + standard therapy	
Guillevin et al 1997 (318)	P	24	59% at 54 months	NA	CYC (0.7 g/m^2 thrice weekly) + tapering Pred	Reappearance of major disease manifestation
Haubitz et al 1998 (328)	R	35 (with ESRD)	49% at 41 months	NA	Heterogeneous	Reappearance of disease
Boomsma et al 2000 (329)	P	100	37% at 35 months	NA	Heterogeneous	Undefined
Fauchais et al 2001 (330)	R	35	60% at 39 months	NA	Heterogeneous	Undefined
Koldingsnes and Nossent 2003 (325)	R	52	60% at 42.5 months	18 months	Heterogeneous	Reappearance of disease after complete or partial remission

Langford et al 2003 (290)	P	42	52% at 32 months	15 months	MTX 20–25 mg/week	Reappearance of disease
Jayne et al 2003 (277)	P	92	18% at 18 months	NA	AZA 2 mg/kg OR CYC 1.5 mg/kg + Pred 10 mg/day	Reappearance of one major or three minor BVAS items
Wegener's Granulomatosis Etanercept Trial Group 2005 † (274)	P	89	30% at 25 months	NA	Eta 25 mg s/c twice weekly + standard therapy	Reappearance of an item on the BVAS/WG
		85	25% at 19 months	NA	Placebo + standard therapy	
Pavone et al 2006 (331)	R	36	16% at 12 months	NA	Heterogeneous	Reappearance of disease requiring immunosuppressive therapy
		36	26% at 24 months			

*Where defined, relapse was considered only after achievement of remission; *Standard therapy was cyclophosphamide and/or prednisolone. It was not offered to all patients, there were no differences in the number of patients on standard therapy in each arm. †Standard therapy was methotrexate or azathioprine depending on renal function, for 12 months following remission; AZA, azathioprine; CYC, cyclophosphamide; ESRD, end-stage renal disease; Eta, etanercept; iv, intravenous; MTX, methotrexate; NA, not available; s/c, subcutaneous; TMP + SMX, trimethoprim + sulphamethoxazole; P, prospective; R, retrospective*

Table 24 Factors associated with GPA relapse with level of evidence

Risk factor	Risk of relapse	LOE	Reference
A fourfold rise in C ANCA/PR3 ANCA titre	RR 42.5 (95% CI 9.48 to 180.8)	3	(329)
Chronic nasal carriage of *Staphylococcus aureus**	RR 7.16 (95% CI 1.63 to 31.50); p = 0.009	2B	(332)
Creatinine clearance >60 ml/min	RR 2.94 (95% CI 1.27 to 6.67); p = 0.01	3	(332)
The presence of ANCA at diagnosis	RR 2.89 (95% CI 1.12 to 7.45)	1B	(319)

Cardiac involvement at diagnosis	RH 2.87 (95% CI 1.09 to 7.58); p = 0.03	3	(325)
Cumulative CYC dose <10 g in the first 6 months	RH 2.83 (95% CI 1.33 to 6.02); p = 0.007	3	(325)
Prednisolone ⩾20 mg/day for <2.75 months	RH 2.41 (95% CI 1.12 to 5.21); p = 0.03	3	(325)
Co-trimoxazole as adjuvant to remission maintenance therapy	RR 0.32 (95% CI 0.13 to 0.79)	1B	(319)

**Nasal carriage of Staphylococcus aureus tended to decrease the relapse rate in Pavone et al; this was not statistically significant. RH, relative hazard; RR, Risk Ratio; LOE Level of Evidence*

Factors associated with relapse

Three factors were associated with relapse. The first was treatment; receiving <10 g (compared to ⩾10 g) of cyclophosphamide in the first 6 months was associated with an increased relapse rate (RR 2.83, 95% CI 1.33 to 6.02) despite maintenance of immunosuppression (325). Patients who tolerated oral cyclophosphamide 2 mg/kg/day received >10 g in 6 months (10 g in 6 months = 55 mg/day). For intravenous therapy, three regimens have been used in trials: (a) 15 mg/kg/pulse, first three pulses twice weekly, then every 3 weeks (333); (b) 0.7 g/m^2 thrice weekly (318); and (c) 0.75 g/m^2/month (334).

At a maximum of 1 g/pulse, only regimen (a) can deliver 10 g of cyclophosphamide in 6 months. This regimen is being validated in a prospective study.

Maintaining a high dose of prednisolone (>20 mg/day) for less than 2.75 months increases risk of relapse (RH 2.41, 95% CI 1.12 to 5.21). This supports the current use of intensive initial therapy.

The use of adjunctive trimethoprim/sulfamethoxazole 160/800 mg twice daily, maintained remission for longer (RR 0.32, 95% CI 0.13 to 0.79), but resulted in a withdrawal rate of 20% (319). However, trimethoprim/sulfamethoxazole as monotherapy for remission maintenance had a higher relapse rate in comparison to

conventional remission maintenance therapy (18% at 18 months with cyclophosphamide 1.5 mg/kg/day or AZA 2 mg/kg/day in combination with prednisolone 10 mg/kg/day; 42% at 23 months with trimethoprim/sulphamethoxazole monotherapy) (277, 327).

The second factor was ANCA; presence of ANCA at diagnosis conferred an increased risk of relapse (RR 2.89, 95% CI 1.12 to 7.45) (319). ANCA are likely to be important in the pathogenesis of disease (335, 336); absence may represent a milder disease less prone to relapse.

In patients who had been positive for ANCA, a fourfold rise in C/PR3 ANCA predicted subsequent relapse (RR 42.5, 95% CI 9.48 to 180.8).29 However, about a third of patients did not suffer a relapse (329). Aggressive treatment solely based on a rise in ANCA titres would expose patients to unnecessary cytotoxic therapy. Persistence of ANCA at the onset of remission has been associated with a high risk of relapse in mixed cohorts (337). Serial ANCA testing for guiding therapy remains controversial; a meta-analysis of 22 studies could not reach a conclusion about the value of serial ANCA testing due to the heterogeneity in the assay methodologies (338).

The final factor was target organ involvement. Cardiac involvement increased risk of relapse (RH 2.87, 95% CI 1.09 to 7.58; p = 0.03) (325). A creatinine clearance >60 ml/min was associated with an increased risk of relapse (RR 2.94, 95% CI 1.27 to 6.67; p = 0.01) (332); perhaps due to non-renal, granulomatous disease (for example otolaryngological involvement), which is more prone to relapse. (339) Chronic nasal carriage of Staphylococcus aureus was an independent risk factor for relapse (RR 7.16; 95% CI 1.63 to 31.50; p = 0.009) (332). The presence of S aureus may provide a nidus of inflammation required by ANCA to produce an inflammatory response (336).

The presence of these risk factors cannot be used to justify treatment decisions.

Relapses have been classified according to severity in some clinical trials, but there have been methodological differences (274, 277). In one study, a major relapse was

defined as the appearance of at least one major (e.g., haematuria) item; minor relapse required the presence of three minor (e.g., myalgia, arthritis, nasal crusting) BVAS items (277). By contrast, in the Wegener's granulomatosis Etanercept Trial, relapses were classified as limited or severe depending on the need for cyclophosphamide and/or reappearance of specific organ involvement (274). The qualification of relapses is useful in comparing interventions since it may make an intervention with a higher overall relapse rate superior, if it lowers the incidence of severe, life-threatening relapse.

Renal survival in GPA

There is a progressive rise in renal mortality over time in patients with GPA. In a retrospective cohort, 7% of patients developed end stage renal disease at 12 months; increasing to 14% at 5 years and 23% at 10 years (264). In two other studies, end stage renal disease occurred in 19% at 38 months, and 23% at 15 months (309, 316). Factors predicting progression to end stage renal disease were as follows. Renal factors: dialysis dependence at diagnosis (RR 3.3 (95% CI 1.3 to 8.8), p = 0.001, Hazard Ratio 4.78 (95% CI 1.27 to 17.86), p = 0.02, level of evidence = 3) (264, 309). A rise in serum creatinine of 100 µmol/litre (HR 1.35 (95% CI 1.11 to 1.49), p = 0.001, level of evidence = 3) (264). A rise in the 24-hour urinary protein of 1 g (Hazard Ratio 1.50 (95% CI 1.08 to 2.07), p = 0.02, level of evidence = 3 (264).

Other factors: a fall in haemoglobin of 1 g/dl (Hazard Ratio 1.64 (95% CI 1.05 to 2.57), p = 0.03, level of evidence 3) (264). An increase in age of 10 years (Hazard Ratio 1.47 (95% CI 0.95 to 2.24), p = 0.08, level of evidence = 3) (264).

Survival

GPA is associated with higher mortality compared to the general population (mortality RR 3.8 (95% CI 2.6 to 5.6), mortality RR 4.0 for men (95% CI 2.5 to 6.3), mortality RR 3.4 for women (95% CI 1.6 to 7.2)) (309). The mean survival for untreated GPA is 5 months and the 2-year mortality is 93% (340).

Immunosuppressive therapy has changed the outlook. In a historical cohort of 265 patients, the median survival of 27 patients not receiving any initial immunosuppression was 4.2 years (341); however, 57 patients treated with azathioprine ± prednisolone and 74 patients treated with oral cyclophosphamide ± prednisolone had a median survival of 7.3 years and 8.5 years, respectively (341). A median survival of 21.7 years was recorded in a series of 155 treated patients (323).

Factors affecting survival

There are three main factors that affect survival (Table 25). They are as follows. Age: a rise of each decade in age increases the risk of death in patients with GPA (HR 2.18, 95% CI 1.38 to 3.42, p<0.001) (264). Over the age of 52 years, the older population has a poorer survival (HR 3.4, 95% CI 1.03 to 11.21, p = 0.04) (312). Two other studies, which stratified patients at 50 and 60 years, respectively, found similar results (323, 342). Patients aged >50 had a HR of 5.73 (95% CI 2.07 to 15.85) for death in a calendar year when compared to younger patients (323). There was no control group to prove that the increasing risk of death was not simply a function of increasing mortality in an older sub-group.

Table 25 Factors affecting survival

Risk factor	Risk of death (95% CI)	Level of evidence	Reference
Dialysis dependence at diagnosis	HR 8.2 (2.03 to 33.11) p = 0.003	3	(264)
VDI ⩾1 at diagnosis	HR 5.54 (1.28 to 24.05) p = 0.022	3	(264)
Impaired renal function at diagnosis	HR 5.10 (1.59–10.16)	3	(323)
A serum albumin level of ⩽30 g/litre at diagnosis	RR 4.5 (1.3 to 16)	3	(309)
Renal involvement at diagnosis*	HR 4.45 (1.48 to 13.65)	3	(323)
Lung involvement at diagnosis†	HR 3.74 (1.26 to 11.13)	3	(323)

Age >52	HR 3.4 (1.03 to 11.21), p = 0.04	3	(312)
Age (rise of 10 years)	HR 2.18 (1.38 to 3.42), p<0.001	3	(264)
Upper respiratory tract involvement at diagnosis‡	HR 0.31 (0.11 to 0.84), p = 0.02	3	(312)

**Affected only univariate analysis, not multivariate analysis. †Did not affect survival. ‡Affected only univariate analysis, not multivariate analysis.*

The second factor is target organ damage. GPA has vasculitic and granulomatous components, each of which may respond to different treatment (343). Upper respiratory tract involvement is the granulomatous end of the spectrum and renal involvement is the pure vasculitis manifestation. Upper respiratory tract involvement is associated with better survival (HR 0.31, 95% CI 0.11 to 0.84, p = 0.02) and renal involvement with poorer survival (HR 4.45, 95% CI 1.48 to 13.65).5 21 This would fit with the clinical observation that vasculitic manifestations are more acute and life-threatening than granulomatous manifestations, which are more likely to be indolent. The presence of lung involvement may be a risk factor for mortality (Hazard Ratio 3.74, 95% CI 1.26 to 11.13) (323), but this is disputed (312) and can only be resolved by larger prospective studies.

The third factor is damage. The presence of even minimal damage is associated with a higher risk of mortality (264). This observation would correlate with data from the original VDI validation exercise, where a comparison of 12 non-survivors vs 47 survivors revealed that the median VDI score for non-survivors was significantly higher than that for survivors (7 vs 4) (136).

Microscopic polyangiitis

There are very few studies of MPA due to the absence of a definition until the Chapel Hill consensus conference (344). It is possible that previously published studies of GPA may have inadvertently included patients with MPA. These are limitations of

classification and we have excluded those papers that do not describe MPA as a separate entity. We have also excluded cohorts with renal limited vasculitis because they have the potential to differentiate into either GPA or MPA.

Remission

In two studies, remission rates for MPA were 75% and 89% (320, 339). Objective inter-study comparison and with GPA (Table 22) cannot be made due to differences in defining remission and variable remission induction regimens.

Relapse

The relapse rates in MPA from three studies are 34% at 70 months (mean time to relapse 43 months) (311), 41% at 32 months (mean time to relapse 22.5 months) (345) and 8% at 18 months (277). The latter was directly compared to the relapse rate in GPA (18% at 18 months), demonstrating that GPA has a higher rate of relapse than MPA (level of evidence = 2B. Variations in trial methodology (treatment, baseline characteristics for the cohort and definition of outcomes) hamper inter-trial comparison.

Survival

The 1-year survival in MPA is 82–92% (345-348), and the 5-year survival estimates are between 45% and 76% (311, 345-347, 349), which is worse than in GPA (RR 1.917, 1.075–3.419, p = 0.025) (Table 26) (350). In two separate studies, the 1-year (83% vs 85%, p = not significant and 87% vs 97%, p<0.01) and 5-year (45% vs 76%, p = 0.02 and 63% vs 91.5%, p<0.01) survival of MPA was lower than GPA (346, 347). The survival advantage of GPA may be lost following the onset of end stage renal disease (351).

Table 26 Survival in AAV

Time	GPA	MPA	EGPA

12 months	85–97% (data from six studies including 398 patients)	82–92% (data from four studies including 252 patients)	93–94% (data from two studies including 155 patients)
24 months	86–97% (data from two studies including 263 patients)	NA	NA
60 months	69–91% (data from seven studies including 427 patients)	45–76% (data from five studies including 217 patients)	60–97% (data from five studies including 187 patients)
120 months	75–88% (data from two studies including 211 patients)	NA	NA

The presence of significant renal insufficiency at diagnosis is an adverse survival marker in MPA (HR 3.69, 95% CI 1.006 to 13.4) (level of evidence = 3) (348).

Eosinophilic Granulomatosis with Polyangiitis

Remission

The search yielded only two papers where EGPA was studied as a distinct diagnosis (310, 352). Disease specific sub-analysis for EGPA was not available in other studies. The remission rate for EGPA is 81–91% (310, 352).

Relapse

Relapse rates in EGPA increase with time; 10%, 15% and 21% at 1, 2 and 4 years in one study (310), and 27% and 35% at 1 and 2 years in another (331). The relapse rate of EGPA maybe lower than MPA (20% vs 34%), as seen in a prospective cohort (which also included PAN) (287). Intravenous methotrexate (0.3 mg/kg/week) and low dose prednisolone as remission maintenance therapy resulted in a relapse rate of 48% after 4 years (313). The median time to relapse was 9 months (313). The variable definition of relapse influences the relapse rate. For example, when defined as “reappearance of disease except asthma and eosinophilia”, the relapse rate was

lower than in comparison with a definition of relapse "…requiring immunosuppression"(310, 331). Gastrointestinal involvement is a risk factor for relapse in EGPA (HR 6.75, 95% CI 1.55 to 29.52; p = 0.011) (level of evidence = 3) (331).

Survival

Patient survival in EGPA is 93–94% at 1 year (348, 352) and 60–97% at 5 years (Table 26) (310, 352-355). The five-factor score (proteinuria >1 g/day, creatinine >1.58 mg/dl, gastrointestinal involvement, cardiomyopathy, neurological involvement) was validated in a heterogeneous cohort of EGPA and PAN (which may have included MPA) (356), but did not include a EGPA specific sub-analysis. The score was indirectly validated in a later study (310). The absence of any of the five factors carries a good prognosis (RR 0.52, 95% CI 0.42 to 0.62; p<0.03) and the presence of two or more of the factors increases the risk of mortality (RR 1.36, 95% CI 1.10 to 1.62; p<0.001) (level of evidence = 3) (310). Of the five factors, cardiomyopathy is an independent risk factor in CSS (HR 3.39, 95% CI 1.6 to 7.3) (level of evidence = 3) (348). Proteinuria >1 g/day was not associated with adverse survival in a prospective cohort (310).

Discussion

This literature review summarises the clinical outcomes and the factors influencing them in studies of AAV. A small number of manuscripts met our selection criteria, indicating a lack of good quality research for outcome measures in AAV. There have only been six randomised controlled trials in AAV, and only one had disease-specific analysis. There are limited data available from structured clinical studies for specific diseases. From the identified papers, it is difficult to compare outcomes due to the variation in trial regimen and differing definitions of clinical states. The identification of risk factors was restricted to multivariate analysis. However, most risk factors are derived from descriptive cohorts and there have been no controlled studies to validate them. Definitions used for inclusion of patients varied considerably. In some instances, the data was published prior to any international classification scheme.

The use of the Chapel Hill Consensus Conference definition has helped identify a homogeneous group of patients with MPA. The variation in methodology of the studies reviewed in this paper formed the basis of the recommendations by EULAR/EUVAS for conduct of studies in AAV (169). The differences between outcomes in the studies we have discussed may be genuine (dependent on stage of disease, organ involvement, therapy and so on) or perceived (due to a variation in the definition of the outcome). Future trial design should address this variation when calculating sample sizes by stratifying patients according to identified risk factors. The outcome measures and results in this paper may require updating in future when data emerges from new studies. Currently, the recommendations and the literature search are restricted to AAV, primarily because most controlled trials and long-term observational studies have focussed on these forms of vasculitis. A similar approach would apply to other forms of primary small vessel vasculitis and may lead to the development and implementation of recommendations in these diseases in future. Disease related damage and the QOL of patients with these chronic debilitating diseases are measures of prognostic and economic importance (152, 289, 315). We have not concentrated on those outcomes, but they are discussed elsewhere.

Health-related quality of life in patients with newly diagnosed antineutrophil cytoplasmic antibody-associated vasculitis. (153)

Authors

Michael Walsh, Chetan Mukhtyar, Alfred Mahr, Karen Herlyn, Raashid Luqmani, Peter Merkel, David Jayne

Introduction

GPA, MPA, and renal-limited vasculitis are among the most common primary systemic vasculitides in adults. They are associated with circulating ANCA and, due to similarities in clinical features, histologic characteristics, treatment, and outcomes are frequently grouped together as AAV. Earlier recognition of AAV and the widespread use of immunosuppressive treatment have significantly reduced its mortality (282, 357).

Patients with AAV are faced with a chronic medical condition and health related QOL, the component of well-being attributed directly to health status, is an increasingly important consideration.

Measuring health-related QOL has been facilitated in the last 20 years by the development and validation of generic instruments such as the Medical Outcomes Study SF-36 (358, 359). These instruments allow investigators to reliably measure several facets or domains of QOL in a multitude of conditions.

Despite the chronic morbidity observed in patients with AAV, there is little known about how disease manifestations affect QOL. Small single-centre studies examining what variables influence QOL have suggested that lung damage, joint involvement, and sinonasal involvement have each been potentially important determinants of physical components of QOL in different studies (152, 360, 361). Determining which disease manifestations influence QOL and in what domains they affect QOL may help

focus treatment for patients with AAV and help evaluate newer therapies. We studied the association between patient characteristics and particular manifestations of AAV and QOL in a multicentre cohort of patients that covered the spectrum of disease activity and manifestations.

Methods

Patients

EUVAS conducted 4 trials that enrolled patients from 70 hospitals in 15 countries between 1995 and 2002 (170, 275-277). All the trials were conducted according to the 1964 Declaration of Helsinki and subsequent amendments. All the patients were newly diagnosed with AAV (either GPA, MPA, or renal-limited vasculitis). One trial enrolled patients with early systemic AAV (creatinine level 150 μmol/L), two enrolled patients with generalized AAV (creatinine level between 150 and 500 μmol/L), and one enrolled patients with severe AAV (creatinine level 500 μmol/L or requiring dialysis). The individual trial eligibility criteria are summarized in Table 27.

Table 27 Summary of included trial eligibility and treatment regimens

Trial	Included disease stage	Included creatinine level (μmol/L)	Induction treatment	Maintenance treatment
(276)	Early systemic	<150	Methotrexate vs. oral cyclophosphamide	Methotrexate vs. oral cyclophosphamide
(277)	Generalised	150-499	Oral cyclophosphamide	Oral cyclophosphamide vs. azathioprine
(275)	Generalised	150-499	IV cyclophosphamide vs. oral cyclophosphamide	Azathioprine
(170)	Severe	>500	Plasma exchange + oral cyclophosphamide vs. IV methylprednisolone + oral cyclophosphamide	Azathioprine

Measures

QOL was evaluated with the SF-36 Health Survey, a generic self-reported health questionnaire administered in the patient's native language whenever possible. The SF-36 measures HRQOL in 8 domains, 4 physical (physical functioning, role physical, bodily pain, and general health) and 4 mental (social functioning, role emotional, mental health, and vitality). The score for each domain was normalized to UK population scores with a mean ± SD of 50 ± 10, with higher scores indicating better quality of life (362, 363). In addition, domains are summarized as a physical composite score and a mental composite score, also with a population mean ± SD of 50 ± 10. A 5-point difference in scores is generally regarded as the minimum clinically important difference (364).

Patients were assessed at baseline for manifestations of AAV in each organ system using BVAS, an instrument with 9 domains (109). Each BVAS item was scored if the sign or symptom started or worsened over the 4 weeks prior to the evaluation. The BVAS produces a summary score for overall disease activity that can range from 0 to 63. The summary score is composed of the sum of each organ domain–specific score. For this analysis, each organ domain was classified as actively involved or not based on $\geq$1 item or no items present at baseline. Serum creatinine was measured at baseline and converted to an estimated glomerular filtration rate using the 4-variable Modification of Diet in Renal Disease equation (365). AAV was sub grouped as GPA or MPA (including renal-limited vasculitis) according to the Chapel Hill Consensus Statement (344).

Statistical Analyses

Summary data is presented as mean (SD) or median (interquartile range) as appropriate for normal and non-normally distributed continuous variables respectively. Baseline characteristics between those included and those excluded for analysis were compared by student's t-test for normally distributed continuous

variables, Mann-Whitney test for non-normally distributed continuous variables and Fisher's exact test for dichotomous data.

Associations between baseline characteristics and physical composite score and mental composite score were determined using mixed-effects linear regression in which each trial served as a random effect. Identical models were fit for physical composite score and mental composite score data. Each model included age, sex, estimated GFR, diagnosis and organ system involvement for each of the nine BVAS organ systems. To explore whether each baseline variable was associated with certain physical or mental domains, we assessed all physical domains simultaneously in a multivariate regression model and all mental domains in a second model. Predictor variables in the multivariate regression models were specified in the same way as the multilevel models but without a random effect for trial. Models for Physical Function, Role Physical, Bodily Pain and General Health scores were simultaneously fit for physical domains and models for Social Function, Mental Health, Role Emotional and Vitality scores were simultaneously fit for mental domains model. Missing predictor covariate data was imputed using chained equation multiple imputation techniques (366). Ten imputation datasets were used to generate all final analyses. Sensitivity analyses using only complete cases were also conducted. Sensitivity analyses in which pulmonary haemorrhage was coded separate from other chest manifestations were also conducted to ensure that estimates for chest involvement were not driven solely by pulmonary haemorrhage. Further sensitivity analyses that included the summary BVAS as a measure of overall disease activity and excluded individual organ involvement variables were conducted. A p-value <0.05 was considered statistically significant with no corrections for multiple comparisons for the physical composite score and mental composite score models. In multivariate models, type I errors due to multiple comparisons were contained by adjusting the significance level by the number of covariates in the model (i.e., adjusted $p<0.004$ for significance) in the multivariate

models. A point estimate of at least 5 points was required to be considered clinically significant. All analyses were performed on Stata v11 (College Station, TX).

Results

Patients

A total of 535 patients were enrolled in the 4 trials. Of these, 346 (65%) had baseline SF-36 data for analysis. Eighty-four percent of patients in (276), 72% of patients in (277), 51% of patients in (275), and 57% of patients in (170) completed baseline SF-36 evaluations. Patients with SF-36 data more frequently had GPA and general ENT manifestations, better renal function, and lower BVAS, and less frequently had renal manifestations compared to those who did not have SF-36 data (Table 28). Eighty-four percent of patients with SF-36 data had complete covariate data available for analysis; in the remaining 16%, at least one predictor variable was multiply imputed.

Table 28 Characteristics of patients included and excluded from this study

	Included (N=346)	Excluded (N=189)	p-value[†]
Mean Age (SD), years	57.1 (13.9)	58.4 (14.9)	0.39
Female (%)	43.9%	50.2%	0.15
GPA (%)	58.5%	41.6%	<0.001
Mean Baseline BVAS (SD)	17.6 (8.5)	19.2 (8.4)	0.041
Median eGFR (IQR), ml/min	33.5 (10.9 to 70.0)	18.9 (7.6 to 51.9)	<0.001[‡]
Organ Involvement (%)			
General	91.9	87.1	0.009
Cutaneous	23.5	23.9	0.91
Mucous Membrane/Eye	30.4	26.4	0.22
ENT	52.9	46.0	0.036
Chest	52.5	46.6	0.071
Cardiac	5.7	4.9	0.69
Abdominal	4.7	6.7	0.18
Renal	86.8	92.3	0.007
Neurologic	20.1	20.8	0.81

†p-values from t-tests for continuous variables or Fisher's exact test for categorical variables except where noted; ‡p-value from Mann-Whitney test; eGFR = estimated GFR

Distribution of SF-36 scores

Figure 9 demonstrates the distribution of SF-36 scores for all patients. For physical composite score, the mean (SD) was 27.6 (12.5) and the median (interquartile range) was 26.7 (18.6 to 36.1). The mean mental composite score was 40.4 (11.9) and the median was 38.9 (30.9 to 50.5). Both the composite scores were significantly lower than the population norm of 50 ($p<0.001$ for both). Of the physical domains, Physical Function and Role Physical scores were the lowest with median (IQR) of 28.6 (14.7 to 42.5) and 21.3 (21.3 to 29.7) respectively. Amongst the mental domains, Social Function scores were the lowest with a median (interquartile range) of 30.6 (17.8 to 43.4).

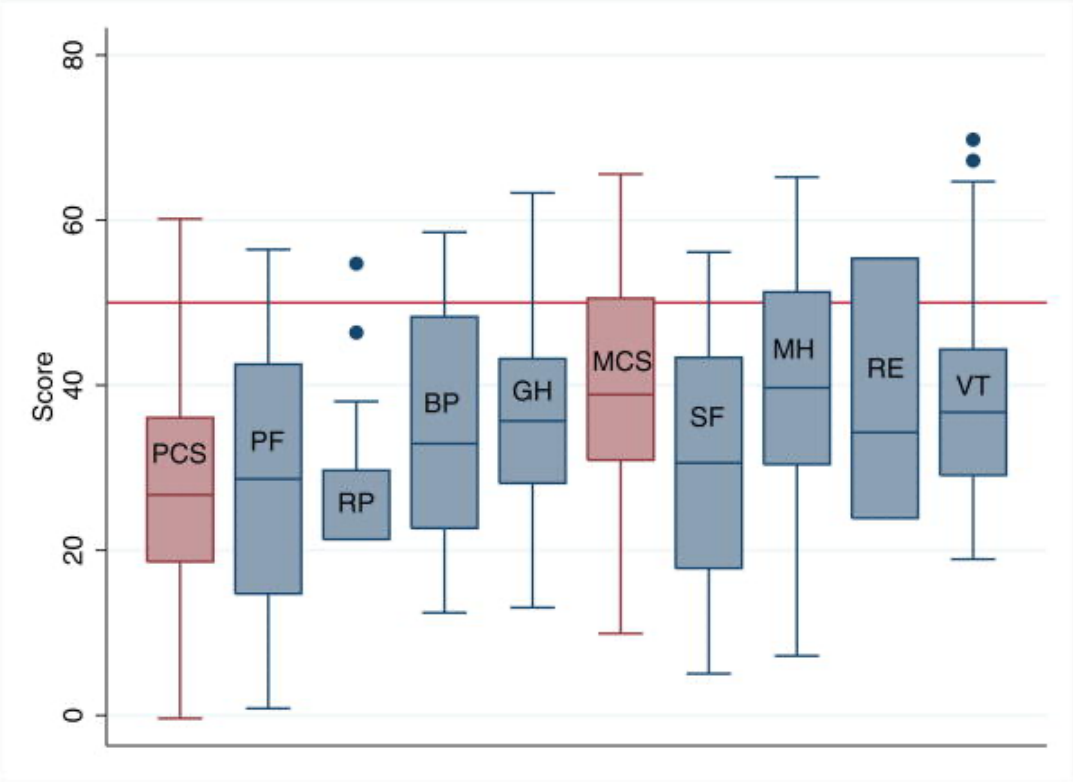

Figure 9 Distribution of Short Form 36 scores in patients with AAV.

Population average is 50 (horizontal line). Boxes represent 25th to 75th percentile with median (embedded horizontal line). Whiskers represent 5th to 95th percentile and dots represent outliers. PCS = Physical Composite Score; PF = Physical Function; RP = Role Physical; BP = Bodily Pain; GH = General Health; MCS = Mental Composite Score; SF = Social Functioning; MH = Mental Health; RE = Role Emotional; VT = Vitality.

Associations with Physical and Mental Composite Scores

Older age was independently associated with lower physical composite score (p=0.029) although a 45-year age difference was required to reach the minimum clinically important difference (0.11 points per year of age). Neurologic activity was the only organ system independently associated with a statistically (p<0.001) and clinically significant (−5.84 points; 95% CI −2.60 to −9.09 points) reduction in physical composite score (Table 29). Chest involvement was associated with a statistically (p=0.027) but not clinically significant (−2.96 points; 95% CI −0.33 to −5.58) reduction in mental composite score (Table 29). No other factors were associated with a significant reduction in mental composite score. Sensitivity analyses using only complete cases did not differ materially from analyses utilizing multiple imputations. Similarly, sensitivity analyses in which pulmonary haemorrhage was considered separately from other chest manifestations did not differ materially from primary analyses and estimates for the effect of pulmonary haemorrhage were like the estimates for other chest manifestations.

Table 29 Mixed-effects multivariable regression models for Physical Composite and Mental Composite Scores of the Short Form 36 questionnaire

	Physical composite score		Mental composite score	
	β (95% CI)	p-value	β (95% CI)	p-value
Age (per year)	−0.11 (−0.21 to −0.012)	0.029	0.036 (−0.066 to 0.14)	0.49
Sex	−2.38 (−4.98 to 0.21)	0.072	−2.32 (−4.88 to 0.24)	0.076
Diagnosis (MPA)	0.68 (−2.85 to 4.22)	0.71	2.34 (−1.19 to 5.87)	0.19
eGFR (per 10 ml/min)	0.058 (−0.48 to 0.59)	0.83	0.38 (−0.11 to 0.87)	0.13
Organ Involvement				
Systemic	−4.83 (−11.08 to 1.41)	0.13	−4.98 (−11.23 to 1.26)	0.12
Cutaneous	−2.42 (−5.51 to 0.66)	0.12	2.22 (−0.87 to 5.32)	0.16

Mucous Membrane/Eye	−2.50 (−5.44 to 0.45)	0.096	−0.48 (−3.45 to 2.48)	0.75
ENT	−1.79 (−5.04 to 1.46)	0.28	2.97 (−0.27 to 6.22)	0.072
Chest	−2.26 (−4.86 to 0.35)	0.089	−2.96 (−5.58 to −0.33)	0.027
Cardiac	0.82 (−5.20 to 6.84)	0.79	−0.97 (−7.08 to 5.12)	0.75
Abdominal	1.69 (−4.86 to 8.25)	0.61	5.20 (−1.45 to 11.84)	0.13
Renal	−2.85 (−7.18 to 1.48)	0.20	0.63 (−3.21 to 4.48)	0.75
Neurologic	−5.84 (−9.09 to −2.60)	<0.001	0.076 (−3.22 to 3.37)	0.96

eGFR, Estimated Glomerular Filtration Rate; ENT, Ear, Nose & Throat

Although few individual organ systems are associated with clinically and statistically significant differences in the physical and mental composite scores, their combined effects may result in clinically significant differences. Sensitivity analyses that included BVAS as an overall measure of disease severity did not show any independent association either. Thus, for most patients with newly diagnosed AAV, overall QOL may be largely a function of having active disease rather than a function of activity in particular organs or severity of activity.

Associations with Individual domain scores

The results of multivariate regression to explore the association of baseline characteristics with each domain of the SF-36 are summarized in Table 30 (physical domains) and Table 31 (mental domains). A p-value of <0.004 was required for statistical significance to reduce the type I error rate. Older age was associated with lower Physical Functioning (p<0.001). An age difference of 20 years was required to reach the minimum clinically important difference of 5 points. Female sex and renal function demonstrated trends towards effects in several domains but none of these met our significance threshold. For renal function, the difference in estimated GFR required to meet the minimum clinically significant difference was approximated 80 ml/min (i.e., the criterion was only met if comparing patients requiring dialysis to those with near normal renal function). There was no difference between those patients with GPA and those with MPA in any domain of the SF-36.

In terms of organ involvement, General manifestations of AAV resulted in lower General Health (−6.50 points, 95% CI −12.07 to −0.93) scores but this did not meet the modified threshold for statistical significance (p=0.022). Neurological activity was associated with statistically and clinically significant lower Physical Functioning scores (−8.48, 95% CI −12.90 to −4.06; p<0.001) and there was a non-significant trend to lower Bodily Pain scores (−4.98, 95% CI −9.14 to −0.81; p=0.019). Other organ manifestations were not associated with differences in health related QOL scores.

Table 30 Multivariate model of association of patient characteristics with physical domains of the SF-36

	Physical functioning	Role Physical	Body pain	General Health
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Age	−0.25 (−0.38, −0.11) *	−0.10 (−0.19, −0.01)	0.061 (−0.07, 0.19)	−0.42 (−0.13, 0.045)
Female	−4.46 (−7.84, −1.08)	−1.42 (−3.71, 0.87)	0.008 (−3.27, 3.29)	−2.03 (−4.21, 0.16)
MPA	0.61 (−4.03, 5.26)	1.61 (−1.52, 4.75)	−0.20 (−4.70, 4.29)	2.15 (−0.84, 5.14)
eGFR (per 10 ml/min)	0.64 (0.00, 1.29)	0.17 (−0.26, 0.61)	−0.04 (−0.67, 0.58)	0.25 (−0.18, 0.67)
Organ Involvement				
General	−5.32 (−4.72, 3.66)	−4.90 (−10.47, 0.68)	−3.48 (−11.49, 4.54)	−6.50 (−12.07, −0.93)
Cutaneous	−0.53 (−4.72, 3.66)	−0.35 (−3.10, 2.40)	−3.02 (−7.03, 0.99)	0.78 (−1.99, 3.53)
Mucous Membrane / Eye	−2.40 (−6.37, 1.56)	−0.42 (−3.05, 2.21)	−3.55 (−7.35, 0.25)	−0.12 (−2.65, 2.40)
ENT	−1.03 (−5.34, 3.26)	−0.29 (−3.19, 2.61)	−1.16 (−5.40, 3.08)	1.29 (−1.46, 4.04)
Chest	−3.46 (−6.89, −0.04)	−2.13 (−4.44, 0.17)	−2.27 (−5.60, 1.05)	−1.61 (−3.90, 0.66)
Cardiac	−3.71 (−12.28, 4.86)	−2.37 (−7.70, 2.96)	0.59 (−7.00, 8.18	4.96 (−0.51, 10.42)

Abdominal	6.31 (−2.61, 15.23)	3.81 (−2.11, 9.73)	−3.69 (−12.46, 5.08)	3.27 (−2.55, 9.10)
Renal	−3.64 (−8.69, 1.41)	−2.04 (5.46, 1.37)	−0.42 (−5.36, 4.52)	−3.36 (−7.15, 0.43)
Nervous	−8.48 (−12.90, 4.06) *	−2.27 (−5.18, 0.64)	−4.98 (−9.14, −0.81)	−2.45 (−5.26, 0.36)

** Reaches statistical significance set at p <0.004*

eGFR, Estimated Glomerular Filtration Rate; ENT, Ear, Nose & Throat

Table 31 Multivariate model of association of patient characteristics with mental domains of the SF-36

	Vitality	Social Functioning	Role Emotional	Mental Health
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Age	0.0028 (−0.10 to 0.11)	0.009 (−0.13 to 0.14)	−0.032 (−0.15 to 0.087)	−0.014 (−0.13 to 0.11)
Female	−2.50 (−5.14 to 0.13)	−1.75 (−5.12 to 1.61)	−2.01 (−4.98 to 0.97)	−3.28 (−6.29 to −0.27)
MPA	−0.44 (−4.05 to 3.16)	0.35 (−4.30 to 5.01)	2.17 (−1.95 to 6.29	3.84 (−0.29 to 7.98)
eGFR (per 10 ml/min)	0.60 (0.10 to 1.11)	0.56 (−0.084 to 1.20)	0.32 (−0.24 to 0.89)	0.24 (−0.33 to 0.83)
Organ Involvement				
Systemic	−3.73 (−10.12 to 2.66)	−6.66 (−15.14 to 1.81)	−7.24 (−14.55 to 0.07)	−3.34 (−10.73 to 4.06)
Cutaneous	0.33 (−2.84 to 3.51)	−2.11 (−6.28 to 2.06)	2.59 (−1.05 to 6.25)	2.20 (−1.46 to 5.87)
Mucous Membrane / Eye	−1.78 (−4.81 to 1.24)	−3.31 (−7.30 to −0.67)	−0.52 (−3.97 to 2.93)	−0.20 (−3.72 to 3.32)
ENT	−0.94 (−4.29 to 2.40)	−0.14 (−4.46 to 4.17)	2.80 (−0.97 to 6.58)	3.89 (0.045 to 7.74)
Chest	−3.02 (−5.70 to −0.34)	−3.47(−6.94 to 0.0003)	−3.32 (−6.35 to −0.29)	−2.78 (−5.88 to 0.32)
Cardiac	1.08 (−5.32 to 7.47)	3.29 (−4.74 to 11.32)	−3.93 (−11.03 to 3.17)	−3.38 (−10.87 to 4.11)

Abdominal	6.74 (−0.11 to 13.59)	4.09 (−5.20 to 13.39)	5.94 (−1.78 to 13.66)	2.71 (−5.07 to 10.48)
Renal	0.53 (−3.36 to 4.42)	−1.82 (−6.85 to 3.19)	−0.98 (−5.46 to 3.48)	0.79 (−3.96 to 5.53)
Nervous	−0.95 (−4.32 to 2.41)	−0.94 (−5.23 to 3.34)	−1.91 (−5.70 to 1.88)	−2.81 (−6.70 to 1.08)

eGFR, Estimated Glomerular Filtration Rate; ENT, Ear, Nose & Throat

Discussion

QOL is increasingly important to consider in the care of patients with AAV. Despite this, there are few studies demonstrating what features of AAV are important determinants of health related QOL. We have demonstrated in a large cohort that includes the full spectrum of severity of AAV that QOL, particularly in physical domains, is significantly reduced at the time of diagnosis. Neurological manifestations of AAV affect QOL most dramatically suggesting they may be an important therapeutic target to improve QOL.

QOL was substantially lower in our AAV patients than population norms. SF-36 scores in our patients also appeared lower than some other recent studies of QOL in patients with AAV (367). However, our study included only patients at the time of diagnosis while others typically measured QOL in a mixture of patients with active and inactive disease. The finding that physical domains of QOL were more affected than mental domains is also similar to other studies as was the lack of association between QOL and renal function, or diagnosis (156). Unique to our study, however, is the assessment of each organ system involvement and the finding that neurological activity most strongly affects health related QOL.

In our study, Role Physical scores were the lowest, a finding consistent with others, suggesting treatments that affect this domain will be of greatest value for improving QOL in patients with AAV (155). Also, we found a possible association between neurological manifestations and bodily pain which may have been an important

determinant in other studies demonstrating neuropathic pain was a significant source of reduced health related QOL. However, unlike other reports, we did not find ENT activity associated with clinically significant reductions in any domain of QOL (152, 361). In fact, those with ENT involvement appeared to have slightly better Mental Health scores compared to those without ENT involvement although this may well be a spurious finding. The discrepancy between ours and other studies may be because ours were newly diagnosed patients with active disease manifestation due to AAV as assessed by a physician at diagnosis. It is possible that persistent symptoms, which may be due to organ scarring or active disease, have a greater impact on patient's health related QOL. This is consistent with the finding that chronic disease damage is associated with lower SF-36 scores in several domains (289).

Few organ manifestations were found to have a clinically and statistically significant association with reduced QOL in our study despite the finding that overall QOL was very impaired. This could be due to a relatively small contribution from individual organ manifestations which together may result in significantly impaired health related QOL. Alternatively, it is possible that generic QOL instruments are insensitive to the effects of many manifestations of AAV. Studies that seek to measure improvement in specific areas of health-related QOL may therefore be best served by using domain / symptom specific instruments in addition to generic instruments as is recommended in other diseases (368).

Our study has several notable strengths. It is, to our knowledge, the largest study of health related QOL in patients with AAV and it covers the full spectrum of disease severity. All patients are newly diagnosed thus limiting confounding by duration of disease which may occur in cross-sectional studies. Finally, the use of a generic instrument allows us to compare the health related QOL of our patients with patients with AAV in other studies and to patients with other diseases.

Our study must also be interpreted within the context of its limitations. A substantial number of patients did not complete the SF-36 and these patients tended to have more severe disease and be older than those who did complete the questionnaire. It seems likely the patients who did not complete the questionnaire were the most ill and may have had the lowest health related QOL. Their exclusion would likely result in an underestimate of the effect of severe manifestations of AAV such as neurological manifestations and severe renal disease. Our sample is also taken from randomized control trials which may limit how representative our patients are compared to a true inception cohort of patients with AAV. However, this limitation is unlikely to have affected the generalizability of the effect estimates of organ manifestations on QOL. Lastly, although patients were newly diagnosed, for some cases, disease activity had been present for some months prior to diagnosis, and some disease manifestations may have caused damage and then become quiescent prior to diagnosis. These potentially confounding effects were not assessed in this study.

In conclusion, patients with AAV have significantly reduced QOL at the time of initial diagnosis. Neurological involvement appears to be an important determinant of health related QOL and may be an important target for treatment and future research. Our study highlights the need to evaluate QOL in clinical trials in AAV because the information it conveys is not encompassed by other, more traditional, vasculitis specific outcome measures.

Chapter 5 Critical Review

In this thesis, I have presented a selection of my contribution to the field of primary systemic vasculitis between the years 2006-2020. A full list of publications during this time is available in Appendix 4.

Chapter 2

GCA is defined as '*Arteritis, often granulomatous, usually affecting the aorta and / or its major branches, with a predilection for the branches of the carotid and vertebral arteries. Often involves the temporal artery. Onset usually in patients older than 50 years and often associated with polymyalgia rheumatica*' (1). With this definition it becomes a distinct pathological entity rather than being just a phenotype of disease (e.g., temporal arteritis). But this definition also means that a definitive diagnosis of GCA can only be made with an arterial specimen. But TAB is not a sensitive test. Klein et al demonstrated that foci of inflammation as short as 300mm in length were present in 17/60 of their specimens which were otherwise completely normal (369). The presence of these 'skip' lesions has dented confidence in TAB as a diagnostic procedure. In 2009, international recommendations advocated in favour of establishing objective diagnosis for GCA in every case using TAB (3). But the low sensitivity of TAB did not allow the recommendations to be translated into common clinical practice (80, 174).

Ultrasonography as a diagnostic modality has been available since the mid-1990's (93). In the absence of formal validation and homogeneity of description, various publications had used different definitions for describing lesions that were thought to be abnormal (94, 204). For a diagnostic measure to receive international acceptance, it needs to be sensitive, specific, reliable, and feasible. The OMERACT initiative has been a pathway to the validation of outcome measures for this purpose (131). Alongside the development of ultrasonography for diagnosis of GCA, there have been publications demonstrating the efficacy of FDG-PET-CT and MR imaging

using high resolution equipment for the same purpose (79, 85). Only ultrasonography has fulfilled the OMERACT filter for use in diagnosing GCA (80). I have presented three papers that demonstrate my participation in this validation process. I present a critique of that work.

GCA vs. Takayasu arteritis

We started with a systematic review of literature to identify previously applied definitions for ultrasonography findings in lesions encountered in large vessel vasculitis. We decided on focussing on key lesions for GCA only. This raises a question about the differentiation between GCA, Takayasu arteritis and those individuals with primary large vessel vasculitis that do not fulfil any classification criteria. Histologically, we know that GCA and Takayasu arteritis are indistinguishable. Phenotypically, we know that GCA can involve the extracranial vessels and that Takayasu arteritis can affect cranial vessels. Mikito Takayasu was an ophthalmologist who observed the pulselessness of the retinal vasculature in an individual with absent pulses (370). Currently, the two concepts of Takayasu arteritis and GCA are separated mainly by age. A recent paper studying the distribution of arterial lesions found that Takayasu arteritis and GCA appear to have equal amount of aortic involvement and the distribution of other arterial involvement appears to be on a spectrum (371). It is not implausible that these two conditions are the same and we should not have been concerned with the phenotypic classification differentiating what may be one pathological entity where the phenotype is affected by still unknown immunogenetic factors. It would be interesting to study whether the incidence of all large vessel vasculitides is comparable in different parts of the world. Currently such a comparison is not possible, because we lack paired data for Takayasu arteritis and GCA in the Far East. What we have ended up calling the 'halo' sign because of the transverse appearance of a concentric hypoechogenicity around an affected artery is probably the same as the 'Macaroni' sign which is the longitudinal appearance of a thickened inflamed artery (372) (Figure 10). The difference in age may not be real either. In Table 4, we provided a description of 25

consecutive cases that we used to validate the ultrasonography service in Norwich. Case 20 fulfilled the American College of Rheumatology 1990 classification criteria for GCA (101) as well as Takayasu arteritis (100). She was >50 years of age and presented with a headache, raised inflammatory markers, and a positive TAB. But she also had arterial bruits, pulse discrepancy and ultrasonographic evidence of extracranial vasculitis. The diagnostics of GCA and Takayasu arteritis have followed different trajectories, and this may be an opportunity to unify the efforts of imaging diagnostics in large vessel vasculitis as well as our general understanding of how these two disease phenotypes might be related.

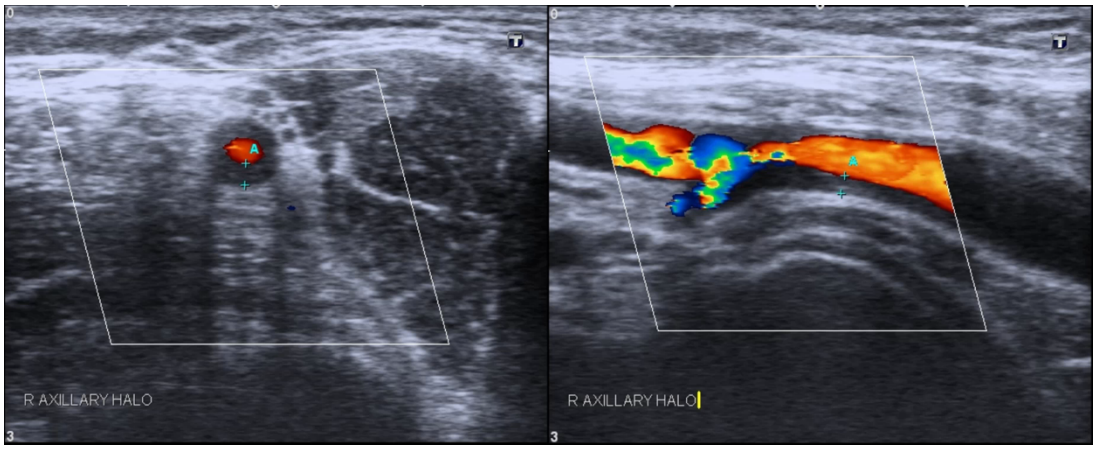

Figure 10 Transverse (left) and Longitudinal (right) views of the same axillary artery on colour doppler ultrasonography demonstrating halo sign and/or macaroni sign. Images acquired using 14 MHz linear probe on Toshiba Viamo ultrasonography machine.

Arterial calibre as an anchor for size of halo

After the systematic review of literature, we held a Delphi to agree on definitions. There was broad consensus on the definition of 'halo' sign as in Table 7. But we decided that the definition could not include a cut-off for thickness of the intima-media complex. Effectively we agreed that the appearance was more important than the size. This is crucial for future research where cut-offs are still being worked on (247). The size of the halo is going to be a function not just of inflammation, but also the size of the artery. Schafer et al have proposed different cut-offs measurements

for different arteries (E.g., superficial temporal, facial, axillary) (247). But there has been no allowance for the variation in size of the arterial diameter of the same artery in different people. The average diameter of the superficial temporal artery at the level of the zygoma is 2.2 mm with a range between 1.0 mm to 5.0 mm (373). In the interest of improving feasibility, it was appropriate that we focussed on the picture rather than the size. But future academic work should consider the size of the halo as a function of the diameter of the artery. This will allow us to produce more accurate cut-offs.

Recognition of artefactual influences on performance of ultrasonography

The validation of the definitions presented as supportive work in Chapter 2 took two different forms. The first was to assess reliability of still and dynamic ultrasonography images. This was important because it improves feasibility. Clinicians may not necessarily have the skill to perform ultrasonography, but our findings demonstrate that images acquired by experts can be read reliably. This provides an opportunity to train other clinician grades (E.g., specialist nurses, physician associates, sonographers) to develop this skill to complement the physician in a GCA service. The second part was to assess the reliability of the actual acquisition of images. We were an experienced group of sonographer-clinicians operating high level equipment. Despite that, in the preliminary meeting, we had fair to moderate reliability for diagnosis of GCA (κ of 0.29-0.51) and poor to fair reliability for identifying vasculitis in specific anatomical segments (κ of 0.02-0.46). All 12 sonographers had participated in the reliability exercise of acquired images and demonstrated excellent reliability (Table 8). I hypothesised that artefactual influences may be responsible for the deterioration in the κ values. A SurveyMonkey™ questionnaire of the 12 sonographers revealed the following highlights

- 11/12 had some difficulty in obtaining images.
- 6 were used to a different brand of ultrasonography machine than the one provided. All 6 of them stated that unfamiliarity of the machine was a factor

in not getting the results that they would have liked. 2/6 that used the same brand struggled with the machines because they were a different model to the ones they were used to

- 8/12 stated that the restricted time of 13 minutes per examination was insufficient
- 7/12 stated that the absence of a history and examination prior to the ultrasonography created a situation where definitions were being tested in an artificial environment
- 5/12 had struggled with an ergonomic factor – couch could not be adjusted, lighting was poor, etc.

Due to these results, the full meeting was modified to include 6 hours of ultrasonography to familiarise the sonographers with the machines, and the amount of time allowed per examination was increased from 13 minutes to 20 minutes for the initial rounds. The reliability after these changes was excellent as shown in Table 10, Table 11 and Table 12. We have been able to demonstrate a practical way to improve the reliability and feasibility of ultrasonography for diagnosis of GCA.

The effect of probe frequency

The third instalment of this work which is the main part of Chapter 2 is the validation of all the above parts functioning together as a service. An important difference here was the resolution of the transducer. All the validation work had used a linear transducer with a max frequency of 18 MHz. The machine used for this work had a linear transducer of max frequency of 14 MHz (example image in Figure 10). There was only one false negative result in this work, and it is possible that the lower resolution may have had a role to play. In the previous paragraphs we have discussed that the size of the halo is likely to be a function of the diameter of the artery. It is equally plausible that the definitions will have to consider the frequency of the transducer (and thus the resolution of the image). Since publishing Chapter 2, the GCA service in Norwich has seen further capital investment in the form of linear

transducers of max 18 MHz and max 22 MHz frequency (174). Anecdotally, my experience is that transducers of higher frequencies allow demonstration of more subtle halo signs. This is similar to the published experience of Noumegni et al who have recently published their experience comparing images acquired by 18-MHz probe and 22-MHz probe being comparable, except in a minority of cases where the diagnosis could only be made by a 22-MHz probe (374).

Single-centre work

This study of 25 cases was done to validate a specific ultrasonography service with the specific parts at work in the Norfolk and Norwich University Hospital. This would be a weakness and a major limitation of the generalisability of this work – if it was a stand-alone piece of work. However, it came in the footsteps of my participation in an international consortium. The use of the same validated techniques that had been used in the reliability exercises were a major strength. In the validation exercises, the technology was being assessed against individuals known to have GCA. In this work, we did not know the diagnosis for certain at the time of the ultrasonography and the final decision on whether GCA was the diagnosis or otherwise was only determined at the end of follow-up at 100 weeks. Diamantopoulos et al (176) and Patil et al (175) have published their pathways leading to better outcomes, but the work presented here is the only published service validation providing a template for other units to follow. The European Federation of Societies for Ultrasonography in Medicine and Biology have made a recommendation for 300 examinations to achieve Level 1 competency. The rarity of GCA does not allow that to be a feasible recommendation. Following the validation exercise presented here, our centre in Norwich receives an average of 140 referrals a year (174), which are all seen by me. A target of 300 supervised examinations is not a practical suggestion and will hamper the development of further centres.

Physician-verified diagnosis

Classification criteria are used to define homogenous cases and are not meant for diagnostic purposes. When they are used for diagnostic purposes, they tend not to perform well (107, 375). In the only classification exercise for primary systemic vasculitis, the American College of Rheumatology created a set of criteria that were tested against diagnoses made by senior clinicians (376). In the validation exercise presented here, we did a 4-way comparison of ultrasonography, TAB, physician-verified diagnoses at baseline and again at 100-weeks. If we suppose that the physician is wiser after 100-weeks of patient data as compared to baseline, then baseline clinical decision making had an inferior reliability (κ = 0.6) compared to ultrasonography (κ = 0.8) (Table 6). This makes two points, firstly – the decision of the physician is still the gold-standard for the diagnosis, but only if informed by enough data; and secondly, physician-verified diagnosis at baseline will be improved by ultrasonography. This is similar to the experience in the development of BVAS. In the validation of BVAS v1, the physician's opinion of disease activity was marked as separately from the assessment with the BVAS v1. There was no relationship between the two assessments (109). But marking the physician global assessment after a systematic assessment as occurred in the validation of BVAS v3 resulted in an excellent correlation between the two forms of assessments (130).

Future work

We used this unique 4-way comparison because we could not test the reliability of a single ultrasonographer in a single centre. But with this blueprint, other centres can commence their own validation which may serve as self-certification. It is not in the interest of any service to be dependent on a single person. In Norwich, we will test the reliability of a second ultrasonographer against my results on the same day.

Since these publications, we have also published a consensus definition of chronic changes of vasculitis in extracranial arteries and tested its robustness under the

auspices of the OMERACT initiative (377). Future research agenda that arises directly from this work includes

1. Studying the phenotype and classification of large vessel vasculitis to understand the clinical and demographic similarities and distinctions between Takayasu arteritis and GCA to complement the imaging work done by Gribbons et al (371).
2. Producing cut-offs for the size of the concentric hypoechogenicity as a function of the diameter of the vessel being tested and considering the frequency of the probe being used. If this proves reliable, we will have a template for ultrasonography of any large artery that may be suspected of having vasculitis.
3. We will test the reliability of a second ultrasonographer in Norwich using a direct comparison against me.

Chapter 3

Early randomized controlled trials in primary systemic vasculitis did not formally measure disease activity or damage (303, 378-381). Tangible quantification of disease activity and differentiation of activity from damage were the two major principles on which the twin clinical tools of BVAS and VDI were designed by the Birmingham Vasculitis Group (109, 136). They revolutionised the metrics of clinical trials in vasculitis. BVAS had to be modified in 1997 (260) before it could be used for the first time (382). VDI has been used unchanged since its first development. In addition to their use to quantify activity and damage respectively, BVAS and VDI assisted clinical decision-making, evolved as prognostic indices, in education and training for assessment of vasculitis, as yardsticks for other measures to be compared to, and were used in clinical trials for purposes beyond their original intent (112). In clinical trials, they were used to define inclusion criteria, compare outcomes in different arms of a clinical trial and pool results from different clinical trials (112).

BVAS v2 produced two scores – BVAS 1 for active disease and BVAS 2 for persistent disease. This meant that correlation of total disease activity against parameters was difficult and usually resulted in ignoring BVAS 2. The use in randomized controlled trials also brought the recognition of items that were redundant and non-discriminatory. This provided an impetus for change. The BVAS v3 was a further modification which was formally validated using OMERACT methodology in a cohort of 313 individuals with primary systemic vasculitis (110). This validation was in a UK cohort. The first wave of randomized controlled trials by the European Vasculitis Study Group had used BVAS v2. To ensure that the BVAS v3 could be adopted without need for further change, it needed modification in a European cohort leading to the work that I have presented in Chapter 4. BVAS v3 was rapidly adopted for use in landmark clinical trials (383-385) and is now the standard of disease activity assessment.

There had been no clinical need to develop or modify the VDI. It had been used successfully without need for change in European clinical trials. But its need for development has been documented in the supportive work presented in Chapter 3.

I have presented 3 papers in this thesis that demonstrate my involvement in the development and change of these indices. I now present a critique of the work that we did.

The exclusion of GCA in BVAS v3 validation

All the versions of BVAS have a common set of rules that govern their use. Only disease manifestations that are attributable to active vasculitis can be scored and contribute towards disease activity. In both validation papers, we did not recruit GCA despite it being the commonest primary systemic vasculitis. Even Takayasu arteritis which was thought to have more systemic involvement was included. Between the three BVAS validation exercises, 26 individuals with Takayasu arteritis had been included (109, 110, 124). The reasoning for excluding GCA was that we thought it

would produce a very limited range of scores because of the dogma that GCA has an unusually homogenous presentation for a primary systemic vasculitis. We reasoned that restricted phenotype of GCA, and the anticipated large numbers might overwhelm the validation. We did not consider that we might know little about the presentations of GCA. In a survey of individuals with GCA, they reported manifestations that are not routinely thought to be related to GCA (386). GCA could affect the domains of BVAS as follows –

- General (score achievable with following manifestations = 3)
    - Myalgia – chiefly through involvement of the branches of the subclavian arteries causing proximal muscle pain which has been mistaken to be polymyalgia rheumatica (387). But also, hip girdle myalgia in those with true polymyalgia rheumatica overlap with GCA.
    - Fever – as a constitutional sign of inflammation (388)
    - Weight loss – as a constitutional sign of inflammation (389)
- Cutaneous (score achievable with following manifestations = 6)
    - Gangrene – because of compromised scalp circulation (390)
- Mucous membranes / eyes (score achievable with following manifestations = 6)
    - Blurred vision and sudden visual loss – because of anterior ischaemic optic neuropathy (391) or central retinal artery obstruction (392)
    - Retinal changes – central retinal artery obstruction (392) or central retinal vein obstruction (393)
- Ear, Nose and Throat (score achievable with following manifestations = 5)
    - Paranasal sinus involvement – chiefly by involvement of the maxillary artery (394)
    - Conductive hearing loss – because the tympanic membrane is supplied by the maxillary artery (395)
- Cardiovascular (score achievable with following manifestations = 4)

    - Loss of pulses – because of involvement of the subclavian or axillary arteries (396)
- Nervous system (score achievable with following manifestations = 9)
    - Headache – archetypal manifestation
    - Meningitis – severe headache with neck pain resembling meningism related to involvement of the middle meningeal artery branch of maxillary artery (397)
    - Stroke – because of vertebral artery involvement (398)

Thus, the range of possible BVAS scores for GCA could be 0-33). Improved understanding of the vasculotomes of GCA and ability to image the individual blood vessels have provided us with the opportunity to validate BVAS v3 for use in GCA. This forms part of a research agenda.

Assessment of disease activity in Behçet's disease

There is a disease specific tool for Behçet's disease in the form of BDCA (121). The validation of BDCA involved checking the interobserver reliability in 19 individuals with Behçet's disease. In the two BVAS v3 papers, we have tested the instrument in 30 individuals with Behçet's disease with a range of scores from 0-19. Arguably, BVAS v3 is better validated than the BDCA for assessment of activity of Behçet's disease not just in terms of numbers of cases involved but also the breadth of validation (Table 2 and Table 3). BDCA is available in Turkish and Korean and has been used in many studies, but BVAS v3 has a role where disease activity of an undifferentiated or a mixed cohort including cases of Behçet's disease need to be studied (399).

BVAS v3 as diagnostic criteria

Above we have considered the possibility that the lack of our knowledge of the myriad manifestations of GCA may have limited the use of BVAS v3 in GCA. But if the attribution rule of BVAS is deliberately ignored in cases where the diagnosis is not known, it may be possible to identify potential multi-system diseases including

primary systemic vasculitis. In an exercise which I presented at a national conference[1], I recruited 49 individuals known to not have primary systemic vasculitis (26 rheumatoid arthritis, 4 reactive arthritis, 3 axial spondyloarthritis, 3 systemic lupus erythematosus, and 13 patients with other diagnoses. I assessed all of them using BVAS v3. The mean (SD) BVAS v3 score was 5.54 (5.9). 35/49 (71%) scored $\leq$5 and 41/49 (84%) scored $\leq$10. Of the 8 with a BVAS v3 >10, 2 had GPA and 1 had rheumatoid vasculitis. 2 individuals had multisystem involvement with SLE and 4 did not have evidence of vasculitis. This work had been done to calibrate the 'noise' in BVAS v3 as part of its development process, but we ended up diagnosing 3 new cases of vasculitis. This concept was developed further to demonstrate that BVAS v3 $\geq$8 had a sensitivity of 72% and a specificity of 78% to differentiate primary systemic vasculitis from rheumatoid arthritis; and a score of $\geq$7 had a sensitivity of 72% and a specificity of 79% to differentiate primary systemic vasculitis from non-systemic rheumatological conditions (130). No validated diagnostic criteria exist in primary systemic vasculitis. It is possible that the addition of more parameters may allow us to formulate the first set of diagnostic criteria for primary systemic vasculitis (111).

Damage as a concept

We developed the CDA as a major extension of the VDI. In the two papers presented in Chapter 3 on this subject, we set out why we wanted to change the VDI and how we were going to do it. The extension did not improve the VDI. The CDA had a broader range of scores (0-26) against the VDI (0-12), but we did not know what the meant. The CDA found damage in only 3% more cases, and only 1 more item of damage as a median. It took more time to fill out as a result was less feasible. In OMERACT filter terms, it was perhaps as 'Discriminatory', but less 'True' (because of

[1] Presented at the British Society for Rheumatology Annual Conference as a Poster on 24/04/2008 (DOI: https://doi.org/10.1093/rheumatology/kem524)

lower reliability) and less 'Feasible' and therefore did not merit use in further clinical trials. The reason for this was almost certainly because it was a clinical tool that was invented without clear purpose. The impetus for change had been to harmonise the conduct of clinical trials between European and American workers. The reason that the VDI had been invented was to clearly differentiate activity from damage. American researchers had wanted clarity of cataloguing and recognition of scars and adverse effects of drugs. But we had not decided on whether this score should reflect prognosis, QOL, disability, treatment resistance or another endpoint. Damage continues to remain a concept that helps us to differentiate activity from damage in our daily practice. QOL is probably the outcome that is of greatest relevance to sufferers of vasculitis, it is plausible that the development of any patient reported outcome measure may inform modifications of how and why we measure damage.

Future work

BVAS v3 and VDI remain the standard of assessment for primary systemic vasculitis in European practice as well as clinical trials. Currently, GCA is the commonest primary systemic vasculitis, and it does not have a validated disease activity tool. BDCA has been used extensively in Behçet's disease but has not been validated to satisfy the OMERACT filter. Future research agenda that arises directly from this work includes

1. Validating the use of BVAS v3 in GCA. To validate or produce a GCA modification of BVAS v3, we will need to better understand the nature of arterial involvement and the specific vasculotome manifestations.
2. Validating the use of BVAS v3 in Behçet's disease.
3. Understanding how damage relates to quality of life and any patient related outcome measure.

Chapter 4

Outcomes are easy to measure and compare if they have been defined clearly. 'Survival' or 'Mortality' related to a particular disease may appear unambiguous because there is a clear distinction between those that survive, and those that don't. But the outcome must be qualified by three important factors – time, clear definition of the disease and the medical interventions that may influence the endpoint. All other outcomes are more ambiguous and rely on clarity of definitions, and therefore, so is their measurement. Arguably, the most important outcome of QOL, is perhaps the most difficult to define and even more difficult to measure. I have presented two papers in Chapter 4 researching outcomes in AAV, and I present a critique of that work.

Effect of classification

GPA, MPA and EGPA have been classified under the umbrella of AAV. The only validated classification criteria for primary systemic vasculitis were published in 1990 (400). Therefore, most studies that were included in this work had defined their cases using these criteria. However, those classification criteria had two major flaws in them. AAV were being classified into separate disease phenotypes using a classification system that did not recognise ANCA. MPA was recognised as a disease concept only in 1994 (344), and therefore studies prior to 1994 probably misclassified them as either GPA or PAN (401). There is a large international effort to produce more relevant classification criteria (111) It is possible that with reclassification, the outcomes described here will have less meaning. We were aware of this and therefore took all the diagnoses as stated in the papers included, at face value. When the classification criteria receive an update, we will look at the effect of the nomenclature and criteria on the outcomes in a local cohort.

Effect of definitions

There have been significant variations in the way that 'Remission' has been defined. When Reinhold-Keller et al defined remission as *"Absence of clinical, serologic, and radiologic (including MR imaging) evidence of disease activity. These conditions had to be sustained for at least 6 months after the discontinuation of the pulse cyclophosphamide treatment, without further immunosuppressive therapy, including withdrawal of prednisolone",* the remission rate was 30% (321). When the same group, defined remission as *"Absence of pathologic findings, irrespective of ANCA titre",* the remission rate was 54% (323). We decided that it was not possible to tease out the variations in the definitions, and that we could report the rates as they had been published. In a separate paper we acknowledged the variations and their effect on the reported outcomes (402). The information from these data went on to inform a consensus document which defined 'remission' and 'relapse' (169). To allow comparison across clinical trials and clinical practice, these definitions need to become part of trial protocols and daily care.

Survival in GPA and MPA

In Table 26, we reported the survival of GPA and MPA at 1, 2 and 5 years as previously published. There was a variation in the data available, which mostly included studies of GPA. The variations were related to the inclusion criteria, the treatments used and the classification of the vasculitis phenotype. EUVAS had conducted 4 randomized controlled trials in 535 individuals with GPA or MPA (170, 275-277). These cases represented the entire clinical spectrum of GPA and MPA and had been treated using homogenous glucocorticoid therapy, and a structured approach to immunosuppressive stratification. We conducted a longitudinal follow-up study of the cases in those 4 clinical trials and reported that the cumulative survival at 1, 2 and 5 years was 88%, 85% and 78% respectively (403). This was lower than the survival for the general population with a mortality ratio of 2.6 (95% CI 2.2-3.1). The data from the systematic review of literature matched the data from the largest

longitudinal study of GPA and MPA. These data represent the outcomes from treatment which is currently state of the art as recommended by EULAR (4). There is a dearth of data related to EGPA because of its exclusion in large clinical trials. International recommendations for EGPA have been largely based on extrapolation of data from clinical trials in GPA and MPA (4, 404). The European Respiratory Society has published EGPA specific management recommendations in 2015 which were largely consensus opinions (405). There is need for dedicated review of literature for EGPA, international recommendations for managing EGPA, and then monitoring survival and other outcomes in EGPA. These form part of a future agenda.

Cardiovascular events in GPA and MPA

We had shown that GPA and MPA had worse survival in Chapter 4 and on longitudinal follow-up (403). A major cause of long-term mortality was due to cardiovascular events. We studied the cardiovascular events in this group.[2] 47% of the cases in the EUVAS trials had developed a cardiovascular problem on follow-up beyond 5 years. Those suffering with MPA (vs GPA) had an odds ratio (95% CI) of 3.04 (1.18, 7.84) for developing angina pectoris or having coronary revascularisation; 2.10 (1.18, 3.75) for developing hypertension. There were statistically similar incidences of myocardial infarction and cerebrovascular accident in GPA and MPA. Using these data, we were also able to create a mathematical model to predict the risk of cardiovascular event (stroke, myocardial infarction, or revascularisation) in individuals with AAV. The predicted risk for an event to occur in AAV $= \frac{1}{1+e^{-risk\ score}}$, where the risk score = $-3.9 + (0.04 * Age) - (0.95 * PR3\ ANCA) + (0.68 * HTN)$ [if PR3 ANCA is positive, the value is 1, otherwise 0; if individual is hypertensive, the value is 1, otherwise 0] (139). This model was tested against a traditional Framingham model

[2] Presented at the British Society for Rheumatology Annual Meeting as an Oral Abstract on 22/04/2008 (DOI: https://doi.org/10.1093/rheumatology/kem503)

and was found to have higher predictive value (139). This does not mean that traditional risk factors like smoking, and lipid levels can be ignored, but that the vascular endothelium of individuals with GPA and MPA must deal with an insult that is greater than the damage caused by nicotine and hypercholesterolemia. This is supported by the evidence that endothelial responses are affected even in seemingly unaffected arteries in individuals with systemic vasculitis (406). This model remains of academic value for now, with blood pressure being the only modifiable variable. We still need a better understanding of the incidence of myocardial infarction and cerebrovascular accident in GPA and MPA before we can design strategies on how to prevent these events or create recommendations on managing the cardiovascular risk in AAV.

Measuring Quality of Life

In Chapter 4, we have presented the largest study to date of studying QOL outcomes in AAV. QOL is a difficult concept to define. It is modified by everyday life events and expectations. To partition that further, by measuring only the health-related QOL, as done by SF-36 is even more exigent. There was no validated patient reported outcome measure in AAV at the time of publication of our paper in Chapter 4. Since then, Robson et al have validated an AAV patient reported outcomes questionnaire (407). Tieu et al have produced a core set of domains which include patient perspectives to measure the impact of glucocorticoid therapy in individuals in rheumatic diseases (408). We have used the SF-36 but recognise the limitations of this exercise. The use of patient reported outcome measure in clinical trials remain an important priority. It is noteworthy that this is perhaps the most important item of what matters to an individual suffering with primary systemic vasculitis and yet, there has not been a single interventional clinical trial that has used any QOL measure or patient reported outcome measure as a primary outcome. As scientists, the focus has been on mechanisms of disease and modification of those pathological processes. But our study has shown that QOL is poor in individuals with AAV. Others have shown that modification of pathological processes by pharmacotherapy and

induction of remission as measured by clinical tools, do not result in commensurate improvement in the QOL (152, 265, 315, 409, 410). The role of comorbidities and their effect on AAV also remain a concern and less amenable to immunosuppression (411)

Interpreting SF-36 in AAV

Using an elaborate statistical model, we were unable to find any one aspect of AAV that might be singularly affecting QOL. The two statistically important findings were that age and neurological involvement impair QOL, but age required a 45-year difference to be clinically meaningful. A 90-year-old individual would have a meaningfully reduced QOL over a 45-year-old. This could be inversely interpreted as demonstrating that chronological age did not matter in AAV, and that all individuals felt QOL at par with those up to 45 years older than them. The multitude of systems involved did not have any relationship with QOL. This could be inversely interpreted that all aspects of AAV including organ involvement, age, severity of disease, treatments work co-dependently to adversely affect the QOL. We know that glucocorticoid therapy is responsible for many adverse effects that invariably affect the QOL. It will be of interest to test glucocorticoid-light regimens against standard therapy using a patient reported outcome measure as the primary endpoint.

Future work

An international exercise to which I have contributed is currently in progress to establish a new set of classification criteria and perhaps diagnostic criteria (111). Once this work is complete, there will be a fresh need to look at how the changes in classification and possibly nomenclature may affect outcomes. Future research work that arises out of the combination of what we have reported so far and the changes that are on the horizon include

1. Studying the effect of classification on the incidence and outcomes of primary systemic vasculitis.

2. We have formed a pan-European consortium to form treatment recommendations for EGPA and design further clinical trials.
3. Longitudinal study of cardiovascular outcomes in a stable population followed by interventional trials.
4. Continue development of patient-reported outcome measures by using them in clinical trials allowing for experience-based modifications.

Conclusions

I have presented a body of work produced over a 15-year period that has influenced the care of individuals with primary systemic vasculitis. Advances in ultrasonography have translated to improved care. BVAS v3 has resulted in uniformity of outcome measure across clinical trials of systemic vasculitis, and in daily bedside assessments in vasculitis clinics. The project for improving CDA demonstrated that VDI remained a clinical tool for daily use but more importantly resulted in the production of paper cases and educational tools that are being used regularly to train a new generation of rheumatology trainees and clinical trialists. We have presented data on historical hard outcomes and studied outcomes related to state-of-the-art treatments. We have attempted to study QOL in AAV which will undoubtedly lead to further development of patient reported outcome measures. In the paragraphs above, I have outlined a rich research agenda which will continue to improve our understanding of these rare conditions.

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Appendix 1 Birmingham Vasculitis Activity Score (version 3)

Tick an item **only** if attributable to active vasculitis. If there are no abnormalities in a section, please tick 'None' for that organ-system.			If **all** abnormalities are due to persistent disease (active vasculitis which is not new/worse in the prior 4 weeks), tick the **PERSISTENT** box at the bottom right corner		
Is this the patient's first assessment?			Yes ○		No ○
	None	Active disease		None	Active disease
1. General	○		6. Cardiovascular	○	
Myalgia		○	Loss of pulses		○
Arthralgia / arthritis		○	Valvular heart disease		○
Fever ≥38° C		○	Pericarditis		○
Weight loss ≥2 kg		○	Ischaemic cardiac pain		○
2. Cutaneous	○		Cardiomyopathy		○
Infarct		○	Congestive cardiac failure		○
Purpura		○	7. Abdominal	○	
Ulcer		○	Peritonitis		○
Gangrene		○	Bloody diarrhoea		○
Other skin vasculitis		○	Ischaemic abdominal pain		○
3. Mucous membranes / eyes	○		8. Renal	○	
Mouth ulcers		○	Hypertension		○
Genital ulcers		○	Proteinuria >1+		○
Adnexal inflammation		○	Haematuria ≥10 RBCs/hpf		○
Significant proptosis		○	Serum creatinine 125-249 µmol/L*		○
Scleritis / Episcleritis		○	Serum creatinine 250-499 µmol/L*		○
Conjunctivitis / Blepharitis / Keratitis		○	Serum creatinine ≥500 µmol/L*		○
Blurred vision		○	Rise in serum creatinine >30% or fall in creatinine clearance >25%		○
Sudden visual loss		○	*Can only be scored on the first assessment		
Uveitis		○	9. Nervous system	○	
Retinal changes (vasculitis / thrombosis / exudate / haemorrhage)		○	Headache		○
4. ENT	○		Meningitis		○
Bloody nasal discharge / crusts / ulcers / granulomata		○	Organic confusion		○
Paranasal sinus involvement		○	Seizures (not hypertensive)		○
Subglottic stenosis		○	Cerebrovascular accident		○
Conductive hearing loss		○	Spinal cord lesion		○
Sensorineural hearing loss		○	Cranial nerve palsy		○
5. Chest	○		Sensory peripheral neuropathy		○
Wheeze		○	Mononeuritis multiplex		○
Nodules or cavities		○	10. Other	○	
Pleural effusion / pleurisy		○	a.		○
Infiltrate		○	b.		○
Endobronchial involvement		○	c.		○
Massive haemoptysis / alveolar haemorrhage		○	d.		○
Respiratory failure		○	PERSISTENT DISEASE ONLY: (Tick here if **all** the abnormalities are due to persistent disease)		☐

References:

Version 1: Luqmani, RA, et al. (1994). "Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis." QJM **87**(11):671-8.

Version 2: Luqmani, RA, et al. (1997). "Disease assessment and management of the vasculitides." Bailliere's Clin Rheumatol **11**(2): 423-46.

Version 3: Mukhtyar C, et al (2008). "Modification and validation of the Birmingham Vasculitis Activity Score (version 3) (Chapter 5)

GLOSSARY AND SCORING FOR BVAS version 3

Rules for scoring BVAS

1. Disease manifestations are scored **only when they are attributable to active vasculitis**. The manifestation should not be scored if there is reasonable evidence of another aetiology for the symptoms e.g. infection, drug reaction, other co-morbidity.
2. Tick "Persistent Disease" box if **all** the abnormalities are due to active (but not new or worse) vasculitis.
3. Specialist opinion, or the results of laboratory or imaging investigations will be required for some items. Excepting those circumstances, the whole form should be completed at the time of the consultation.
4. The bands of serum creatinine should be scored **only** on the first visit.
5. Items marked with an asterisk (*) are not compatible with 'persistent' disease. These manifestations always suggest new or worse disease when due to active vasculitis.

Manifestation	Definition	Persistent	New / Worse
1. General	**Maximum scores**	**2**	**3**
Myalgia	Pain in the muscles	1	1
Arthralgia or arthritis	Pain in the joints or joint inflammation	1	1
Fever ≥38° C	Documented oral / axillary temperature. If rectal temperature is measured, raise threshold to 38.5° C	2	2
Weight Loss ≥2 kg	Loss of dry body weight without dieting	2	2

2. Cutaneous	**Maximum scores**	**3**	**6**
Infarct	Area of tissue necrosis or splinter haemorrhages	1	2
Purpura	Subcutaneous or submucosal haemorrhage in the absence of trauma	1	2
Ulcer	A disruption in the continuity of the skin	1	4
Gangrene	Extensive tissue necrosis	2	6
Other skin vasculitis	Livedo reticularis, subcutaneous nodules, erythema nodosum, etc	1	2

3. Mucous Membranes / eyes	**Maximum scores**	**3**	**6**
Mouth ulcers / granulomata	Aphthous stomatitis, deep ulcers, strawberry gingival hyperplasia	1	2
Genital ulcers	Ulcers on the genitalia or perineum	1	1
Adnexal inflammation	Salivary or lacrimal gland inflammation.	2	4
Significant proptosis	>2 mm protrusion of the eyeball	2	4
Scleritis / Episcleritis	Inflammation of the sclera	1	2
Conjunctivitis / Blepharitis / Keratitis	Inflammation of the conjunctiva, eyelids or cornea - but not due to sicca syndrome	1	1
Blurred vision	Deterioration of visual acuity from previous or baseline	2	3
Sudden visual loss*	Acute loss of vision	*	6
Uveitis	Inflammation of the uvea (iris, ciliary body, choroid)	2	6
Retinal changes (vasculitis, thrombosis / exudate / haemorrhage)	Sheathing of retinal vessels or evidence of retinal vasculitis on fluorescein angiography; thrombotic retinal arterial or venous occlusion; soft retinal exudate	2	6

	(exclude hard exudates) / retinal haemorrhage		

4. ENT	**Maximum scores**	**3**	**6**
Bloody nasal discharge / crusts / ulcers / granulomata	Bloody, mucopurulent, nasal secretion, light or dark brown crusts frequently obstructing the nose, nasal ulcers or granulomatous lesions observed on rhinoscopy	2	4
Paranasal sinus involvement	Tenderness or pain over paranasal sinuses (usually confirmed by imaging)	1	2
Subglottic stenosis	Stridor or hoarseness due to inflammation and narrowing of the subglottic area observed by laryngoscopy	3	6
Conductive hearing loss	Hearing loss due to middle ear involvement (usually confirmed by audiometry)	1	3
Sensorineural hearing loss	Hearing loss due to auditory nerve or cochlear damage (usually confirmed by audiometry)	2	6

5. Chest	**Maximum scores**	**3**	**6**
Wheeze	Wheeze on clinical examination	1	2
Nodules or cavities*	New lesions detected on imaging	*	3
Pleural effusion / pleurisy	Pleural pain and/or friction rub on clinical assessment; radiologically confirmed pleural effusion.	2	4
Infiltrate	Detected on chest X-ray or CT scan	2	4
Endobronchial involvement	Endobronchial pseudotumor or ulcerative lesions. NB: smooth stenotic lesions to be included in VDI; subglottic lesions to be recorded in the ENT section.	2	4
Massive haemoptysis / alveolar haemorrhage	Major pulmonary bleeding, with shifting pulmonary infiltrates	4	6
Respiratory failure	The need for artificial ventilation	4	6

6. Cardiovascular	**Maximum scores**	**3**	**6**
Loss of pulses	Clinical absence of peripheral arterial pulsation in any limb	1	4
Valvular heart disease	Clinical or echo detection of aortic / mitral / pulmonary valve involvement	2	4
Pericarditis	Pericardial pain / friction rub on clinical assessment	1	3
Ischaemic cardiac pain	Typical clinical history of cardiac pain leading to myocardial infarction or angina.	2	4
Cardiomyopathy	Significant impairment of cardiac function due to poor ventricular wall motion confirmed on echocardiography	3	6
Congestive cardiac failure	Heart failure by history or clinical examination	3	6

7. Abdominal	**Maximum scores**	**4**	**9**

Peritonitis	Typical abdominal pain suggestive of peritoneal involvement	3	9
Bloody diarrhoea	Of recent onset	3	9
Ischaemic abdominal pain	Typical abdominal pain suggestive of bowel ischaemia, confirmed by imaging or surgery	2	6

8. Renal	**Maximum scores**	**6**	**12**
Hypertension	Diastolic >95 mm Hg	1	4
Proteinuria	>1+ on urinalysis or >0.2g/24 hours	2	4
Haematuria	'Moderate' on urinalysis or ≥10 RBC per high power field, usually accompanied by red cell casts	3	6
Serum creatinine 125-249 µmol/L	At first assessment only	2	4
Serum creatinine 250-499 µmol/L		3	6
Serum creatinine **≥**500 µmol/L		4	8
>30% rise in creatinine or >25% fall in creatinine clearance *	Progressive worsening of renal function. Can be used at each assessment if the renal function has deteriorated from prior value	*	6

9. Nervous system	**Maximum scores**	**6**	**9**
Headache	Unaccustomed & persistent headache	1	1
Meningitis	Clinical evidence of meningism	1	3
Organic confusion	Impaired orientation, memory or other intellectual function in the absence of metabolic, psychiatric, pharmacological or toxic causes.	1	3
Seizures (not hypertensive)	Clinical or EEG evidence of aberrant electrical activity in the brain	3	9
Stroke	Focal neurological signs lasting >24 hours due to a CNS vascular event	3	9
Spinal cord lesion	Clinical or imaging evidence of spinal cord involvement	3	9
Cranial nerve palsy	Clinical evidence of cranial nerve palsy – score VIII nerve palsy as sensorineural hearing loss, do not score ocular palsies if they secondary to pressure effects	3	6
Sensory peripheral neuropathy	Objective sensory deficit in a non-dermatomal distribution	3	6
Mononeuritis multiplex	Single or multiple specific motor nerve palsies	3	9

Appendix 2 Vasculitis Damage Index

VASCULITIS DAMAGE INDEX (VDI)

This is for recording organ damage that has occurred in patients ***since the onset of vasculitis.*** Patients often have co-morbidity before they develop vasculitis, **which must not be scored.** Record features of active disease using the Birmingham Vasculitis Activity Score 2003 (BVAS). A new patient should ***usually have a VDI score of zero,*** unless:(a) they have had vasculitis for more than three months of onset of disease. **And** (b) the damage has developed or become worse since the onset of vasculitis

1. Musculoskeletal	**No**	**Yes**
None	☐	
Significant muscle atrophy or weakness		○
Deforming/erosive arthritis		○
Osteoporosis/vertebral collapse		○
Avascular necrosis		○
Osteomyelitis		○
2. Skin/Mucous membranes		
None	☐	
Alopecia		○
Cutaneous ulcers		○
Mouth ulcers		○
3. Ocular		
None	☐	
Cataract		○
Retinal change		○
Optic atrophy		○
Visual impairment/diplopia		○
Blindness in one eye		○
Blindness in second eye		○
Orbital wall destruction		○
4. ENT		
None	☐	
Hearing loss		○
Nasal blockage/chronic discharge/crusting		○
Nasal bridge collapse/septal perforation		○
Chronic sinusitis/radiological damage		○
Subglottic stenosis (no surgery)		○
Subglottic stenosis (with surgery)		○
5. Pulmonary		
None	☐	
Pulmonary hypertension		○
Pulmonary fibrosis		○
Pulmonary infarction		○
Pleural fibrosis		○
Chronic asthma		○
Chronic breathlessness		○
Impaired lung function		○
6. Cardiovascular		
None	☐	
Angina/angioplasty		○
Myocardial infarction		○
Subsequent myocardial infarction		○
Cardiomyopathy		○
Valvular disease		○
Pericarditis ≥ 3 mths or pericardectomy		○
Diastolic BP ≥ 95 or requiring antihypertensives		○

Name:
Trial Number:
Date:
Centre:

7. Peripheral vascular disease	**No**	**Yes**
None	☐	
Absent pulses in one limb		○
2nd episode of absent pulses in one limb		○
Major vessel stenosis		○
Claudication >3 mths		○
Minor tissue loss		○
Major tissue loss		○
Subsequent major tissue loss		○
Complicated venous thrombosis		○
8. Gastrointestinal		
None	☐	
Gut infarction/resection		○
Mesenteric insufficiency/pancreatitis		○
Chronic peritonitis		○
Oesophageal stricture/surgery		○
9. Renal		
None	☐	
Estimated/measured GFR ≤ 50%		○
Proteinuria ≥ 0.5g/24hr		○
End stage renal disease		○
10. Neuropsychiatric		
None	☐	
Cognitive impairment		○
Major psychosis		○
Seizures		○
Cerebrovascular accident		○
2nd cerebrovascular accident		○
Cranial nerve lesion		○
Peripheral neuropathy		○
Transverse myelitis		○
11. Other		
None	☐	
Gonadal failure		○
Marrow failure		○
Diabetes		○
Chemical cystitis		○
Malignancy		○
Other		○

Total VDI Score. Record the number of positive Items (1 point for each). The VDI score can either increase or remain the same over time. remember to carry forward any previous items of damage ☐

Appendix 3 Combined Damage Assessment Index

Combined Damage Assessment Index (CDA)

Protocol: Investigator Name MR Number Visit ID Number:	Date of Birth: Sex (Circle): Male Female Weight: _____ . _____ kg S Creatinine _____ . ____ mg/dL Race (Circle): Black White Asian Other:_____

Instructions: This is for recording organ damage that has occurred in patients since the onset of vasculitis. Co-morbidity that exists before the onset of vasculitis must not be scored. A new patient should have a CDA of zero unless he has had vasculitis for at least 6 months, and the damage has developed or become worse since the onset of vasculitis. A finding must be present for 6 months to be scored. Damage is irreversible, and only rarely should a scored item not be carried forward. Where applicable, please include the primary data values, in addition to marking the relevant box

Musculoskeletal — *None:* Δ

- ☐ Osteoporosis/vertebral collapse
- Bone fracture:
  - ☐ *Due to renal dystrophy*
  - ☐ *Due to osteoporosis*
  - ☐ *Due to both*
- Muscle atrophy due to glucocorticoids:
  - ☐ *Normal strength, atrophy on exam*
  - ☐ *Weak on examination, normal ADLs*
  - ☐ *Weak and has difficulty with ADLs*
- ☐ Avascular necrosis
- ☐ Deforming/erosive arthritis
- ☐ Osteomyelitis

Skin/Membranes — *None:* Δ

- ☐ Alopecia
- ☐ Mouth ulcers
- ☐ Cutaneous scarring
- ☐ Cutaneous ulcers
- ☐ Striae
- ☐ Gangrene with permanent tissue loss
- ☐ Easy bruising

Ocular — *None:* Δ

☐ Proptosis	L	R	B
☐ Pseudotumor	L	R	B
☐ Scleral thinning	L	R	B
☐ Scleral perforation	L	R	B
☐ Optic nerve edema	L	R	B
☐ Optic nerve atrophy	L	R	B
☐ Retinal changes	L	R	B
☐ Retinal artery occlusion	L	R	B
☐ Retinal vein occlusion	L	R	B
☐ Low vision	L	R	B
☐ Diplopia	L	R	B
☐ Blindness	L	R	B
☐ Cataracts	L	R	B
☐ Glaucoma	L	R	B
☐ Orbital wall destruction	L	R	B

Ear — *None:* Δ

☐ Sensorineural hearing loss	L	R	B
☐ Conductive hearing loss	L	R	B
☐ Tympanic membrane perforation or scarring	L	R	B
☐ Tinnitus	L	R	B
☐ Eustachian tube dysfunction	L	R	B
☐ Auricular cartilage deformity	L	R	B
☐ Cholesteatoma	L	R	B

Nose — *None:* Δ

- ☐ Chronic rhinitis/crusting
- ☐ Nasolacrimal duct obstruction
- ☐ Nasal bridge collapse/saddle nose
- ☐ Nasal septal perforation
- ☐ Anosmia
- ☐ Ageusia

Sinuses — *None:* Δ

- ☐ Chronic sinusitis
- ☐ Neo-ossification of sinuses

Subglottic stenosis — *None:* Δ

- ☐ *No intervention required*
- ☐ *Intervention required*

Pulmonary — *None:* Δ

- ☐ Irreversible loss of lung function
- ☐ Fixed large airway obstruction
- ☐ Pulmonary hypertension
- ☐ Pulmonary fibrosis
- ☐ Pulmonary embolism
- ☐ Pulmonary infarction
- ☐ Vena caval filter
- ☐ Continuous oxygen dependency
- ☐ Chronic asthma
- ☐ Pleural fibrosis
- ☐ Chronic breathlessness

FEV1 _____ _____ . _____

FVC _____ _____ . _____

RVSP _____ _____

Cardiac — *None:* Δ

Hypertension: ***BP*** _____ / _____

- ☐ *Pre-HTN: SBP 130-139 or DBP 80-89*
- ☐ *Stage I: SBP 140-149 or DBP 90-99*
- ☐ *Stage II: SBP >149 or DBP >99*
- ☐ Angina
- ☐ Myocardial infarction
- ☐ Percutaneous coronary intervention
- ☐ Coronary artery bypass graft

LV dysfunction: ***EF:*** ___ ____ %

- ☐ *NYHA Class I/II*
- ☐ *NYHA Class III/IV*
- ☐ Third degree AV block
- ☐ Valvular disease:

Specify:

- ☐ Pericarditis or pericardectomy

Vascular Disease — *None:* Δ

- ☐ Absent pulses in 1 limb
- ☐ 2nd episode of absent pulses in 1 limb
- ☐ Major vessel stenosis
- ☐ Claudication > 3 months
- ☐ Minor tissue loss
- ☐ Major tissue loss
- ☐ Subsequent major tissue loss
- ☐ Deep venous thrombosis
- ☐ Complicated venous thrombosis
- ☐ Carotid artery disease
- ☐ Renal artery stenosis
- ☐ Arterial thrombosis/occlusion

Specify:

Gastrointestinal — *None:* Δ

- ☐ Gut infarction/resection
- ☐ Hepatic fibrosis
- ☐ Mesenteric insufficiency/pancreatitis
- ☐ Esophageal stricture/surgery
- ☐ Chronic peritonitis

Renal — *None:* Δ

- ☐ Estimated/measured GFR<50%
- ☐ Chronic kidney disease
- ☐ End-stage renal disease
- ☐ Dialysis
- ☐ Renal transplant

Proteinuria:

- ☐ *< 3g/24h*
- ☐ *>3g/24h*

Neurologic — *None:* Δ

- ☐ Seizures
- ☐ Transverse myelitis

Sensory polyneuropathy:

- ☐ *Mild*
- ☐ *Moderate*
- ☐ *Severe*
- ☐ Motor neuropathy (mononeuritis)
- ☐ Neuropathic pain
- ☐ Cerebrovascular accident
- ☐ 2nd Cerebrovascular accident
- ☐ Cranial nerve lesion, ***Specify:***

Psychiatric — *None:* Δ

- ☐ Cognitive impairment
- ☐ Anxiety disorder due to vasculitis
- ☐ Mood disorder due to vasculitis
- ☐ Major psychosis

Endocrine — *None:* Δ

- ☐ Diabetes insipidus
- ☐ Premature ovarian failure
- ☐ Azoospermia
- ☐ Impaired fasting glucose
- ☐ Diabetes mellitus

Hematology/Oncology — *None:* Δ

- ☐ Bladder cancer
- ☐ Cervical cancer
- ☐ Hematopoetic malignancy
- ☐ Solid tumor malignancy

Specify:

- ☐ Refractory cytopenia
- ☐ Myelodysplastic syndrome

Other — *None:* Δ

- ☐ Weight gain > 10 lbs/4.4 kg
- ☐ Fibromyalgia

Drug-induced cystitis:

- ☐ *with microscopic hematuria*
- ☐ *with gross hematuria*
- ☐ *requiring transfusion*
- ☐ *requiring cystectomy*
- ☐ Damage requiring surgical intervention

Specify:

- ☐ Medications to manage side effects of immunosuppressive agents

Specify:

- ☐ Hypogammaglobulinemia

Damage not otherwise specified: _____

***Physician Global Assessment*: mark line to indicate the total burden of damage in this patient:**

NONE |_____| MAXIMUM

Signature: _____ **Date** _____

Appendix 4 List of publications indexed on Medline (2006-2020)

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