

Workshop

# The Future of Damage Assessment in Vasculitis

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**ABSTRACT.** Damage denotes the aspects of chronic disease that do not reverse with therapy. This concept is particularly important for the primary systemic vasculitides, since the careful differentiation between activity and damage may help avoid unnecessary exposure to cytotoxic medications. Damage significantly influences both longterm prognosis and quality of life. Because the primary systemic vasculitides have diverse manifestations, the use of a damage assessment instrument is crucial to ensure reproducibility. The Vasculitis Damage Index (VDI) is the only validated measure for damage assessment in vasculitis. Use of the VDI in recent clinical trials has shown that it may not adequately determine the full spectrum of damage experienced by patients with vasculitis of small- and medium-size vessels. We propose reexamining the way in which damage is assessed, focusing on vasculitides of small- and medium-size vessels, and outline an initiative to create a substantially revised and improved damage assessment instrument using data-driven approaches. This initiative is part of a larger international effort to create a unified approach to disease assessment for the primary systemic vasculitides. (*J Rheumatol* 2007;34:1357–71)

*Key Indexing Terms:*

VASCULITIS

OUTCOMES

DAMAGE

Although clinical trials of vasculitis frequently focus on disease activity, for the individual patient the most concerning

issue may actually be damage (i.e., the disease sequelae that are unlikely to respond to immunosuppressive agents).

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International interest has led to a new initiative that will reexamine the way damage in vasculitis is assessed. In 2004, an international group of investigators with an interest in vasculitis began reexamining 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<sup>1</sup>. The VCRC-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 (VCRC; [www.RareDiseasesNetwork.org/vcrc](http://www.RareDiseasesNetwork.org/vcrc)) and the European Vasculitis Study Group (EUVAS; [www.vasculitis.org](http://www.vasculitis.org)), and is supported by grants from the US National Institutes of Health and the European League Against Rheumatism. Our report provides an introduction to 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 in order to ensure reproducibility among clinicians from diverse backgrounds and with different levels of experience. The aim of a damage index is to catalog the forms of damage that occur as a consequence of vasculitis, so that they can be consistently identified and recorded as a measure of the cumulative burden of disease.

The Vasculitis Damage Index (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 1)<sup>2</sup>. 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 considered to 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 reexamine 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 outcomes measures. This reexamination 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 current status of outcome measures in vasculitis<sup>2</sup>. As a starting point, the group concentrated on the ANCA-associated vasculitides, i.e., Wegener’s granulomatosis (WG) and microscopic polyangiitis (MPA), which have recently been the focus of important clinical trials in the US and in Europe<sup>3-5</sup>. 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 the ANCA-associated vasculitides (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 Combined Damage Assessment index (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 flare (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 enrollment, it may also be important to specify the level of baseline damage.

We propose to reexamine the assessment of damage in vasculitis in 4 phases (Figure 1):

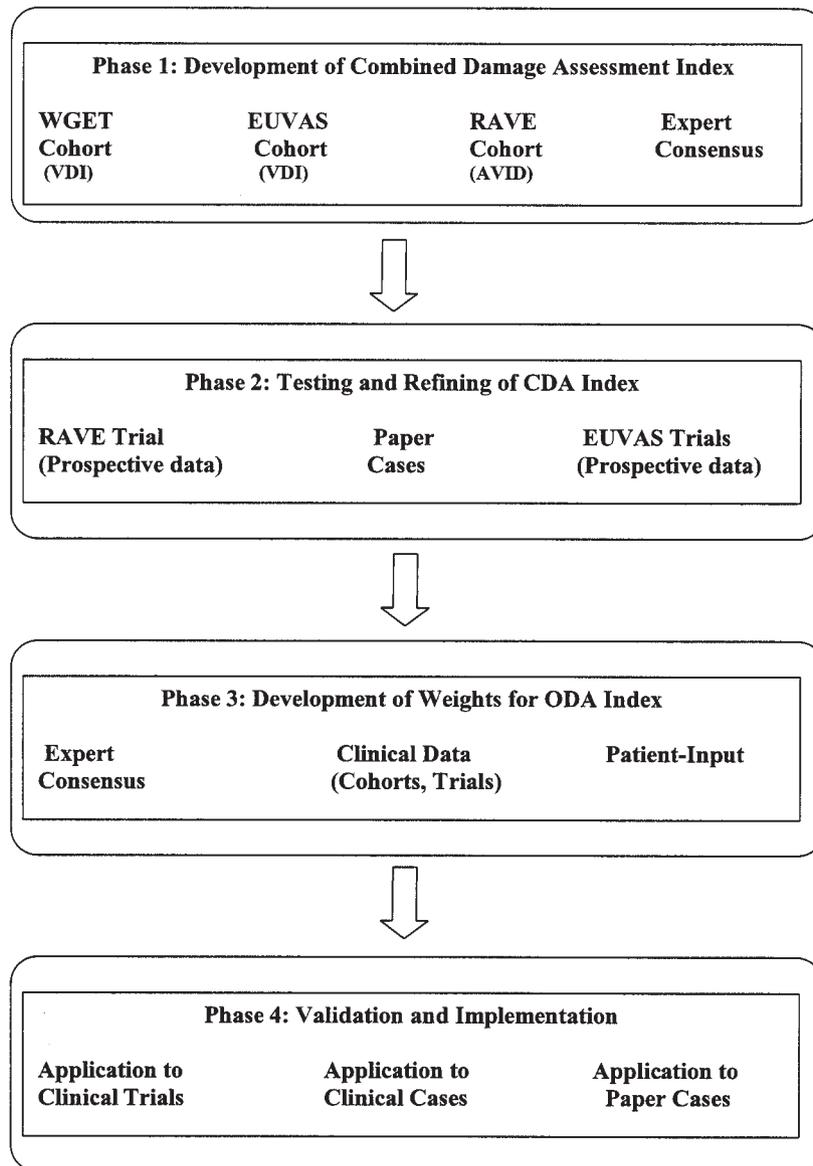


Figure 1. The process of the VCRC-OMERACT damage assessment initiative.

- 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 of 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 etiology. 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 ANCA-associated Vasculitis Index of Damage (AVID), was specifically designed for AAV because of the primacy of these diseases internationally in vasculitis research (Appendix 2).

At the OMERACT 7 conference, we reexamined the basic elements used to define damage, and created the following guidelines for AVID:

- Irreversibility: Unlike the VDI, the AVID 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 AVID, 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 (AVID-V); items of damage attributed to the consequences of treatment (AVID-T); and items of damage for which the attribution is unclear (AVID-U).
- Grading and weighting: In the VDI, scoring of damage is binary (i.e., either an item is present or it is not). AVID 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 AVID was taking place, a EUVAS-based initiative began to reexamine 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. The EUVAS Study Group proposed to accomplish this by conducting a retrospective longterm 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 Combined Damage Assessment (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 1. Development of the CDA will be data-driven, taking advantage of the data acquired by the application of the VDI and AVID to large cohorts of patients with WG and MPA enrolled in clinical trials in the US and in Europe, as well as a new patient-derived outcomes project.

#### *The Wegener's Granulomatosis Etanercept Trial (WGET) Cohort*

The WGET was a multicenter, double-blinded trial that randomized 180 patients with active WG to receive adjunctive treatment with etanercept (or placebo) in addition to standard-of-care therapies<sup>6</sup>. The addition of tumor necrosis factor

blockade did not alter disease outcomes<sup>3</sup>, thus providing the opportunity to examine the spectrum of damage accrued by a well characterized cohort of patients with AAV.

In the WGET, the VDI was applied at the time of enrollment and then every 6 months until trial closeout, and it revealed the broad spectrum of damage experienced by patients with WG<sup>7</sup>. 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, endstage renal disease-gonadal failure, and diabetes were all reported in 5%–10% of patients.

Study of damage in the WGET 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 WGET 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 WGET cohort also revealed a previously unsuspected relationship between WG and both solid tumor malignancy<sup>8</sup> and venous thromboembolic disease<sup>9</sup>. Analysis of the WGET data indicated that 26% of the items listed in the VDI were not scored by any patient in the WGET cohort; the majority of these items described the consequences of large-vessel vasculitis, which are rare events among patients with WG. Additionally, several WGET investigators were frustrated by the lack of gradation in the VDI, which prevents recording different degrees of damage.

The mean followup period of patients in the WGET cohort was 1.8 years<sup>3</sup>. Longer followup 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 WGET 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 AVID, we will also collect information on the additional items of damage identified by the WGET 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 longterm followup data collection for WGET will include a substantial portion of the questions planned for use by EUVAS in the longterm EUVAS trial cohort study, outlined next.

### *The European Vasculitis Study Group (EUVAS) Cohort*

We are also in the process of conducting a retrospective long-term outcome study of the first 567 patients entered into EUVAS trials (to determine patient survival and morbidity<sup>10</sup>). 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 centers 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 (Appendix 3). 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 enrollment and at Year 1 and Year 5.

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

- By definition, 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 ANCA-Associated Vasculitis (RAVE) Trial Cohort*

The RAVE trial is a multicenter, randomized, double-blind, placebo-controlled trial designed to compare the efficacy of rituximab versus cyclophosphamide for the induction of sustained remission. The trial began enrollment in December 2004, and has a total goal of 200 subjects. Both AVID and the VDI are applied to every patient in the RAVE trial at the time of enrollment 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 AVID 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 quality of life, or mortality). Data from the RAVE trial will be useful to determine the correlation between the total damage scores from AVID and the VDI, and their correlation with several factors, including cumulative BVAS/WG activity scores<sup>11</sup>, initial physician global assessment, 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:

- Reexamination of specific items of damage: AVID is the result of expert consensus, which was used to identify specific items of damage thought to be relevant to the assessment of WG 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 fulfill the requirements of the OMERACT filter, particularly with regard to truth (i.e., does the new instrument effectively capture all forms of damage) and discrimination (i.e., is the AVID instrument 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 etiology. Examining damage according to etiology, 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 RAVE trial dataset will provide an additional dataset for validation of prognostic data derived from the analyses in the long-term WGET 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 VCRC-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 (Appendix 4). 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 AVID, some form and style from AVID (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 centers in the US and Europe with expertise in the evaluation of patients with AAV will be asked to select 2 patients with WG 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 centers 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<sup>12</sup> and systemic lupus erythematosus<sup>13</sup>. This exercise will permit calculation of odds ratios of mortality based on arbitrary cutoffs (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 intraclass correlation coefficients.

*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 VCRC will facilitate data collection, and make CDA no more onerous than the VDI.

#### *Application of CDA to Clinical Trials*

The AVID instrument, as it is being used in the RAVE trial, includes a majority of the elements of the draft CDA that are applicable to WG and MPA. The data on AVID in RAVE will therefore provide significant insight into the performance of the full CDA in these diseases. In future clinical trials sponsored by the VCRC and EUVAS, we will use both the CDA and the VDI to compare the ability of these instruments to fulfill 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<sup>14</sup>, 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

Table 1. Draft proposal of the Combined Damage Assessment Index. (Continued next page)

**Musculoskeletal**

- Osteoporosis/vertebral collapse
- Bone fracture
  - Due to renal dystrophy
  - Due to osteoporosis
  - Due to both
- Muscle atrophy due to glucocorticoids
  - 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 edema
- 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 pericardectomy

**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
- Esophageal stricture/surgery
- Chronic peritonitis

**Renal**

- Estimated/measured GFR<50%
- Chronic kidney disease
- Endstage 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

Table 1. Continued

<b>Psychiatric</b>	Hematopoietic malignancy
Cognitive impairment	Solid tumor malignancy
Anxiety disorder due to vasculitis	Refractory cytopenia
Mood disorder due to vasculitis	Myelodysplastic syndrome
Major psychosis	<b>Other</b>
<b>Endocrine</b>	Weight gain > 10 lbs/4.4 kg
Diabetes insipidus	Fibromyalgia
Premature ovarian failure	Drug-induced cystitis
Azoospermia	With microscopic hematuria
Impaired fasting glucose	With gross hematuria
Diabetes mellitus	Requiring transfusion
<b>Hematology/Oncology</b>	Requiring cystectomy
Bladder cancer	Damage requiring surgical intervention
Cervical cancer	Medications to manage side effects of immunosuppressive agents

of disease due to damage experienced by a patient is crucial to 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, longterm disability, the SF-36, physician global assessment, 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 number of nonexclusive approaches to this important question, each of which has inherent advantages and disadvantages, as follows.

#### *(1) 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 as a consequence of damage, need for surgical intervention as a consequence 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 modeling 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 WGET 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 longterm 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.

#### *(2) 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).

#### *(3) 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 enrollment and to predict a poor outcome (e.g., mortality, endstage 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 WG or MPA at 2 visits, 1 year apart. At both timepoints, investigators will be asked to record a physician global assessment of damage using a 10-point Likert scale and to collect other key outcome measures such as activity scores, quality of life 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 analyze 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 Churg-Strauss syndrome, Behçet's disease, cryoglobulinemic vasculitis, polyarteritis nodosa, Henoch-Schönlein purpura, 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, endstage 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, endstage 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 reexploration 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:

*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.

*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.

*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 in particular, if the extra level of complexity is worth the additional information accrued.

*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.

*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.

*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 WG 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 VCRC-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 US 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.

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Articles presented at the OMERACT 8 Conference St. Julian's Bay, Malta, May 10–14, 2006

1. Biomarkers and Surrogate Endpoints
2. Imaging
3. Outcome Measures
4. Workshops and Special Interest Groups

Parts 1, 2, and 3 appeared in the March, April, and May issues of *The Journal*.

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**APPENDIX 1. The Vasculitis Damage Index**

	No	Yes	Name		
<b>1. Musculoskeletal</b>			<b>Trial Number</b>		
None	<input type="checkbox"/>		<b>Date</b>		
Significant muscle atrophy or weakness		<input type="radio"/>	<b>Centre</b>		
Deforming/erosive arthritis		<input type="radio"/>			
Osteoporosis/vertebral collapse		<input type="radio"/>			
Avascular necrosis		<input type="radio"/>			
Osteomyelitis		<input type="radio"/>			
<b>2. Skin/Mucous membranes</b>			<b>7. Peripheral vascular disease</b>	No	Yes
None	<input type="checkbox"/>		None	<input type="checkbox"/>	
Alopecia		<input type="radio"/>	Absent pulses in one limb		<input type="radio"/>
Cutaneous ulcers		<input type="radio"/>	2 <sup>nd</sup> episode of absent pulses in one limb		<input type="radio"/>
Mouth ulcers		<input type="radio"/>	Major vessel stenosis		<input type="radio"/>
<b>3. Ocular</b>			Claudication >3 months		<input type="radio"/>
None	<input type="checkbox"/>		Minor tissue loss		<input type="radio"/>
Cataract		<input type="radio"/>	Major tissue loss		<input type="radio"/>
Retinal change		<input type="radio"/>	Subsequent major tissue loss		<input type="radio"/>
Optic atrophy		<input type="radio"/>	Complicated venous thrombosis	<input type="checkbox"/>	<input type="radio"/>
Visual impairment/diplopia		<input type="radio"/>	<b>8. Gastrointestinal</b>		
Blindness in one eye		<input type="radio"/>	None	<input type="checkbox"/>	
Blindness in second eye		<input type="radio"/>	Gut infarction/resection		<input type="radio"/>
Orbital wall destruction		<input type="radio"/>	Mesenteric insufficiency/pancreatitis		<input type="radio"/>
<b>4. ENT</b>			Chronic peritonitis		<input type="radio"/>
None	<input type="checkbox"/>		Oesophageal stricture/surgery		<input type="radio"/>
Hearing loss		<input type="radio"/>	<b>9. Renal</b>		
Nasal blockage/chronic discharge/crusting		<input type="radio"/>	None	<input type="checkbox"/>	
Nasal bridge collapse/septal perforation		<input type="radio"/>	Estimated/measured GFR ≤ 50%		<input type="radio"/>
Chronic sinusitis/radiological damage		<input type="radio"/>	Proteinuria ≥ 0.5g/24hr		<input type="radio"/>
Subglottic stenosis (no surgery)		<input type="radio"/>	End stage renal disease		<input type="radio"/>
Subglottic stenosis (with surgery)		<input type="radio"/>	<b>10. Neuropsychiatric</b>		
<b>5. Pulmonary</b>			None	<input type="checkbox"/>	
None	<input type="checkbox"/>		Cognitive impairment		<input type="radio"/>
Pulmonary hypertension		<input type="radio"/>	Major psychosis		<input type="radio"/>
Pulmonary fibrosis		<input type="radio"/>	Seizures		<input type="radio"/>
Pulmonary infarction		<input type="radio"/>	Cerebrovascular accident		<input type="radio"/>
Pleural fibrosis		<input type="radio"/>	2 <sup>nd</sup> cerebrovascular accident		<input type="radio"/>
Chronic asthma		<input type="radio"/>	Cranial nerve lesion		<input type="radio"/>
Chronic breathlessness		<input type="radio"/>	Peripheral neuropathy		<input type="radio"/>
Impaired lung function		<input type="radio"/>	Transverse myelitis		<input type="radio"/>
<b>6. Cardiovascular</b>			<b>11. Other</b>		
None	<input type="checkbox"/>		None	<input type="checkbox"/>	
Angina/angioplasty		<input type="radio"/>	Gonadal failure		<input type="radio"/>
Myocardial infarction		<input type="radio"/>	Marrow failure		<input type="radio"/>
Subsequent myocardial infarction		<input type="radio"/>	Diabetes		<input type="radio"/>
Cardiomyopathy		<input type="radio"/>	Chemical cystitis		<input type="radio"/>
Valvular disease		<input type="radio"/>	Malignancy		<input type="radio"/>
Pericarditis ≥ 3 months or pericardectomy		<input type="radio"/>	Other		<input type="radio"/>
Diastolic BP ≥ 95 or requiring antihypertensives		<input type="radio"/>	<div style="border: 1px solid black; padding: 5px;">                     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.                 </div>		

## APPENDIX 2. ANCA-associated Vasculitis Index of Damage (AVID)

<b>AVID Worksheet</b>	Investigator _____	Patient Name _____
Version 0.4 Date _____	Site _____	ID # _____

<i>For every patient, please record the following information:</i>		Gender M / F
Age (in years) _____	Weight (in kg) _____	Race: White / Black / Hispanic
Serum Creatinine (mg/dL) _____		Asian / Other

### Musculoskeletal

- Osteoporosis
- Bone fracture
  - Due to renal dystrophy
  - Due to osteoporosis
  - Due to both
- Significant muscle atrophy or weakness due to glucocorticoids
  - Normal strength, but evidence of atrophy present
  - Weakness on examination, but normal ADLs
  - Weak and has difficulty with ADLs
- Avascular necrosis

### Skin/Mucous membranes

- Cutaneous scarring
- Cutaneous ulcers
- Striae
- Gangrene with permanent tissue loss, specify: \_\_\_\_\_
- Easy bruising

### Ocular (Left, right, or both: L, R, or B)

Does the patient have any of the following?

- Orbital disease
  - L R B Proptosis
  - L R B Pseudotumor
- Scleral disease
  - L R B Scleral thinning
  - L R B Scleral perforation
- Optic nerve disease
  - L R B Optic nerve edema
  - L R B Optic nerve atrophy
- Retinal vascular disease
  - L R B Retinal vein occlusion
  - L R B Retinal artery occlusion
- Visual impairment
  - L R B Low vision
  - L R B Blindness
- Cataracts
- Glaucoma

### Ear (Left, right, or both: L, R, or B)

- L R B 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

### Nose

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

### Sinuses

- Chronic sinusitis
- Bony erosion of sinuses
- Neo-ossification of the sinuses
- Anosmia
- Ageusia

### Subglottic stenosis

- No intervention required
- Intervention required, specify: \_\_\_\_\_

### Pulmonary

- Irreversible loss of lung function
  - FEV1 \_\_\_\_\_
  - FVC \_\_\_\_\_
- Fixed large airway obstruction
  - FEV1 \_\_\_\_\_
  - FVC \_\_\_\_\_
- Pulmonary hypertension
  - NYHA class I or II
  - NYHA class III or IV
  - RSVP \_\_\_\_\_
- Pulmonary embolism
  - Vena caval filter
- Continuous oxygen dependency

## APPENDIX 2. *Continued*

### Cardiovascular

- Hypertension
  - SBP: \_\_\_\_\_
  - DBP: \_\_\_\_\_
  - Antihypertensive medications?
- Angina
- Myocardial infarction
- Percutaneous coronary intervention
- Coronary artery bypass graft
- Carotid artery disease
- Left ventricular dysfunction
  - NYHA Class I/II
  - NYHA Class III/IV
  - EF \_\_\_\_\_%
- Third degree AV block
- Valvular disease
  - Please specify valve(s) and lesion(s): \_\_\_\_\_
  - \_\_\_\_\_
- Deep venous thrombosis
- Renal artery stenosis
- Arterial thrombosis or occlusion  
Specify site and describe tissue loss, if any \_\_\_\_\_
- \_\_\_\_\_

### Gastrointestinal

- Gut infarction more than six months ago
- Hepatic fibrosis

### Renal

- Chronic kidney disease
- Dialysis
- Renal transplant
- Proteinuria
  - < 3.0g/24 h
  - >3.0g/24h

### Neurologic

- Cranial nerve lesion Specify: \_\_\_\_\_
- Chronic pachymeningitis
- Mass lesion (*due to the underlying vasculitis*)
- Cerebrovascular accident
- Sensory polyneuropathy
  - Mild
  - Moderate
  - Severe

- Motor neuropathy
  - Left upper extremity
  - Left lower extremity
  - Right upper extremity
  - Right lower extremity
- Neuropathic pain

### Psychiatric

- Cognitive impairment
- Anxiety disorder due to vasculitis
- Mood disorder due to vasculitis

### Endocrine

- Diabetes insipidus
- Premature ovarian failure
- Azospermia
- Impaired fasting glucose
- Diabetes mellitus

### Hematology/Oncology

- Bladder cancer
- Cervical cancer
- Hematopoietic malignancy
- Solid tumor malignancy
- Refractory cytopenia
- Myelodysplastic syndrome
- Hypogammaglobulinemia

For malignancy, specify \_\_\_\_\_

### Other

- Weight gain > 10 lbs or 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 the side-effects of immunosuppressive agents. Specify: \_\_\_\_\_
- \_\_\_\_\_
- Other forms of damage due to the vasculitis, therapy, or both that has not been adequately recorded by this instrument. Specify: \_\_\_\_\_
- \_\_\_\_\_
- Miscellaneous notes: \_\_\_\_\_
- \_\_\_\_\_



