EULAR Recommendations for Conducting Clinical Studies and/or Clinical Trials in Systemic Vasculitis:

Focus on ANCA-associated vasculitis

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ABSTRACT

Objectives:

To develop EULAR recommendations for conducting clinical studies and/or clinical trials in systemic vasculitis.

Methods:

An expert consensus group was formed consisting of rheumatologists, nephrologists and specialists in internal medicine representing 5 European countries and the USA, a clinical epidemiologist and representatives from regulatory agencies. Using an evidence-based and expert opinion-based approach in accordance with the standardised EULAR operating procedures, the group identified 9 topics for a systematic literature search through a modified Delphi technique. On the basis of research questions posed by the group, recommendations were derived for conducting clinical studies and/or clinical trials in systemic vasculitis.

Results:

Based on the results of the literature research the expert committee concluded that sufficient evidence to formulate guidelines on conducting clinical trials was available only for anti-neutrophil cytoplasm antibody associated vasculitides (AAV). It was therefore decided to focus the recommendations on these diseases. Recommendations for conducting clinical trials in AAV were elaborated and are presented in this summary document. It was decided to address vasculitis-specific issues rather than general issues of trial methodology. The recommendations address the following areas related to clinical studies of vasculitis: definitions of disease, activity states, outcome measures, eligibility criteria, trial design including relevant endpoints, and biomarkers. On the basis of expert opinion, a number of aspects of trial methodology were deemed important for future research.

Conclusions: On the basis of expert opinion, recommendations for conducting clinical trials in AAV were formulated. Furthermore, the expert committee identified a strong need for well designed research in non AAV systemic vasculitides.

Abbreviations

AAV	-	Anti-neutrophil cytoplasm antibody associated vasculitis
ANCA		Anti-neutrophil cytoplasm antibody
ACR	-	American College of Rheumatology
BVAS	-	Birmingham Vasculitis Activity Score
BVAS1+2	-	Birmingham Vasculitis Activity Score as used in EUVAS studies
BVAS/WG	-	Birmingham Vasculitis Activity Score for Wegener's granulomatosis
cANCA		Cytoplasmic anti-neutrophil cytoplasm antibody
CHCC	-	Chapel Hill Consensus conference
CRP	-	C-reactive protein
CSS	-	Churg-Strauss syndrome
CT	-	Computerised tomography
CYC	-	Cyclophosphamide
DEI	-	Disease Extent Index
ELISA	-	Enzyme linked immunoassay
EMEA	-	European Medicinal Agency
ENT	-	Ear, Nose and Throat
EULAR	-	European League Against Rheumatism
EUVAS	-	European Vasculitis Study Group
ESCISIT	-	European Standing Committee for International clinical Studies including therapeutics
ESR	-	Erythrocyte sedimentation rate
FDA	-	Food and Drug Administration
FFS	-	Five Factor Score
GC	-	Glucocorticoids
GCA	-	Giant cell arteritis
GFR	-	Glomerular filtration rate
HBV	-	Hepatitis B virus
HCV	-	Hepatitis C virus
IFT	-	Indirect immunofluorescence testing
INSSYS	-	International Network for the Study of Systemic Vasculitis
K/DOQI	-	Kidney Disease Quality Outcome Initiative
MCII	-	Minimal Clinical Improvement Indicator
MDRD	-	Modification of Diet in Renal Disease
MPA	-	Microscopic polyangiitis
MPO	-	Myeloperoxidase
MRI	-	Magnetic resonance imaging
MTX	-	Methotrexate
OMERACT	-	Outcome Measures in Rheumatology
PAN	-	Polyarteritis nodosa
p-ANCA	-	Perinuclear anti-neutrophil cytoplasm antibody
PASS	-	Patient Acceptable Symptom State
PET	-	Positron emission tomography
PR3	-	Proteinase 3
PSV	-	Primary systemic vasculitis
RCT	-	Randomized controlled clinical trials
SF 36	-	Short Form 36 questionnaire
VCRC	-	Vasculitis Clinical Research Consortium

VDI - Vasculitis Damage Index
WG - Wegener's granulomatosis
WGET - Wegener's granulomatosis Etanercept trial

Keywords

Vasculitis; clinical trial; ANCA; Wegener's granulomatosis; microscopic polyangiitis

INTRODUCTION

The primary systemic vasculitides (PSV) are clinically distinct diseases which are usually characterized by inflammation of the blood vessel wall without identifiable cause .

Due to the rarity of PSV and the inherent diagnostic difficulties in these complex diseases, clinical research in the past was limited to single centre cohort studies or open-label case series. However, substantial progress has been made in the past decade firstly by the development of new diagnostic tools, e.g. ANCA serology, and secondly by the formation of collaborative research groups like the European Vasculitis study group (EUVAS), the International Network for the Study of Systemic Vasculitis (INSSYS), the French Vasculitis Study Group, and the Vasculitis Clinical Research Consortium (VCRC). Independently, these groups have conducted a number of randomized controlled clinical trials (RCT) utilising standardised clinical measurement scores. The results of these trials have had significant effect on patient care in clinical practice [1-4]. Despite these improvements, there are still enough variations among these trials to make cross-study comparisons difficult and these variations impair extrapolations of results to treatment in everyday clinical practice. Among the most controversial differences between the respective studies were variations in: definitions of disease; disease stages; activity stages; outcome measures; duration of treatment; duration of observation; and use of concomitant medications.

Based on a proposal by EUVAS to the European Standing Committee for International clinical studies including therapeutics (ESCISIT), a group of experts was formed including members of EUVAS and VCRC. The aim of this working group was to formulate recommendations for conducting clinical trials in PSV. For the process of developing these recommendations we used the EULAR standardised operating procedures for the elaboration, evaluation, dissemination and implementation of recommendations [5, 6]. Published evidence in the form of high-quality RCT's was found primarily for vasculitides associated with antineutrophil cytoplasm antibodies (ANCA). We therefore focussed the recommendations on the ANCA-associated vasculitides (AAV): Wegener's granulomatosis (WG), microscopic polyangiitis (MPA) and Churg-Strauss syndrome (CSS). However, many of the issues addressed in these recommendations are likely to be relevant to other types of vasculitis and these generic issues are outlined in the beginning of each section.

The aim of these recommendations is not to cover all general aspects related to planning and conducting a clinical trial, but rather to address critical issues that are specific for vasculitis. General aspects of trial methodology are beyond the scope of these recommendations and recommendations for good clinical practice and updates regarding legal requirements for conducting clinical trials should be closely followed. Requirements for the conduct of clinical trials in Europe including good clinical practice (GCP) have been implemented in the European Clinical Trial Directive [7]. Web pages of the health agencies contain further helpful advice (http://emea.eu.int; http://fda.gov; http://eudract.emea.eu.int). Recommendations for standardized assessment of adverse events in rheumatology have been elaborated by the OMERACT (Outcome Measures in Rheumatology) Drug Safety group [8]. The European Commission recently published a regulation regarding the conditional approval of drugs for the treatment, prevention and diagnosis of seriously debilitating or life threatening diseases where there is an unmet clinical need [9]. The primary systemic vasculitides clearly fall within the scope of this document.

It is recommended that biostatisticians should be involved in the earliest stages of planning a clinical trial in PSV. The recommendations on design and outcomes in clinical trials in systemic sclerosis by the American College of Rheumatology (ACR) cover many relevant issues related to statistical analyses and sample size calculations in rare systemic autoimmune diseases and should be considered in planning a trial in PSV [10]. We would strongly recommend that trials in vasculitis, with the exception of pilot studies, should only be undertaken if sufficient numbers can be recruited to satisfy the sample size requirements; this effectively means that almost all studies will need to be multi-centred, thus further emphasising the need for standardisation of protocols and assessments.

This working group concentrated on the most controversial issues including (1) definitions of disease and activity stages, (2) primary and secondary outcome measures, (3) eligibility criteria including a definition of clinically meaningful endpoints, (4) trial design, and (5) use of biomarkers.

METHODS

These recommendations were developed according to the standardised operating procedures for the elaboration of recommendations by the EULAR standing committees [5].

Consensus on methods and focus of the recommendations

An expert committee was formed including 7 rheumatologists (BH, WG, PB, PM, DS, HY, RL), one nephrologist (DJ), one clinical immunologist (JCT), two specialists in internal medicine (LG, AM), one clinical epidemiologist (HR), one research fellow (OF) and representatives from the EMEA (Jordi Llinares) and the FDA (Food and Drug Administration) (JW). It was decided to develop recommendations that are applicable to studies of all types of systemic vasculitis. Due to the rarity of some of the diseases it was anticipated that the available evidence might vary considerably between the different types of vasculitis and that the recommendations would have to be focused on certain diseases where sufficient evidence was available. Using a modified Delphi technique, the group identified nine specific issues which were transformed into research questions for the systematic literature research.

Systematic Literature Research

The systematic literature research was performed without time limit using the databases of PubMed, Embase and the Cochrane Library. The literature search was performed in two stages. Initially the search word vasculitis limited to RCTs was used to identify high quality therapeutic clinical trials. In the second stage key words from the research questions which had been identified through the modified Delphi technique were used together with the names of the respective diseases for the systematic literature research (A detailed description of the search strategy will be published separately). Since the trials identified were largely heterogeneous in many methodological aspects (e.g. inclusion criteria, outcome assessment), a formal quality scoring was not done. The results of the literature research were summarized in several tables that included those data from the identified studies that were relevant for the specific research topic selected by the committee (i.e. eligibility criteria, definition of disease states and activity states, outcome, adverse event reporting). Categories of evidence were applied according to Shekelle et al. [11].

Expert opinion approach

Based on the results of the literature research, draft recommendations were prepared by the convenors. During the second meeting of the group, the results of the systematic literature research and the draft recommendations were presented and discussed. The systematic literature research revealed that some of the issues addressed in the research questions (e.g. adverse event recording) had no vasculitis-specific elements that warranted the formulation of a specific recommendation. For other issues such as imaging procedures, the available literature was found to be inconclusive. Furthermore, the literature search revealed that for most types of vasculitis, the available evidence was scarce and often of poor quality. The expert committee therefore decided to focus the recommendations on the ANCA-associated vasculitides (AAV) where a sufficiently large amount of published evidence was found. It was decided that each recommendation should include a generic section which would apply to all forms of vasculitis, followed by more specific recommendations for the AAV. In some instances, however, trials involving mixed cohorts of patients with PAN and AAV have been included, in the review. According to EULAR operating procedures, these generic issues are coined “points to consider” reflecting the lower level of evidence [5].

After discussion, the expert committee agreed on 5 recommendations with several subtopics addressed in each recommendation. The strength of the recommendations was graded from A (highest) to D (lowest) according to Shekelle et al [11]. Due to the large amount of data generated from the literature research it was decided to focus the data on essential issues underlining the recommendations in this paper and to summarize the more comprehensive material in a separate review article.

RESULTS

Literature Search

In total 58 papers were selected. The primary search yielded 1207 hits (1047 Pubmed, 1 Cochrane , Embase 159). Duplications, irrelevant articles, and non original reports were excluded. In addition studies with less than 25 patients, involving only paediatric patients and studies in secondary vasculitis were also excluded. 16 studies involving patients with AAV and PAN, 3 with GCA and 1 study in hepatitis C associated cryoglobulinaemia were identified. The second stage search produced 370 results. After limiting the results to English language and papers with abstracts, 268 remained. These 268 results were scrutinized further to select 38 articles. The remainder were discarded for one or more of the following reasons - small cohorts (< 50 patients), inadequate follow up (< 1 year), lack of good quality statistics, inappropriate or heterogeneous patient population, basic science research which did not reflect the outcomes which we were studying, and duplicate data sets.

1. Definitions of disease- and activity states

1.1 Remission

Generic points to consider. Remission should be defined as the absence of disease activity. Since most types of vasculitis tend to flare or may have fluctuating levels of disease activity ("grumbling disease"), a definition for remission should be qualified by the duration spent in remission. Because early relapse is common in vasculitis and the frequency of relapse varies among different types of PSV, definitions of remission should always be qualified by a minimum length of time after remission was attained. Furthermore, definitions of remission should include the use of ongoing immunosuppressive therapy. While in some types of vasculitis such as the AAV, there is evidence for a need to continue some form of immunosuppressive therapy to prevent relapses, such evidence is weak or lacking for other types vasculitis, often due to the absence of well-designed studies. Finally, if biomarkers with a high prognostic value exist for certain diseases, these biomarkers may be included in a definition of remission (e.g. absence of disease activity *combined with* presence of low or undetectable levels of the biomarker).

Recommendations for AAV. In 8 of 16 published randomized controlled clinical trials (RCTs) and in the majority of open label studies in patients with AAV including CSS, remission was defined as the complete absence of disease activity attributable to active vasculitis [1-4, 12-16]. Depending on the disease stage, and the type and length of induction therapy, rates of remission ranged from 90 to 94 %. The expert committee therefore concludes that in studies on induction treatment in AAV, the complete absence of clinical disease activity while receiving immunosuppressive therapy is a realistic and feasible endpoint. Thus, the use of the term “remission” defined as the *complete* absence of active clinical disease is recommended. However, for this and all the following definitions, the term “active disease” is not restricted to vasculitic manifestations of the disease, but also includes other clinical features of AAV such as granulomatous manifestations such as retro-orbital tumours or lung nodules in WG or eosinophilic pneumonia in CSS. The use of other previously used wordings such as “disease control” or “recovery” or less precise definitions such as “partial remission”, “stabilization” or “improvement” [12, 13, 17-19] is discouraged.

The absence of disease activity should be checked systematically according to a validated and published disease activity score list (e.g. BVAS or BVAS/WG) [20].

In all the studies in AAV mentioned above, patients were still on some form of immunosuppressive medication at the time that remission was attained and there is evidence that continued immunosuppression following remission can reduce the risk of relapses [21, 22]. Therefore, each definition of remission should include the type, duration and allowed maximum dosage of any immunosuppressive therapy including glucocorticoids (GC) at the time of remission. The term glucocorticoid includes prednisolone, prednisone and methylprednisolone. In order to determine whether or not the absence of clinical symptoms is actually related to the effects of the experimental drug under study and not simply as a result of high-dose GC therapy, it is proposed that “remission” should only be defined as occurring when a patient has attained a stable low dose of prednisolone or prednisone of $\leq$ 7.5 mg per day for a defined period. Although data from comparative trials are lacking, it has been documented in large cohort studies [23, 24] that many patients require low doses of GC (≤7.5 mg) to control minor symptoms (e.g. arthralgia, nasal crusting) after attaining remission. Therefore, the complete withdrawal of GC is not necessarily required in order to define a patient as

being in a state of remission; however, the allowable dose or dose range of GC used among patients in “remission” must be defined.

Comparison of Kaplan Meier curves of relapse-free survival from randomized controlled clinical trials with similar induction regimens [2, 25, 26] shows that the probability of relapse is particularly high within the first 6 months of remission. Therefore, the minimum duration spent in remission should be stated in each study protocol.

1.2 Response

Generic points to consider. It is possible to apply clinical assessment methods to provide a quantifiable measure of improvement from baseline disease activity in patients with vasculitis. In the case of patients who are refractory to investigational agents, remission rates are lower than amongst patients responding to standard therapy. Therefore, analysis of partial improvement or response may be clinically relevant and may constitute a meaningful secondary endpoint. It is proposed that a definition of response should include the minimum degree of improvement of the respective outcome measure and this should be quantified (e.g. 50 % reduction of the BVAS score).

Recommendations for AAV. With the exception of one study reporting remission in all patients [27], remission is only achieved in 35-83% of patients with AAV who are refractory to conventional therapy with cyclophosphamide (CYC) + GC [28-34]. Thus, in these difficult to treat patients, partial improvement is clinically relevant, if remission cannot be attained and the clinical status of the patient does not require a further escalation of therapy. Therefore, we define “response” as $\geq$ 50 % reduction in the disease activity score. Since this definition is arbitrary, studies and trials may vary in their definition of the size of the response (e.g. 30% or 70 % response), but the 50 % response rate should be measured and reported, to allow comparison across different trials and studies.

1.3 Refractory disease

Generic points to consider. Patients who fail to attain remission following induction therapy with the “standard regimen” are termed “refractory”. “Refractory disease” is the only disease state that refers to therapy. Such “standard therapy” for a specific type of vasculitis must therefore be defined precisely (eg optimal therapy with appropriate doses of cyclophosphamide or methotrexate, in conjunction with steroid). Definitions of refractory disease should include the type of immunosuppressants used, their maximum

and/or cumulative dosage and the duration of administration. Refractory disease can also mean the inability to taper GC after a defined duration of treatment. Therefore the taper regimen for GC and a cut-off dose after a defined time period of treatment should be defined. In view of the different nature and response to treatment, definitions for refractory disease are expected to be different for the distinct types of vasculitis and it is acknowledged that such definitions may be arbitrary.

Recommendations for AAV. Currently CYC with GC is regarded as standard therapy for induction of remission for patients with generalised and severe AAV. By contrast, in patients with localised WG and early systemic WG and MPA many investigators regard MTX with GC as an alternative induction agent since MTX appears to be similarly effective to CYC but less toxic [1]. Results from RCTs show that current standard therapy fails to induce remission in up to ten percent of patients with AAV [1-3, 12, 28, 35]. Although the term “refractory” has been applied in the majority of studies of refractory disease, definitions of how long and in which doses CYC and GC have been given vary considerably [28-34, 36]. Because the response rate to cyclophosphamide in AAV increases with its cumulative dosage and the time course over which the drug is given, currently available data are insufficient to define a clear “cut-off” cumulative dosage or time frame to rule out efficacy, [37]. In general, a first response should be seen after either two to four weeks of treatment with either daily oral CYC (2mg/kg) and GC (1mg/kg) [2]; or pulse intermittent high dose cyclophosphamide (15mg/kg or 0.6-0.7 g/m^2 body surface area) with GC [38]. By contrast, remission is usually attained after 8 to 12 weeks of therapy [1, 12]. The possibility to induce remission by prolonged administration of CYC & GC must be weighed against (a) the increasing risk of long-term toxicity and (b) the increasing risk of irreversible end-organ failure or other damage due to uncontrolled disease for an extended time-period. In view of the considerations outlined above, we propose to define “refractory disease” as either (a) unchanged or increased disease activity after four weeks treatment with daily oral CYC (2-3mg/kg) and GC [2] or pulse intermittent high dose cyclophosphamide (15mg/kg or 0.6-0.7 g/m^2 body surface area) with GC [1], or (b) lack of response, defined as $\leq$ 50% reduction in the disease activity score and / or lack of improvement of at least one major item, after 4-6 weeks of treatment or, (3) chronic persistent disease, defined as presence of at least one major or three minor items on the disease activity score list (eg BVAS or BVAS/WG), despite 8 weeks of treatment. As these definitions are arbitrary,

investigators may use modified definitions depending on the design of the individual study, but must clearly outline their definition of refractory disease.

In addition, patients who are intolerant to therapy with daily oral CYC and GC or pulse intermittent high dose cyclophosphamide (15mg/kg or 0.6-0.7 g/m^2 body surface area) with GC, (e.g repeated cytopenias), or who have contraindications against the use of cyclophosphamide (e.g. haemorrhagic cystitis) have been included in studies of refractory disease in the past. These patients have been defined as having “refractory” disease if (i) the disease is not controlled with the best available alternative standard therapy for a defined duration of treatment and (ii) if escalation with an experimental drug is clinically indicated. However, since these patients are possibly distinct in terms of complications of therapy, probability of response or damage, they should not be included into the term “refractory disease”, but subgroup analyses should be performed in order to detect differences in outcome compared to CYC-treated refractory patients according to the above definitions.

1.4 Grumbling disease.

Generic points to consider. It is well recognized that many patients, who are defined as being otherwise in remission, report symptoms such as arthralgia, fatigue or low grade nasal crusting. Often these symptoms are difficult to verify, persist for an extended period of time and are difficult to distinguish from damage. In clinical practice, this low activity disease state usually does not warrant an escalation of therapy beyond a modest increase in the dose of the current medication or addition of low dose GC, balancing the potential benefit versus the risk of complication of more intense therapy.

Recommendations for AAV. Further research is needed to develop evidence-based criteria on how to classify minor symptoms as either representing disease activity or damage. This is particularly important for endonasal disease in patients with WG where no criteria exist for grading severity and extent; further research is needed to assess and quantify the activity of endonasal disease and to distinguish such inflammatory activity from damage. Until more data are available, the expert committee recommends that persisting minor symptoms should be recorded as active disease if a modest increase in the GC dose improves or resolves these complaints.

1.5 Relapse.

Generic points to consider . Definitions for relapse were provided in 11 of 16 prospective RCT's in AAV [1-3, 12-14, 17-19, 35, 39-41] and in two [4, 15] of three studies of giant cell arteritis (GCA) [4, 15, 42]. In all studies, relapse was defined as the re-occurrence or new onset of disease activity attributable to active inflammation and we recommend using this definition for future trials. In order to analyse the clinical relevance of each relapse, relapses should be recorded as either "minor" or "major". A *major relapse* should be defined as the reoccurrence or new onset of potentially organ- or life threatening disease activity that can not be treated with an increase of GC alone and requires further escalation of therapy (i.e. the administration of cyclophosphamide). All other relapses should be classified as "minor".

Recommendations for AAV

Based on the available evidence there are no specific further recommendations for patients with AAV at present.

In conclusion there is evidence from several RCTs supporting the use of the activity states remission, response and relapse (type 1b evidence). The term refractory disease is supported by its use in several non-randomised and cohort studies (type 2b evidence).

2. Disease Assessment and Outcome Measures

2.1 Disease Activity

Generic points to consider. In view of the multi-system nature of the vasculitides and the lack of reliable biomarkers, the following disease activity measures have been developed with the intention of capturing overall changes of disease activity: Groningen Index [43], Vasculitis Activity Index [44]; the Birmingham Vasculitis Activity Score (BVAS) [45] together with the modifications of BVAS as used in the EUVAS studies (BVAS1+2) [46]; and BVAS for Wegener's granulomatosis (BVAS/WG) [47]. Of these activity measures, only the BVAS and its derivatives have been widely used in clinical trials. BVAS and its derivatives are based on the concept that items are scored if there is a physician decision to treat the abnormality with immunosuppressive therapy (ie that the item represents active disease requiring treatment) and do not represent damage or infection.

Recommendations for AAV. The original version of BVAS was used in 4 RCT [12, 28, 40, 48] and the BVAS/WG in one [3]. The majority of open-label studies over the last 5 years also used a version of BVAS. The BVAS was usually used to define remission and relapse [2, 3, 12, 25, 40]. Although limitations of BVAS and BVAS/WG are acknowledged, both have been found to be useful for disease assessment in WG [20]. The limited data available [49] suggest that the various variants of BVAS are comparable and the use of either of these in studies in WG is recommended. Currently, initiatives by EULAR and VCRC to improve existing disease assessment tools within the OMERACT process are in progress [20].

2.2 Disease Extent

Generic points to consider. The concept of disease extent has been developed as a complementary measure to disease activity as measured by the BVAS. The Disease Extent Index (DEI) is available as a validated measure for WG [50] and was used in 3 RCT [2, 25, 40] and several open-label studies [33, 51-53]. As the DEI appears to provide prognostic information [54] that complements BVAS and can be calculated from the BVAS score sheet without additional information, its use is recommended.

2.3 Physician Global Assessment

Generic points to consider. The physician global assessment has only been applied in 2 trials to date [26, 55] and is a subjective measure that is highly correlated with the BVAS and its derivative [45, 47]. There is not yet sufficient data or experience to properly assess the utility of the physician global assessment as an outcome measure in clinical trials of vasculitis.

2.4 Damage

Generic points to consider. Damage caused by vasculitis or its treatment may ultimately prove more troublesome than disease activity to the individual patient. Damage is defined as a non-healing scar which will not respond to immunosuppressive therapy. The Vasculitis Damage Index (VDI) [56] is currently the only validated damage assessment tool available. The VDI is based on the concept of recording the consequences of having developed vasculitis and its treatment. Patients suffer the morbidity of the disease, its treatment or intercurrent illness; all of these factors can result in scarring. Prior to 2003, there was only one published therapeutic study which

systematically recorded disease scars [36]. This study defined “sequelae” as clinical manifestations which persisted, remained stable and where no further improvement was expected. In the analysis there was a summary of the observed sequelae [36]. All of the recently published randomised controlled trials [1, 2, 57] and one-open label trial [30] assessed damage using the VDI. These studies recorded measurable changes in damage scores over time and associated the level of damage with adverse events [1, 2, 57]. We recommend the use of a damage assessment tool in all trials of vasculitis.

Recommendations for AAV. Recurrent and persistent disease activity is largely responsible for the damage suffered by patients with Wegener’s granulomatosis. Several large case series have highlighted the problem of long-term morbidity in vasculitis [23, 58]. In a longitudinal cohort of 158 patients with Wegener’s granulomatosis from the National Institutes of Health, 86% of patients suffered permanent damage as a consequence of the disease itself and 42% treatment-related morbidity [58]. This damage included end-stage renal disease, chronic pulmonary dysfunction, diminished hearing, saddle-nose deformities, blindness and death [58]. The use of the VDI is recommended for future trials in AAV.

2.5 Quality of life and generic health status measures:

Generic points to consider. Although data on quality of life are lacking for many types of vasculitis, clinical experience suggests that PSV is associated with impaired quality of life for patients with these diseases. The expert committee recommends that all further studies include a measure of quality of life and, unless a superior tool becomes available, the Short Form Questionnaire 36 (SF 36) should be used. Comparison with measures of disease damage in vasculitis is recommended.

Recommendations for AAV. Quality of life is impaired in patients with AAV and carries a high socioeconomic burden [59, 60]. Early clinical trials in vasculitis did not include a functional outcome measure. However, over the last 3 years all published randomized controlled trials and a number of open label studies [27, 30, 51] made an attempt to include a measure of quality of life with the SF 36 [61]. Treatment was associated with significant improvement in the SF36 scores [1, 2, 26, 27].

With the exception of the SF36, all the above mentioned clinical instruments for measuring disease require adequate training to ensure that assessors are evaluating

patients in a standardised fashion. In EUVAS studies it has been shown that training observers significantly improves agreement amongst individuals [62].

In conclusion there is evidence from several RCTs supporting the use of the BVAS, DEI, VDI and SF36 in clinical trials of vasculitis (Grade 1b evidence).

3. Eligibility Criteria

3.1 Diagnosis

Generic points to consider. Since several studies have shown that classification criteria are not suitable for the primary diagnosis of vasculitis [63, 64], it has to be ascertained that a patient classified according to published classification criteria does in fact suffer from a vasculitic disease. It is acknowledged that it is not always possible to obtain a biopsy and that biopsy results may be falsely negative. Therefore, only in patients with a *typical* clinical appearance (according to ACR classification criteria), surrogate parameters of vasculitis (i.e. erythrocyte casts in urine, rapid-onset mononeuritis multiplex, alveolar haemorrhage etc.) or immunological parameters (eg. ANCA, cryoglobulins, etc.) may substitute for histology if disorders with a similar clinical appearance (i.e. infections, malignancies) have been specifically excluded.

Recommendations for AAV. The expert committee recommends that in most cases a biopsy should be obtained showing typical features of the disease in order to delineate that there is a definite diagnosis available. However patients without a confirmatory biopsy, but compatible clinical picture may also be included if either (a) specific imaging techniques (angiography, MRI/CT imaging etc.) or surrogate parameters are strongly suggestive of vasculitis, glomerulonephritis and/or granuloma, or (b) patients with a clinical diagnosis of microscopic polyangiitis (MPA) or WG are anti-PR3/C-ANCA or anti-MPO/P-ANCA positive. For example, the following surrogate parameters and clinical or radiographic findings can support a clinical diagnosis of WG or MPA in patients without confirmatory biopsy who are anti-PR3/C-ANCA or anti-MPO/P-ANCA positive: fixed pulmonary infiltrates/nodules or cavitations, subglottic stenosis, retroorbital granuloma, red cell casts or dysmorphic erythrocytes in the urine, diffuse alveolar haemorrhage, mononeuritis multiplex and episcleritis.

3.2 Disease Classification

Generic points to consider. The diagnostic classification of systemic vasculitides is based on the classification by the American College of Rheumatology (ACR) [65] and the disease definitions as agreed by the Chapel Hill Consensus conference (CHCC) [66]. Although both of these classifications have their limitations, they can be helpful when applied to clinical studies. The ACR criteria were derived from analysis of the histopathology and clinical picture of real cases and were tested for sensitivity and specificity, while the CHCC definitions were made on expert opinion only. However, the ACR criteria do not include microscopic polyangiitis and the CHCC definitions are primarily a classification based on histopathology and are not diagnostic criteria. As a consequence, although virtually all studies included one or both sets of classifications, there was considerable heterogeneity in the requirement for histological, serological or radiological surrogate markers.

Until new classifications schemes are developed, we recommend that the ACR criteria and/or the CHCC definitions should be used for classification of patients with vasculitis in clinical studies. The use of serologic and radiographic surrogate markers as additional criteria for classification may enhance the ACR criteria and CHCC definitions. However, investigators should also report how many patients fulfilled the ACR/CHCC criteria, in order to allow comparison across different trials and to demonstrate how the modifications using serology and surrogate markers affected classification.

Recommendations for AAV. The EUVAS group required the following criteria for a diagnosis of AAV: history of a chronic inflammatory disease lasting at least 4 weeks with the exclusion of other causes such as infection or malignancy supported by characteristic histology on biopsy and/or a positive ELISA for either PR3 or MPO antibodies and a classical cANCA on immunofluorescence [67].

We recommend that the ACR criteria should be used for classification of patients with WG, because these criteria are evidence-based. In addition, the CHCC definitions should be applied to distinguish patients with MPA. The use of ANCA as additional criterion for classification of AAV as used in the EUVAS and WGET studies is to be encouraged (see section 5.1 for details).

3.3 Disease states

Generic points to consider. It is well recognised that patients with PSV can follow different disease courses. Whereas some patients can experience mild or moderate

symptoms (such as sinusitis or arthritis) for many years before finally developing more severe manifestations which eventually lead to a diagnosis of vasculitis, other patients present after a short prodromal phase with life-threatening manifestations. Therefore, patients with vasculitis should be categorized into clearly defined disease states.

Recommendations for AAV. The EUVAS and the WGET groups classified patients to different disease states (table 2). The EUVAS group classified patients for inclusion criteria in randomised controlled trials using the following disease states: localised, early systemic, generalised and severe renal disease [67]. The WGET group introduced limited versus severe disease on the basis of consensus definitions and stratified patients accordingly [26]. At present there are no data which convincingly demonstrate the superiority of one of the classification systems over the other and there is no consensus among investigators as to which of these two sets of disease states should be preferred. However, work towards consensus definitions based on the analysis of large cohorts (EULAR, WGET) is in progress. At present, we recommend the use of either the EULAR or WGET/VCRC classification, but not to modify these definitions until consensus definitions have been agreed on.

3.4 Concomitant diseases

Generic points to consider and recommendations for AAV. Patients with concomitant autoimmune disorders can be studied if these diseases have no features of the PSV under study. However, it must be considered that in such patients, the accompanying autoimmune disease may later exhibit features similar to the PSV under study (e.g. rheumatoid arthritis with rheumatoid vasculitis). Patients with unrelated autoimmune disorders (e.g. Hashimoto thyroiditis) must not be excluded. Patients with systemic vasculitis due to a virus infection, such as cryoglobulinemic vasculitis in Hepatitis C virus (HCV) infection or Hepatitis B virus (HBV)-associated polyarteritis nodosa (PAN), or patients with drug-induced vasculitis, should be studied as a pathogenetically and clinically separate entities.

3.5 Age and gender

Children and elderly patients have rarely been included in clinical trails in PSV except for the childhood specific vasculitides such as Kawasakis disease. Thus, there is insufficient

evidence to formulate recommendations on cut-off limits for age. Therefore, research in children and elderly people with vasculitis is encouraged. There is currently no evidence that gender affects outcome of patients with vasculitis.

The use of the ACR classification and the CHCC definitions are recommended as inclusion criteria. This is standard practice in several randomised controlled trials (extrapolated 1b evidence), and means that the diagnosis of vasculitis has to be based on clinical presentation, biopsy and/ or surrogate markers

4. Trial design

4.1 Endpoints

4.1.1 Mortality

Generic points to consider. In clinical trials the expected mortality in vasculitis depends on diagnosis and disease severity and ranges approximately from 0-25% at 1 year [68, 69]. Mortality is likely to be a useful outcome measure only in studies of severe vasculitis. In future studies of moderate and mild vasculitis, mortality should be carefully monitored to ensure that it does not significantly rise above these figures.

Recommendations for AAV. The mortality in RCTs ranged from 0-27.4% [68, 69] at one year reflecting different disease severity at inclusion. Prospective and retrospective outcome studies reported 1 year survival between 77.5-99% [23, 70] and a 5 year survival between 45 (for MPA) - 81% [71, 72] with some centres reporting a 10 year survival up to 88% [23]. The strongest factors predictive of mortality were advanced age [22-24, 70, 72-74] and renal involvement [21-24, 70, 72, 74]. Further identified risk factors were cardiomyopathy, lung haemorrhage, gut involvement requiring surgery and male sex. The initial BVAS and the Five Factor Score (FFS) were found to be predictive of mortality; for example patients with CSS or PAN who had a FFS of 0 vs >2 had a 5 year survival of 88.9% vs 55% in CSS and PAN [75], [76]. The VDI at 2 years was also predictive of future mortality, although this is based on a study of only 120 patients [77]. It is difficult to compare mortality rates for individual diseases as most studies included more than one diagnosis. In one series of 99 patients with PSV it was found that MPA

carried a worse prognosis compared to WG or CSS [71]. By contrast, in one large RCT, relapse rates were lower for MPA compared to WG [2].

The committee recommends that comparative long-term studies in large well defined cohorts should be conducted in order to retrieve more precise data on prognosis of the various types of PSV. The above mentioned predictive factors for mortality should be systematically recorded.

4.1.2 Combined outcomes: remission and relapse

Generic points to consider and recommendations for AAV. As discussed in section 4.1.1, mortality is rarely a useful primary endpoint of clinical trials although it remains an important endpoint of long-term studies. Therefore, for therapeutic trials, the successful induction and maintenance of remission are the preferred primary endpoints. Response as defined in section 1 can be a useful secondary endpoint, particularly in studies of refractory disease. Consensus definitions for remission, relapse and other disease states and recommendations on how to apply these recommendations into clinical trial protocols are outlined in section 1.

4.1.3 Organ-specific outcome and damage

Generic points to consider. Besides active inflammatory disease, irreversible end-organ damage as a result of previously active vasculitis can represent an important endpoint of therapeutic trials and particularly long-term studies. Damage can be recorded either globally using a quantitative instrument such as the VDI (see section 2.4) or can be focused on a single organ system or organ. Examples of such end-organ specific outcomes are renal function in glomerulonephritis, visual loss or other ischaemic events in GCA or symptomatic vascular stenoses in Takayasu Arteritis. Reviewing the available published evidence, there is insufficient data to recommend the routine use of imaging procedures such as high resolution CT of the chest, magnetic resonance imaging (MRI) or positron emission tomography (PET) as primary outcome measures in vasculitis. However, the expert committee identified a clear need for well designed diagnostic studies that evaluate the sensitivity and specificity of these techniques for the evaluation of disease activity in vasculitis (see research agenda, table 5). Furthermore, there are

few or no data on potentially relevant outcomes from the patients' perspective which address the impact of disease activity and damage on quality of life.

Recommendations for AAV. End stage renal failure represents a significant impact on the quality of life and long-term prognosis in patients with AAV. Therefore, we encourage therapeutic trials aimed at reducing the frequency of end-stage renal failure. For such studies, the expert committee recommends that data are provided on the proportion of patients who are dialysis-independent as an indicator of renal survival. This definition has been successfully used in a trial which evaluated the effect of plasma exchange in severe renal AAV [78]. Renal function should be assessed using the glomerular filtration rate (GFR) and chronic renal disease should be defined as outlined below in section 5.2. There are few data on the impact of end organ damage in the ENT region in patients with WG, but the expert committee identified a strong need for research in this area. For the global assessment of damage, the use of the VDI is recommended (see section 2.4 for definitions and details). There are very few well conducted studies on long-term outcome in vasculitis which might help to identify clinically relevant endpoints (e.g. damage) and the expert committee has therefore set this issue on the research agenda. Future trial designs should incorporate a commitment to providing long-term outcome data and all patients should be followed up for at least 5 years.

4.1.4 Use of glucocorticoid- or cytotoxic drug-sparing regimens as a trial outcome

Generic points to consider. The prolonged use of high-dose GC or the use of alkylating agents for treatment of PSV often results in substantial toxicity. The goal of some treatment regimens for PSV in both clinical practice and clinical trials has been to reduce the burden from GC usage (so-called "steroid-sparing" regimens) or avoid prolonged use of CYC. Clinical studies in several types of PSV have used GC-sparing and/or CYC-avoidance or reduction as an important outcome in many types of vasculitis [1-4, 15, 42]. Protocols aimed at "GC-sparing" or demonstrating the ability to reduce the burden of toxic therapies are acceptable and should be encouraged.

Recommendations for AAV. Prolonged and repeated use of GC and or CYC is a common problem faced by patients with AAV and the avoidance of these medications has been either the primary or secondary goal of several trials [1-3, 12, 35, 40]. GC-sparing is difficult to demonstrate unless long-term follow-up of study patients is conducted and such studies are feasible. Equivalency studies aimed at reducing the total burden of CYC have been conducted [1, 2] and more are planned. It is

recommended that trials in AAV should be designed to reduce patients' total exposure to GC or CYC and that the details of the treatment regimens are clearly outlined.

4.2 Use of Placebo and Randomisation

Generic points to consider. In order to make disease assessment instruments such as BVAS as objective as possible, comprehensive glossaries have been developed and investigators have been trained in their use (i.e. to strictly apply the definitions given for each item). However, despite these efforts, disease evaluation using these assessment tools is not always free of subjectivity. This limitation of disease assessment in vasculitis in clinical trials can be partially overcome by proper randomisation, either against placebo, or standard therapy. However, given the high mortality of untreated systemic vasculitis, the use of placebo must be restricted to situations where it is fully justified. We recommend that placebo may be used as an adjunct to standard therapy for induction treatment. Placebo may also be used in studies on maintenance therapy in cases where there is no strong evidence that withdrawal of maintenance therapy results in a high rate of severe flares.

Recommendations for AAV. There is evidence from randomized controlled trials that CYC can induce remission in around 90% of patients with AAV [1-3]. In patients with "early systemic" or "limited" disease (table 2), methotrexate (MTX) is an effective alternative [1, 3]. Therefore, in studies of induction therapy, the investigational treatment should be randomized against either CYC or MTX, depending on the disease stage. Alternatively, the investigational agent may be randomized against placebo if both are used as adjuncts to induction therapy with MTX or CYC [3]. In a large study of methotrexate compared with cyclophosphamide as induction therapy of vasculitis, relapse rates after complete withdrawal of immunosuppressive therapy were high despite 12 months of induction treatment with MTX or CYC [1]. Therefore, the experts committee recommends that for studies on maintenance therapy, investigational agents should be randomized against standard therapy (i.e. azathioprine [2] or methotrexate [13]) rather than only placebo.

4.3 Combined analysis of related types of vasculitis

Generic points to consider. In the past, due to the rarity of PSV, it was difficult to recruit a population with a single diagnosis that was sufficiently large to perform an efficacy analysis in a RCT. In order to resolve this problem, patients with distinct types of PSV have been randomized together in some previous RCTs (e.g WG and MPA, or MPA, CSS and PAN) [1, 2, 12, 28]. Although there are no comparative long-term-follow-up studies of patients with different types of PSV who were subjected to a uniform type of treatment, the available evidence suggests that the outcome of certain PSVs may differ despite similar treatment.

Recommendations for AAV. Although comparative long-term studies are still lacking, the available evidence from cohort studies and therapeutic trials suggests that the outcome of WG, MPA, and CSS may differ in several aspects. For example, relapse rates are significantly higher in patients with WG compared to patients with MPA [2]. In addition, analysis of features present only in one disease (e.g. granulomatous inflammation in WG) may be inconclusive due to the low number of subjects with theses features in a mixed study population. Weighing these issues against the risk of failing to achieve an adequate sample size, the expert committee recommends that groups of different types of AAV may be amalgamated only if common endpoints exist, identical treatments are used, disease type is a stratification variable for randomisation, and a subgroup analyses based on diagnosis is performed and reported.

4.4 Disease duration and previous therapy

Generic points to consider. While the majority of RCTs in PSV included only newly diagnosed patients with active disease [2, 12, 14, 17-19, 35, 40], some studies allowed the inclusion of previously treated patients [3, 13, 28, 41]. There are no data allowing definite conclusions on the impact of combining results from previously treated and newly diagnosed patients in a single study. Thus, we recommend that if trials include new and previously treated patients, combined analysis of common endpoints can be undertaken, but in addition, subgroup analyses should be performed.

Recommendations for AAV. There are limited data suggesting that previously treated patients with AAV may have less severe disease, but a lower therapeutic response, higher damage and greater susceptibility to adverse events, which may lead to a bias when mixing this subgroup of patients with newly diagnosed cases. For example, in a

longitudinal cohort study of 155 patients with WG, the disease extent in 99 relapsing patients was significantly lower at relapse than at diagnosis [23]. However, since the inclusion of only newly diagnosed patients may limit the number of available subjects, investigators may include patients with both newly diagnosed or relapsing disease, but this should be clearly stated from the outset in the trial protocol and sub-group analyses should be conducted.

4.5 Concomitant therapy

Generic points to consider. In general, concurrent interventional therapy that might independently affect the outcome of the trial should be discontinued or, if necessary, washed out prior to trial entry. The wash-out-period before entry should be at least 5 half-lives of the previous medication to rule out any interference. This restriction does not apply, if this co-medication is part of the study protocol (e.g. addition of an experimental therapy to existing immunosuppression in refractory patients) or given for other reasons (e.g. low dose GC given for asthma in CSS), but the dosage should be stable and not be changed at least two weeks prior to the study. A clearly defined protocol for GC taper should be described in the study protocol and criteria for delaying taper or increasing the dosage should be provided. It should be stated whether or not the inability to adhere to the GC taper protocol represents a treatment failure. Furthermore, it must be stated if pneumocystis carinii prophylaxis with low-dose trimethoprim–sulfamethoxazole was given as full dosage of this medication has been shown to reduce the risk of relapse in patients with WG [41].

In conclusion systemic vasculitis has been shown in controlled trials and observational studies to have an appreciable mortality and high relapse rate (1b evidence). There are examples of previous RCTs which recruited either different types of vasculitis or patients with different disease duration (extrapolated 1b evidence).

5. Biomarkers

5.1 Biomarkers relating to diagnosis

Generic points to consider. ANCA directed against proteinase-3 (PR3) and myeloperoxidase (MPO) are diagnostic markers for generalized WG and MPA,

respectively. Therefore, determination of ANCA is recommended for classification of patients with medium and small vessel vasculitis in clinical trials. Biomarkers which characterise other forms of vasculitis include: quantitative tests for Hepatitis C and circulating cryoglobulins in cryoglobulinemic vasculitis; and Hepatitis B serology in HBV-associated polyarteritis nodosa.

Recommendations for AAV. ANCA are not included in the ACR classification criteria or CHCC definitions. Therefore, ANCA were listed in the inclusion criteria in only 6 of 16 RCTs [1, 2, 13, 39-41] in patients with AAV. In fact, eligibility criteria should not be too restrictive in terms of ANCA and the following issues should be considered: Although PR-3/C-ANCA are highly sensitive markers of WG, up to 30 % of patients with MPA are PR-3/C-ANCA positive without displaying typical clinical or histomorphological features of WG [79]. Thus, a diagnosis based solely on the ANCA subtype may lead to misclassification. ANCA should be determined by both indirect immunofluorescence testing (IFT) and immunoassay (ELISA), since determination with IFT alone is too non-specific and commercially available ELISA kits show large variations in terms of sensitivity and specificity [80]. Given the variations of results of ANCA testing between different laboratories [81], analysis in a central laboratory is recommended, if this is feasible. Patients with localized WG are ANCA-positive in only 50 % of cases. Even patients with generalized WG may be ANCA-negative or show anti-MPO-ANCA-positivity. There is some evidence that these ANCA-negative or anti-MPO/P-ANCA positive patients represent clinically distinct subtypes [82] and that the outcome of patients with anti-PR3/C-ANCA may differ from that of anti-MPO/P-ANCA positive patients [2]. Therefore, we recommend that ANCA is tested by immunofluorescence and ELISA, ANCA subtypes should be reported, and that subgroup analyses by ANCA type are performed, if applicable. We recommend central testing of ANCA in a single laboratory for any studies specifically testing the role of ANCA in predicting disease activity

5.2 Biomarkers reflecting disease activity

Generic points to consider. Acute phase reactants such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are not specific, but are quite sensitive markers of

disease activity in virtually all types of systemic vasculitis. Surprisingly, only three of 16 RCTS in AAV have reported levels of CRP [40], ESR or both [1, 2] as secondary outcomes. Among three RCTs in GCA, ESR was reported in one trial [4] and ESR and CRP in another [16]. However, ESR and CRP may be (falsely) low in patients who received high doses of GC shortly prior to the first study visit. Although non-specific, an increase of ESR and/or CRP levels in patients reporting new symptoms that may be related but are not specific for a relapse (e.g. arthralgia, myalgia, fatigue), warrants further work-up and closer follow-up to rule out a relapse. However, in view of the poor specificity of both ESR and CRP, changes in these parameters should not be regarded as sole measures of response or activity and must always be interpreted in the clinical context; potential interfering factors such as intercurrent infections and variable dosing of GC prior to study enrolment, must be considered. Despite these limitations, serial determinations of acute phase reactants are recommended in any study in systemic vasculitis.

Recommendations for AAV. A recent review analysed 22 studies that address the validity of serial ANCA measurements for monitoring disease activity in AAV [83]. Considerable differences in study methodology precluded quantitative meta-analytic calculations. In line with previous reviews [79, 84], the analysis revealed that the available evidence was insufficient to conclude that serial measurements of ANCA should be performed routinely in clinical practice to assess patients or predict future disease activity. However, for the purpose of clinical trials and studies, the expert committee encourages serial ANCA measurements in order to obtain more valid data on the prognostic value of serial ANCA measurements. Serial ANCA measurements are particularly important in studies evaluating therapies that directly aim to reduce circulating ANCA levels (e.g. anti-B cell therapy, immunoadsorption).

In AAV, evaluation of renal disease is particularly important given its high prevalence and impact on outcome. Urine should be analysed microscopically for erythrocyte casts and/or dysmorphic erythrocytes as surrogate parameters of glomerular erythrocyturia. In addition, urine protein excretion should be quantified. Urine protein electrophoresis (i.e. early glomerular vs. tubular proteins) can be a helpful additional surrogate parameter for the serial evaluation of glomerulonephritis [85]. A prospective analysis of 96 patients with AAV and moderate renal involvement has shown that the glomerular filtration rate at baseline is the most potent predictor of renal function apart from histological features

[86]. Recently, the Kidney Disease Quality Outcome Initiative (K/DOQI) recommended a consensus definition and classification for chronic kidney disease which is based on the glomerular filtration rate (GFR) [87]. The K/DOQI defined chronic kidney disease by consensus as a GFR of < 60 mL/min/1.73m for 3 months or more [87]. GFR can be estimated from calibrated serum creatinine and estimating equations, such as the Modification of Diet in Renal Disease (MDRD) study equation or the Cockroft-Gault formula [87, 88]. We recommend the use of these consensus definitions and formulas for calculations of GFR in clinical studies in vasculitis.

In conclusion there is currently no conclusive evidence regarding the predictive value of serial ANCA testing in systemic vasculitis. There is however data from observational and cohort studies implicating ANCA as prognostic marker (type 3 evidence). The GFR at entry has been shown to be a strong predictor of renal outcome in AAV in an RCT (type 1b evidence).

DISCUSSION

These recommendations were developed following the EULAR standardised operating procedures for the elaboration, evaluation, dissemination and implementation of recommendations [5, 6]. It was the intention of the steering group to base the recommendations on research evidence as closely as possible. A systematic literature research that included articles published up to January 2006 revealed that with the exception of a few studies in GCA, RCTs and prospective long-term studies in PSV were primarily conducted in AAV. Although a greater number of open-label studies were identified, the majority of these studies did not contain a strict protocol and were rather case series or cohort studies that did not allow a systematic analysis. Furthermore, the majority of well-designed RCTs conducted in PSV were done in AAV. Therefore, it was decided to focus the recommendations on AAV as the data available for other types of AAV were found to be too heterogeneous and not robust enough for an evidence-based approach. Although many aspects of these recommendations may be generalized to studies in other types of vasculitis, the lack of robust data on PSV other than AAV limits our recommendations for non-AAV PSV.

A formal quality scoring of manuscripts was not performed, since even the trials which only studied patients with AAV were heterogeneous in many methodological aspects (e.g. inclusion criteria, outcome assessment).

The expert committee reported that there is a strong need for well designed clinical research in vasculitis. A number of particularly important unresolved issues were discussed within the expert committee and have been summarized in a research agenda (table 5).

The steering group hopes that these recommendations will be a helpful structure for the development of future studies in vasculitis. The committee encourages all colleagues in and beyond the vasculitis research community to discuss these recommendations and evaluate their usefulness in designing and conducting clinical trials. Given the fast growing amount of evidence in the field of vasculitis, it is planned to update these recommendations in the future. It is proposed that these recommendations should be updated after no later than five years from publication.

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References

1. De Groot K, Rasmussen N, Bacon PA, Tervaert JW, Feighery C, Gregorini G, et al.: Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum. 2005; 52(8): 2461-9.

2. Jayne D, Rasmussen N, Andrassy K, Bacon P, Cohen Tervaert JW, Dadoniene J, et al.: A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med 2003; 349(1): 36-44.

3. The Wegener's Granulomatosis Etanercept (WGET) Research Group: Etanercept plus standard therapy for Wegener's granulomatosis. N Engl J Med 2005; 352(4): 351-61.

4. Hoffman GS, Cid MC, Hellmann DB, Guillevin L, Stone JH, Schousboe J, et al.: A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. Arthritis Rheum 2002; 46(5): 1309-18.

5. Dougados M, Betteridge N, Burmester GR, Euller-Ziegler L, Guillemin F: EULAR standardised operating procedures for the elaboration, evaluation, disemination and implementation of recommendations endorsed by the EULAR standing commitees. Ann Rheum Dis 2004; 63: 1172-1176.

6. Zochling J, van der Heijde D, Dougados M, Braun J: The process of producing recommendations for rheumatic diseases - what is the evidence? Ann Rheum Dis 2005; 24: 24.

7. Directive 2001/20/EC of the European Parliament and the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the member states relating to the implementation of good clinical practice in the conduct of clinical

trials on medicinal products for human use. Official Journal of the European Communities 2001; L121: 34-44.

8. Lassere MN, Johnson KR, Boers M, Carlton K, Day RO, de Wit M, et al.: Standardized assessment of adverse events in rheumatology clinical trials: summary of the OMERACT 7 drug safety module update. J Rheumatol. 2005; 32(10): 2037-41.

9. Commission regulation No. 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of regulation (EC) No 726/2004 of the European Parliament and of the Council. Official Journal of the European Union 2006; L92: 6-7.

10. White B, Bauer EA, Goldsmith LA, Hochberg MC, Katz LM, Korn JH, et al.: Guidelines for clinical trials in systemic sclerosis (scleroderma). I. Disease-modifying interventions.The American College of Rheumatology Committee on Design and Outcomes in Clinical Trials in Systemic Sclerosis. Arthritis Rheum. 1995; 38(3): 351-60.

11. Shekelle PG, Woolf SH, Eccles M, Grimshaw J: Clinical guidelines: developing guidelines. Bmj 1999; 318(7183): 593-6.

12. Adu D, Pall A, Luqmani RA, Richards NT, Howie AJ, Emery P, et al.: Controlled trial of pulse versus continuous prednisolone and cyclophosphamide in the treatment of systemic vasculitis. QJM 1997; 90(6): 401-9.

13. de Groot K, Reinhold-Keller E, Tatsis E, Paulsen J, Heller M, Nolle B, et al.: Therapy for the maintenance of remission in sixty-five patients with generalized Wegener's granulomatosis. Methotrexate versus trimethoprim/sulfamethoxazole. Arthritis Rheum 1996; 39(12): 2052-61.

14. Gayraud M, Guillevin L, Cohen P, Lhote F, Cacoub P, Deblois P, et al.: Treatment of good-prognosis polyarteritis nodosa and Churg-Strauss syndrome: comparison of steroids and oral or pulse cyclophosphamide in 25 patients. French Cooperative Study Group for Vasculitides. Br J Rheumatol 1997; 36(12): 1290-7.

15. Jover JA, Hernandez-Garcia C, Morado IC, Vargas E, Banares A, Fernandez-Gutierrez B: Combined treatment of giant-cell arteritis with methotrexate and prednisone. a randomized, double-blind, placebo-controlled trial. Ann Intern Med 2001; 134(2): 106-14.

16. Chevalet P, Barrier JH, Pottier P, Magadur-Joly G, Pottier MA, Hamidou M, et al.: A randomized, multicenter, controlled trial using intravenous pulses of methylprednisolone in the initial treatment of simple forms of giant cell arteritis: a one year followup study of 164 patients. J Rheumatol 2000; 27(6): 1484-91.

17. Guillevin L, Jarrousse B, Lok C, Lhote F, Jais P, Le Thi Huong Du D, et al.: Longterm-followup after treatment of polyarteriitis nodosa and Chrug-Strauss angiitis with comparison of steroids, plasma exchange and cyclophosphamide to steroids and plasma exchange. A prospective randomized trial of 71 patients.The cooperative Study Group for Polyarteritis nodosa. J Rheumatol 1991; 18: 567-574.

18. Guillevin L, Lhote F, Cohen F, Jarousse B, Lortholary O, Généreau T, et al.: Corticosteroids plus pulse cyclophosphamide and plasma exchanges versus corticosteroids plus pulse cyclophosphamide alone in the treatment of polyarteriitis nodosa and Chrug-Strauss syndrome patients with factors predicting poor prognosis. A prospective, randomized trial in sixty-two patients. Arthritis Rheum 1995; 38: 1638-1645.

19. Guillevin L, Fain O, Lhote F, Jarrousse B, Le Thi Huong D, Bussel A, et al.: Lack of superiority of steroids plus plasma exchange to steroids alone in the treatment of polyarteriitis nodosa and Churg-Strauss syndrome. a prospective, randomized trial in 78 patients. Arthritis Rheum 1992; 35: 208-215.

20. Merkel PA, Seo P, Aries P, Neogi T, Villa-Forte A, Boers M, et al.: Current status of outcome measures in vasculitis: focus on Wegener's granulomatosis and microscopic polyangiitis. report from OMERACT 7. J Rheumatol. 2005; 32(12): 2488-95.

21. Booth AD, Almond MK, Burns A, Ellis P, Gaskin G, Neild GH, et al.: Outcome of ANCA-associated renal vasculitis: a 5-year retrospective study. Am J Kidney Dis 2003; 41(4): 776-84.

22. Slot MC, Tervaert JW, Boomsma MM, Stegeman CA: Positive classic antineutrophil cytoplasmic antibody (C-ANCA) titer at switch to azathioprine therapy associated with relapse in proteinase 3-related vasculitis. Arthritis Rheum 2004; 51(2): 269-73.

23. Reinhold-Keller E, Beuge N, Latza U, de Groot K, Rudert H, Nolle B, et al.: An interdisciplinary approach to the care of patients with Wegener's granulomatosis: long-term outcome in 155 patients. Arthritis Rheum 2000; 43(5): 1021-32.

24. Guillevin L, Cohen P, Gayraud M, Lhote F, Jarrousse B, Casassus P: Churg-Strauss syndrome. Clinical study and long-term follow-up of 96 patients. Medicine (Baltimore) 1999; 78(1): 26-37.

25. de Groot K, Jayne D, Tesar V, Savage C: Randomised controlled trial of daily oral versus pulse cyclophosphamide for induction of remission in ANCA-associated systemic vasculitis. Kidney Blood Press Res 2005; 28: 195 [Abstract].

26. TheWGETresearchgroup: Design of the Wegener's granulomatosis etanercept trial (WGET). Control Clin Trials 2002; 23: 450-468.

27. Keogh KA, Ytterberg SR, Fervenza FC, Carlson KA, Schroeder DR, Specks U: Rituximab for Refractory Wegener's Granulomatosis: Report of A Prospective, Open-Label Pilot Trial. Am J Respir Crit Care Med 2005; 13: 13.

28. Jayne D, Chapel H, Adu D, Misbah S, O'Donoghue D, Scott D, et al.: Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity. QJM 2000; 93(7): 433-9.

29. Lamprecht P, Voswinkel J, Lilienthal T, Nolle B, Heller M, Gross WL, et al.: Effectiveness of TNF-alpha blockade with infliximab in refractory Wegener's granulomatosis. Rheumatology (Oxford) 2002; 41(11): 1303-7.

30. Birck R, Warnatz K, Lorenz HM, Choi M, Haubitz M, Grunke M, et al.: 15-Deoxyspergualin in patients with refractory ANCA-associated systemic vasculitis: a six-month open-label trial to evaluate safety and efficacy. J Am Soc Nephrol 2003; 14(2): 440-7.

31. Aries PM, Hellmich B, Both M, Nolle B, Voswinkel J, Holl-Ulrich K, et al.: Lack of efficacy of Rituximab in Wegener's Granulomatosis with refractory granulomatous manifestations. Ann Rheum Dis 2006(65): 853-858.

32. Schmitt WH, Birck R, Heinzel P, Gobel U, Choi M, Warnatz K, et al.: Prolonged treatment of refractory Wegener's granulomatosis with 15-deoxyspergualin: an open study in seven patients. Nephrol Dial Transplant 2005; 20(6): 1083-92.

33. Schmitt W, Hagen E, Neumann I, Nowack R, Flores-Suarez LF, van der Woude F: Treatment of refractory Wegener's granulomatosis with antithymocyte globulin (ATG): an open study in 15 patients. Kidney Int 2004; 65(4): 1440-8.

34. Booth A, Harper L, Hammad T, Bacon P, Griffith M, Levy J, et al.: Prospective study of TNFalpha blockade with infliximab in anti-neutrophil cytoplasmic antibody-associated systemic vasculitis. J Am Soc Nephrol 2004; 15(3): 717-21.

35. Guillevin L, Cordier J, Lhote F, Cohen P, Jarrousse B, Royer I, et al.: A prospective, multicenter, randomized trial comparing steroids and pulse cyclophosphamide versus steroids and oral cyclophosphamide in the treatment of generalized Wegener's granulomatosis. Arthritis Rheum 1997; 40: 2187-2198.

36. Bartolucci P, Ramanoelina J, Cohen P, Mahr A, Godmer P, Le Hello C, et al.: Efficacy of the anti-TNF-alpha antibody infliximab against refractory systemic vasculitides: an open pilot study on 10 patients. Rheumatology 2002; 41: 1126-1132.

37. Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, et al.: Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med 1992; 116(6): 488-98.

38. de Groot K, Adu D, Savage C: The value of pulse cyclophosphamide in ANCA-associated vasculitis: meta-analysis and critical review. Nephrol Dial Transplant 2001; 16: 2018-2027.

39. Jayne DR, Chapel H, Adu D, Misbah S, O'Donoghue D, Scott D, et al.: Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity. Qjm 2000; 93(7): 433-9.

40. Haubitz M, Schellong S, Gobel U, Schurek HJ, Schaumann D, Koch KM, et al.: Intravenous pulse administration of cyclophosphamide versus daily oral treatment in patients with antineutrophil cytoplasmic antibody-associated vasculitis and renal involvement: a prospective, randomized study. Arthritis Rheum 1998; 41(10): 1835-44.

41. Stegeman CA, Tervaert JW, de Jong PE, Kallenberg CG: Trimethoprim-sulfamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granulomatosis. Dutch Co-Trimoxazole Wegener Study Group. N Engl J Med 1996; 335(1): 16-20.

42. Spiera RF, Mitnick HJ, Kupersmith M, Richmond M, Spiera H, Peterson MG, et al.: A prospective, double-blind, randomized, placebo controlled trial of methotrexate in the treatment of giant cell arteritis (GCA). Clin Exp Rheumatol 2001; 19(5): 495-501.

43. Kallenberg CG, Tervaert JW, Stegeman CA: Criteria for disease activity in Wegener's granulomatosis: a requirement for longitudinal clinical studies. APMIS Suppl. 1990; 19: 37-9.

44. Whiting-O'Keefe QE, Stone JH, Hellmann DB: Validity of a vasculitis activity index for systemic necrotizing vasculitis. Arthritis Rheum. 1999; 42(11): 2365-71.

45. Luqmani RA, Bacon PA, Moots RJ, Janssen BA, Pall A, Emery P, et al.: Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis. Qjm 1994; 87(11): 671-8.

46. Luqmani RA, Exley AR, Kitas GD, Bacon PA: Disease assessment and management of the vasculitides. Baillieres Clin Rheumatol. 1997; 11(2): 423-46.

47. Stone JH, Hoffman GS, Merkel PA, Min YI, Uhlfelder ML, Hellmann DB, et al.: A disease-specific activity index for Wegener's granulomatosis: modification of the Birmingham Vasculitis Activity Score. International Network for the Study of the Systemic Vasculitides (INSSYS). Arthritis Rheum 2001; 44(4): 912-20.

48. Guillevin L, Cohen P, Mahr A, Arene J, Mouthon L, Puechal X, et al.: Treatment of polyarteritis nodosa and microscopic polyangiitis with poor prognosis factors: a prospective trial comparing glucocorticoids and six or twelve cylophospahmide pulses in sixty-five patients. Arthritis Rheum 2003; 49: 93-100.

49. Merkel PA, Cuthbertson D, Hellmich B, Hoffman G, Jayne D, Kallenberg CG, et al.: Comparison of Disease Activity Measures for ANCA-associated vasculitis. Arthritis Rheum 2004; 50: S229-230.

50. de Groot K, Gross W, Herlyn K, Reinhold-Keller E: Development and validation of a disease extent index for Wegener's granulomatosis. Clin Nephrol 2001; 55: 31-8.

51. Metzler C, Fink C, Lamprecht P, Gross WL, Reinhold-Keller E: Maintenance of remission with leflunomide in Wegener's granulomatosis. Rheumatology 2004; 63: 339-40.

52. Metzler C, Hellmich B, Gause A, Gross WL, de Groot K: Churg Strauss syndrome--successful induction of remission with methotrexate and unexpected high cardiac and pulmonary relapse ratio during maintenance treatment. Clin Exp Rheumatol 2004; 22(6 Suppl 36): S52-61.

53. Reinhold-Keller E, Fink C, Herlyn K, Gross WL, de Groot K: High rate of renal relapse in 71 patients with Wegener's granulomatosis under maintenance of remission with low-dose methotrexate. Arthritis Care Res 2002; 47: 326-332.

54. Eisenberger U, Fakhouri F, Vanhille P, Beaufils H, Mahr A, Guillevin L, et al.: ANCA-negative pauci-immune renal vasculitis: histology and outcome. Nephrol Dial Transplant. 2005; 20(7): 1392-9. Epub 2005 Apr 26.

55. Stone JH, Uhlfelder ML, Hellmann DB, Crook S, Bedocs NM, Hoffman GS: Etanercept combined with conventional treatment in Wegener's granulomatosis: a six-month open-label trial to evaluate safety. Arthritis Rheum 2001; 44(5): 1149-54.

56. Exley AR, Bacon PA, Luqmani RA, Kitas GD, Gordon C, Savage CO, et al.: Development and initial validation of the Vasculitis Damage Index for the standardized clinical assessment of damage in the systemic vasculitides. Arthritis Rheum 1997; 40(2): 371-80.

57. Seo P, Min YI, Holbrook JT, Hoffman GS, Merkel PA, Spiera R, et al.: Damage caused by Wegener's granulomatosis and its treatment: prospective data from the Wegener's Granulomatosis Etanercept Trial (WGET). Arthritis Rheum. 2005; 52(7): 2168-78.

58. Hoffman G, Kerr G, Leavitt R, Hallahan C, Lebovics R, Travis W, et al.: Wegener's granulomatosis: an analysis of 158 patients. Ann Intern Med 1992; 116: 488-499.

59. Koutantji M, Harrold E, Lane SE, Pearce S, Watts RA, Scott DG: Investigation of quality of life, mood, pain, disability, and disease status in primary systemic vasculitis. Arthritis Rheum. 2003; 49(6): 826-37.

60. Reinhold-Keller E, Herlyn K, Wagner-Bastmeyer R, Gutfleisch J, Peter HH, Raspe HH, et al.: Effect of Wegener's granulomatosis on work disability, need for medical care,

and quality of life in patients younger than 40 years at diagnosis. Arthritis Rheum. 2002; 47(3): 320-5.

61. McHorney CA, Ware JE, Jr., Rogers W, Raczek AE, Lu JF: The validity and relative precision of MOS short- and long-form health status scales and Dartmouth COOP charts. Results from the Medical Outcomes Study. Med Care. 1992; 30(5 Suppl): MS253-65.

62. Luqmani R, Bacon P, Rasmussen N, Jayne D: Validation of the Birmingham Vasculitis Activity Score (BVAS) for use in European multi-centre clinical trials. Arthritis Rheum 2000; 43 (Suppl): S574.

63. Rao J, Allen N, Pincus N: Limitations of the 1990 American College of Rheumatology classification criteria in the diagnosis of vasculitis. Ann Intern Med 1998; 129: 345-352.

64. Sorensen S, Slot O, Tvede N, Petersen J: A prospective study of vasculitis patients collected in a five year period: evaluation of the Chapel Hill nomenclature. Ann Rheum Dis 2000; 59: 478-482.

65. Leavitt R, Fauci A, Bloch D, Michel B, Hunder G, Arend W, et al.: The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. Arthritis Rheum 1990; 33: 1101-1107.

66. Jennette JC, Falk RJ, Andrassy K, Bacon PA, Churg J, Gross WL, et al.: Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum 1994; 37(2): 187-92.

67. Jayne DR, Rasmussen N: Treatment of antineutrophil cytoplasm autoantibody-associated systemic vasculitis: initiatives of the European Community Systemic Vasculitis Clinical Trials Study Group. Mayo Clin Proc. 1997; 72(8): 737-47.

68. Jayne D: Evidence-based treatment of systemic vasculitis. Rheumatology (Oxford) 2000; 39(6): 585-95.

69. Gaskin G, Savage CO, Ryan JJ, Jones S, Rees AJ, Lockwood CM, et al.: Anti-neutrophil cytoplasmic antibodies and disease activity during long-term follow-up of 70 patients with systemic vasculitis. Nephrol Dial Transplant. 1991; 6(10): 689-94.

70. Mahr A, Girard T, Agher R, Guillevin L: Analysis of factors predictive of survival based on 49 patients with systemic Wegener's granuomatosis and prospective follow-up. Rheumatology 2001; 40: 492-498.

71. Lane SE, Watts RA, Shepstone L, Scott DG: Primary systemic vasculitis: clinical features and mortality. Qjm. 2005; 98(2): 97-111. Epub 2005 Jan 17.

72. Weidner S, Geuss S, Hafezi-Rachti S, Wonka A, Rupprecht HD: ANCA-associated vasculitis with renal involvement: an outcome analysis. Nephrol Dial Transplant. 2004; 19(6): 1403-11. Epub 2004 Apr 6.

73. Bligny D, Mahr A, Toumelin PL, Mouthon L, Guillevin L: Predicting mortality in systemic Wegener's granulomatosis: a survival analysis based on 93 patients. Arthritis Rheum. 2004; 51(1): 83-91.

74. Guillevin L, Le Thi Huong D, Godeau P, Jais P, Wechsler B: Clinical findings and prognosis of polyarteritis nodosa and Churg-Strauss angiitis: a study in 165 patients. Br J Rheumatol 1988; 27(4): 258-64.

75. Guillevin L, Lhote F, Gayraud M, Cohen P, Jarousse B, Lortholary O, et al.: Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome. Medicine 1996; 75: 17-28.

76. Gayraud M, Guillevin L, le Toumelin P, Cohen P, Lhote F, Casassus P, et al.: Long-term followup of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: analysis of four prospective trials including 278 patients. Arthritis Rheum 2001; 44(3): 666-75.

77. Exley AR, Bacon PA, Luqmani RA, Kitas GD, Carruthers DM, Moots R: Examination of disease severity in systemic vasculitis from the novel perspective of damage using the vasculitis damage index (VDI). Br J Rheumatol. 1998; 37(1): 57-63.

78. Gaskin G, Jayne D: Adjuctive Plasmaexchange is superior to methylprednisolone in acute renale failure due to ANCA-associated glomerulonephritis. J Am Soc Nephrol 2002; 13: F-FC010.

79. Savige J, Pollock W, Trevisin M: What do antineutrophil cytoplasmic antibodies tell us? Best Pract Res Clin Rheumatol 2005; 19: 263-276.

80. Holle JU, Hellmich B, Backes M, Gross WL, Csernok E: Variations in performance characteristics of commercial enzyme immunoassay kits for the detection of antineutrophil cytoplasmatic antibodies: What is the optimal cut-off ? Ann Rheum Dis 2005; 64: 1773-1779.

81. Csernok E, Holle J, Hellmich B, Cohen Tervaert J, Kallenberg C, Limburg P, et al.: Evaluation of capture ELISA for detection of antineutrophil cytoplasmic antibodies against proteinase-3 in Wegener's granulomatosis: First results from a multicenter study. Rheumatology 2004; 43: 174-180.

82. Reinhold-Keller E, de Groot K, Holl-Ulrich K, Arlt AC, Heller M, Feller AC, et al.: Severe CNS manifestations as the clinical hallmark in generalized Wegener's granulomatosis consistently negative for antineutrophil cytoplasmic antibodies (ANCA). A report of 3 cases and a review of the literature. Clin Exp Rheumatol 2001; 19(5): 541-9.

83. Birck R, Schmitt WH, Kaelsch IA, van der Woude FJ: Serial ANCA determinations for monitoring disease activity in patients with ANCA-associated vasculitis: systematic review. Am J Kidney Dis. 2006; 47(1): 15-23.

84. Langford CA: Antineutrophil cytoplasmic antibodies should not be used to guide treatment in Wegener's granulomatosis. Clin Exp Rheumatol 2004; 22 (suppl.36): S3-S6.

85. Niederstadt C, Happ T, Tatsis E, Schnabel A, Steinhoff J: Glomerular and tubular proteinuria as markers of nephropathy in rheumatoid arthritis. Rheumatology (Oxford). 1999; 38(1): 28-33.

86. Hauer HA, Bajema IM, Van Houwelingen HC, Ferrario F, Noel LH, Waldherr R, et al.: Determinants of outcome in ANCA-associated glomerulonephritis: a prospective clinico-histopathological analysis of 96 patients. Kidney Int 2002; 62(5): 1732-42.

87. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, et al.: Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2005; 67(6): 2089-100.

88. Froissart M, Rossert J, Jacquot C, Paillard M, Houillier P: Predictive performance of the modification of diet in renal disease and Cockcroft-Gault equations for estimating renal function. J Am Soc Nephrol. 2005; 16(3): 763-73. Epub 2005 Jan 19.

89. Jayne D: Update on the European Vasculitis Study Group (EUVAS). Curr Opin Rheumatol 2001; 13: 48-55.

Table 1. Recommendation for use and definition of activity states in vasculitis

Activity State	Definition
Remission	absence of disease activity attributable to active disease qualified by the need for ongoing stable maintenance immunosuppressive therapy. The term "active disease" is not restricted to vasculitis only, but also includes other inflammatory features like granulomatous inflammation in WG or tissue eosinophilia in CSS.
Response	50% reduction of disease activity score and absence of new manifestations
Relapse	reoccurrence or new onset of disease attributable to active vasculitis
major relapse	reoccurrence or new onset of potentially organ- or life threatening disease
minor relapse	reoccurrence or new onset of disease which is neither potentially organ- threatening nor life threatening
Refractory disease	1) unchanged or increased disease activity in acute AAV after four weeks treatment with standard therapy in acute AAV, *or* 2) lack of response, defined as $\leq$ 50% reduction in the disease activity score, after 6 weeks of treatment, *or* 3) *chronic, persistent disease* defined as presence of at least one major or three minor items on the disease activity score list, (eg BVAS or BVAS/WG) after $\geq$ 12 weeks of treatment.
Low Activity Disease State	Persistence of minor symptoms (e.g. arthalgia, myalgia) that respond to a modest increase of the GC dose and do not warrant an escalation of therapy beyond a modest dose increase of the current medication

Table 2. Definitions for disease stages used for subclassification of patients with WG in clinical trials

Study Group	*Clinical subgroup*	*Systemic vasculitis outside ENT Tract and lung*	*Threatened vital organ function*	*Other definitions*	*Serum creatinine [µmol/L]*	*Reference*
EUVAS	Localised	no	no	No constitutional symptoms, ANCA typically negative	< 120	
	Early systemic	yes	no	Constitutional symptoms present, ANCA positive or negative	< 120	
	generalised	yes	yes	ANCA positive	< 500	[2]
	severe	yes	Organ failure	ANCA positive	> 500	[89]
	refractory	yes	yes	Refractory to standard therapy	any	[89]
WGET Research Group/VCRC	Limited	Allowed, but not required	no	not severe	≤ 124, if haematuria, but no red blood cell casts present	[3]
	Severe	yes	yes	organ- or life-threatening disease, implies need for remission-induction with cyclophosphamide	any	[3]

Table 3. Recommendations for eligibility criteria for clinical trials in PSV

1. A diagnosis of vasculitis based on a compatible clinical picture and histopathology or surrogate parameters
2. Definition of the type of vasculitis according to published criteria by using CHCC definitions and/or ACR classification criteria
3. Definition of disease stage(s) of eligible patients (e.g. localized/generalized)
4. Definition of activity states (e.g. refractory or relapsing)
5. Definition of other patient characteristics

a) Newly diagnosed or previously treated?

b) Type and duration of previous immunosuppressive therapy (previously treated patients only)

c) Demographic details

d) Serologic status (e.g ANCA +/-, anti-MPO vs. anti-PR3)

Table 4. Final set of recommendations for conducting clinical trials in systemic vasculitis based on both evidence and expert opinion

1. For clinical trials or studies, patients with vasculitis should be categorized into clearly defined activity states. It is recommended to use the following terms: remission, response, refractory disease and relapse; definitions for these activity states are provided (table 1). Grade of recommendation B
2. Comprehensive disease assessment in vasculitis requires the recording of disease activity, damage and function. We recommend the use of a form of the Birmingham Vasculitis Activity Score, the Disease Extent Index, the Vasculitis Damage Index and the Short Form 36. All investigators need to be trained to use these instruments. Grade of recommendation A
3. Inclusion criteria should contain precise disease definitions. First of all, the clinical diagnosis should be based on the ACR-classification criteria or CHCC-definitions. Ideally, the definite diagnosis should be based on typical biopsy findings and/or highly specific immune phenomena (eg. ANCA). A biopsy showing typical features of the disease under study (e.g. necrotizing vasculitis, granulomatous inflammation, glomerulonephritis) should be listed as an inclusion criterion, but patients without confirmatory biopsy, but compatible clinical picture may also be included if either (a) specific investigations (angiography, MRI/CT imaging, neurophysiology) or surrogate parameters are strongly suggestive of vasculitis, glomerulonephritis and/or granuloma, and/or (b) patients with a clinical diagnosis of MPA or WG are anti-PR3/C-ANCA or anti-MPO/P-ANCA positive. The disease status of study patients should be reported. Grade of recommendation B.
4. Given the high mortality of untreated systemic vasculitis, the use of placebo must in general be restricted to an adjunct to standard therapy for induction treatment. Placebo may be used in studies of maintenance therapy, but only if there is no high risk that withdrawal of maintenance therapy will result in a high rate of severe flares. Trials of vasculitis may include patients with different types of vasculitis (e.g. WG and MPA) and distinct disease duration (eg. newly diagnosed and relapsing patients) if a) identical treatment protocols are prescribed, b) identical endpoints and outcome measure are used, c) both combined and subgroup analyses are performed and reported, and d) sufficient numbers of patients with each individual disease and sub group are recruited for the relevant analyses. Grade of recommendation B

5. Biomarkers such as CRP and/or ESR should be determined regularly as serologic markers of disease activity, but results must be interpreted in the context of the clinical findings. In trials involving AAV we recommend the serial determination of ANCA. Renal function should be assessed by the GFR using estimating equations like the MDRD or Cockroft-Gault formula. Microscopic examination of urine and quantification of proteinuria are recommended to monitor the activity of glomerulonephritis. Grade of recommendation C.

Table 5. Research agenda

1. Development and validation of disease assessment tools for all types of PSV
2. Evaluation of novel imaging techniques like magnetic resonance imaging or Positron emission tomography in the assessment of disease activity
3. Long-term outcome and cohort studies to identify relevant endpoints for all types of PSV
4. Incorporation of the patients' perspective in outcome assessment
5. Identification and evaluation of novel biomarkers (genomics, proteomics)
6. Systematic evaluation of adverse events in vasculitis
7. Research in children and elderly people with vasculitis
8. Assessment of disease activity and damage in the ENT region in patients with WG
9. RCTs in vasculitides other than AAV