EXTENDED REPORT

EULAR recommendations for conducting clinical studies and/or clinical trials in systemic vasculitis: focus on anti-neutrophil cytoplasm antibody-associated vasculitis

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Objectives: To develop the European League Against Rheumatism (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 five 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 nine 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 consider vasculitis-specific issues rather than general issues of trial methodology. The recommendations deal with the following areas related to clinical studies of vasculitis: definitions of disease, activity states, outcome measures, eligibility criteria, trial design including relevant end points, and biomarkers. 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.

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

Owing 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—for example, antineutrophil cytoplasm antibody (ANCA) serology—and secondly by the formation of collaborative research groups like the European Vasculitis Study (EUVAS) Group, the International Network for the Study of Systemic Vasculitis, the French Vasculitis Study Group and the Vasculitis Clinical Research Consortium (VCRC). Independently, these groups have conducted a number of randomised controlled clinical trials (RCTs) using standardised clinical measurement scores. The results of these trials have had a 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 the following: definitions of disease, disease stages, activity stages, outcome measures, duration of treatment, duration of observation and use of concomitant drugs.

Based on a proposal by EUVAS to the European Standing Committee for International clinical studies including therapeutics, 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 European League Against Rheumatism (EULAR) standardised operating procedures for the elaboration, evaluation, dissemination and implementation of recommendations.[5 6] Published evidence in the form of high-quality RCTs was found primarily for vasculitides associated with ANCA. We therefore focused the recommendations on the ANCA-associated vasculitides (AAV):

Abbreviations: AAV, antineutrophil cytoplasm antibody-associated vasculitis; ANCA, antineutrophil cytoplasm antibody; ACR, American College of Rheumatology; BVAS, Birmingham Vasculitis Activity Score; BVAS/WG, Birmingham Vasculitis Activity Score for Wegener's granulomatosis; CHCC, Chapel Hill Consensus Conference; CRP, C reactive protein; CSS, Churg–Strauss syndrome; CYC, cyclophosphamide; DEI, Disease Extent Index; EULAR, European League Against Rheumatism; EUVAS, European Vasculitis Study Group; ESR, erythrocyte sedimentation rate; GC, glucocorticoid; GCA, giant cell arteritis; GFR, glomerular filtration rate; HBV, Hepatitis B virus; MPA, microscopic polyangiitis; MPO, myeloperoxidase; MTX, methotrexate; PAN, polyarteritis nodosa; PR3, proteinase 3; PSV, primary systemic vasculitis; RCT, randomised controlled trial; SF-36, Short Form 36; VCRC, Vasculitis Clinical Research Consortium; VDI, Vasculitis Damage Index; WG, Wegener's granulomatosis; WGET, Wegener's Granulomatosis Etanercept Trial

Wegener's granulomatosis (WG), microscopic polyangiitis (MPA) and Churg–Strauss syndrome (CSS). However, many of the issues dealt with 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. The 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, 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 standardised assessment of adverse events in rheumatology have been elaborated by the Outcome Measures in Rheumatology Drug Safety group.[8] The European Commission recently published a regulation on 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 PSV 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 be undertaken only if sufficient number of patients can be recruited to satisfy the sample-size requirements; this effectively means that almost all studies will need to be multicentred, 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 end points, (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 seven rheumatologists (BH, WLG, PB, PAM, DGIS, HY, RAL), one nephrologist (DJ), one clinical immunologist (JWC-T), two specialists in internal medicine (LG, AM), one clinical epidemiologist (HR), one research fellow (OF) and representatives from the EMEA (Jordi Llinares) and the Food and Drug Administration (JWC-T). It was decided to develop recommendations that are applicable to studies of all types of systemic vasculitis. Because of 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, keywords from the research questions that 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 (eg, inclusion criteria, outcome assessment), a formal quality scoring was not carried out. The results of the literature research were summarised in several tables that included those data from the identified studies that were relevant for the specific research topic selected by the committee (ie, 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 considered in the research questions (eg, 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 polyarteritis nodosa (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 five recommendations, with several subtopics considered in each recommendation. The strength of the recommendations was graded from A (highest) to D (lowest) according to Shekelle *et al*.[11] Owing 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 summarise 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 and 159 Embase). Duplications, irrelevant articles and non-original reports were excluded. In addition, studies with <25 patients, studies involving only paediatric patients and studies in secondary vasculitis were also excluded. In all, 16 studies involving patients with AAV and PAN, three with giant cell arteritis (GCA) and one study with 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 scrutinised 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 that we were studying, and duplicate datasets.

Definitions of disease and activity states

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 (see table 2). Furthermore, definitions of remission should include the use of ongoing immunosuppressive therapy. Although 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 of 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 (eg, absence of disease activity combined with the presence of low or undetectable levels of the biomarker).

Recommendations for AAV: In 8 of 16 published 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 end point. 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 like granulomatous manifestations such as retro-orbital tumours, 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'', ''stabilisation'' 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 (eg, Birmingham Vasculitis Activity Score (BVAS) or BVAS for WG (BVAS/WG)).[20]

In all the studies in AAV mentioned above, patients were still taking some form of immunosuppressive drug at the time when 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 (GCs) at the time of remission. The term glucocorticoid includes prednisolone, prednisone and methylprednisolone. 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 ⩽7.5 mg/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 (eg, arthralgia, nasal crusting) after attaining remission. Therefore, the complete withdrawal of GC is not necessarily required 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 RCTs 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.

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 among patients responding to standard treatment. Therefore, analysis of partial improvement or response may be clinically relevant and may constitute a meaningful secondary end point. 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 (eg, 50% reduction in the BVAS).

Recommendations for AAV: With the exception of one study reporting remission in all patients,[27] remission is achieved in only 35–83% of patients with AAV who are refractory to conventional treatment with cyclophosphamide (CYC) and 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 treatment. Therefore, we define ''response'' as ⩾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 (eg, 30% or 70% response), but the 50% response rate should be measured and reported, to allow comparison across different trials and studies.

Refractory disease

Generic points to consider: Patients who fail to attain remission following induction treatment with the standard regimen are termed refractory. Refractory disease is the only disease state that refers to treatment. Such standard therapy for a specific type of vasculitis must therefore be defined precisely (eg, optimal therapy with appropriate doses of cyclophosphamide or methotrexate (MTX), 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 GCs after a defined duration of treatment. Therefore, the taper regimen for GCs 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 in 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 seems to be similarly effective as CYC but less toxic.[1] Results from RCTs show that current standard therapy

fails to induce remission in up to 10% 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 CYC 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 2–4 weeks of treatment with either daily oral CYC (2 mg/kg) and GC (1 mg/kg),[2] or pulse-intermittent high-dose CYC (15 mg/kg or 0.6–0.7 g/m^2 body surface area) with GC.[38] By contrast, remission is usually attained after 8–12 weeks of treatment.[1 12] The possibility of inducing remission by prolonged administration of CYC and GC must be weighed against (1) the increasing risk of long-term toxicity and (2) 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 (1) unchanged or increased disease activity after 4 weeks of treatment with daily oral CYC (2–3 mg/kg) and GC[2] or pulse-intermittent high-dose CYC (15 mg/kg or 0.6–0.7 g/m^2 body surface area) with GC[1]; or (2) lack of response, defined as $\leqslant$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 treatment with daily oral CYC and GC or pulse-intermittent high-dose CYC (15 mg/kg or 0.6–0.7 g/m^2 body surface area) with GC (eg, repeated cytopenias), or who have contraindications against the use of CYC (eg, haemorrhagic cystitis) have been included in studies of refractory disease in the past. These patients have been defined as having refractory disease (1) if the disease is not controlled with the best available alternative standard therapy for a defined duration of treatment and (2) if escalation with an experimental drug is clinically indicated. However, since these patients are possibly distinct in terms of complications of treatment, probability of response or damage, they should not be defined as having refractory disease, but subgroup analyses should be performed in order to detect differences in outcome compared with CYC-treated refractory patients according to the above definitions.

Grumbling disease

Generic points to consider: It is well recognised 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 treatment beyond a modest increase in the dose of the current drug or addition of low-dose GC, balancing the potential benefit versus the risk of complication of more intense treatment.

Recommendations for AAV: Further research is needed to develop evidence-based criteria on how to classify minor symptoms as representing either 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.

Relapse

Generic points to consider: Definitions for relapse were provided in 11 of 16 prospective RCTs in AAV[1–3 12–14 17–19 35 39–41] and in two[4 15] of three studies of 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. 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 re-occurrence or new onset of potentially organ- or life-threatening disease activity that cannot be treated with an increase of GC alone and requires further escalation of treatment (ie, the administration of CYC). All other relapses should be classified as minor.

Recommendations for AAV: On the basis of 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).

Disease assessment and outcome measures

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 BVAS[45] together with the modifications of BVAS as used in the EUVAS studies (BVAS 1+2)[46] and BVAS for WG (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 a physician decides to treat the abnormality with immunosuppressive therapy (ie, the item represents active disease requiring treatment) and if the items do not represent damage or infection.

Recommendations for AAV: The original version of BVAS was used in four RCTs[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 the 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 on WG is recommended. Currently, initiatives by EULAR and VCRC to improve existing disease assessment tools within the Outcome Measures in Rheumatology process are in progress.[20]

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 three RCTs[2 25 40] and several open-label studies.[33 51–53] As the DEI seems to provide prognostic information[54] that complements BVAS and can be calculated from the BVAS score sheet without additional information, its use is recommended.

Physician global assessment

Generic points to consider: The physician global assessment has been applied only in two trials to date,[26 55] and is a subjective measure 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.

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. Before 2003, there was only one published therapeutic study that 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 the recently published RCTs[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 in patients with WG. Several large case series have highlighted the problem of long-term morbidity in vasculitis.[23 58] In a longitudinal cohort of 158 patients with WG from the National Institutes of Health, 86% of patients had permanent damage as a consequence of the disease itself and 42% had 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.

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 that, 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 RCTs 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 SF-36 scores.[1 2 26 27]

With the exception of the SF-36, 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 among individuals.[62]

In conclusion, there is evidence from several RCTs supporting the use of the BVAS, DEI, VDI and SF-36 in clinical trials of vasculitis (grade 1b evidence).

Eligibility criteria

Diagnosis

Generic points to consider: Since several studies have shown that classification criteria (see box 2) 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 (ie, 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 (ie, infections, malignancies) have been specifically excluded.

Recommendations for AAV: The expert committee recommends that in most cases a biopsy specimen 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 with a compatible clinical picture, may also be included if either (1) specific imaging techniques (angiography, MRI/CT, etc) or surrogate parameters are strongly suggestive of vasculitis, glomerulonephritis and/or granuloma, or (2) patients with a clinical diagnosis of MPA or WG are anti-proteinase 3 (PR3)/C-ANCA or anti-myeloperoxidase (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, retro-orbital granuloma, red cell casts or dysmorphic erythrocytes in the urine, diffuse alveolar haemorrhage, mononeuritis multiplex and episcleritis.

Disease classification

Generic points to consider: The diagnostic classification of systemic vasculitides is based on the classification by the ACR[65] and the disease definitions as agreed by the Chapel Hill Consensus Conference (CHCC).[66] Although both 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, whereas the CHCC definitions were based on expert opinion only. However, the ACR criteria do not include MPA, 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 be used for classification of patients with vasculitis in clinical studies. The use of serological and radiographical 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 Wegener's Granulomatosis Etanercept Trial (WGET) studies is to be encouraged (see the section "Biomarkers relating to diagnosis" for details).

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 categorised into clearly defined disease states.

Recommendations for AAV: The EUVAS and the WGET groups classified patients into different disease states (table 1). The EUVAS group classified patients for inclusion criteria in RCTs 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 that 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 the WGET/VCRC classification, but not to modify these definitions until consensus definitions have been agreed on (table 2).

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 (eg, rheumatoid arthritis with rheumatoid vasculitis). Patients with unrelated autoimmune disorders (eg, Hashimoto thyroiditis) must not be excluded. Patients with systemic vasculitis due to a virus infection, such as cryoglobulinaemic vasculitis in hepatitis C virus infection or hepatitis B virus (HBV)-associated PAN, or patients with drug-induced vasculitis should be studied as pathogenetically and clinically separate entities.

Age and gender

Children and elderly patients have rarely been included in clinical trials in PSV, except for the childhood-specific vasculitides such as Kawasaki's disease. Thus, evidence available is insufficient to formulate recommendations on the cut-off limits for age. Therefore, research in children and elderly people with vasculitis is encouraged. There is currently no evidence that gender affects the outcome of patients with vasculitis.

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

Trial design

Endpoints

- Mortality

  – Generic points to consider

In clinical trials, the expected mortality in vasculitis depends on diagnosis and disease severity, and ranges approximately from 0 to 25% at 1 year.[69 70] 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 to 27.4%[69 70] at 1 year, reflecting different disease severity at inclusion. Prospective and retrospective outcome studies reported a 1-year survival between 77.5% and 99%,[23 71] and a 5-year survival between 45% (for MPA) and 81%,[72 73] with some centres reporting a 10-year survival up to 88%.[23] The strongest factors predictive of mortality were advanced age[22–24 71 73–75] and renal involvement.[21–24 71 73 75] Further identified risk factors were cardiomyopathy, lung haemorrhage, gut involvement requiring surgery and male sex. The initial BVAS and the Five Factor Score were found to be predictive of mortality—for example, patients with CSS or PAN who had a Five Factor Score of 0 vs >2 had a 5-year survival of 88.9% vs 55% in CSS and PAN.[76 77] The VDI at 2 years was also predictive of future mortality, although this is based on a study of only 120 patients.[78] It is difficult to compare mortality for individual diseases as most studies included more

Table 1 Definitions for disease stages used for subclassification of patients with Wegener's granulomatosis 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	Jayne *et al*[2]
	Severe	Yes	Organ failure	ANCA-positive	>500	Jayne[68]
	Refractory	Yes	Yes	Refractory to standard therapy	Any	Jayne[68]
WGET Research Group/VCRC	Limited	Allowed, but not required	No	Not severe	⩽124, if haematuria, but no red blood cell casts present	WGET Research Group[3]
	Severe	Yes	Yes	Organ- or life-threatening disease, implies need for remission induction with CYC	Any	WGET Research Group[3]

ANCA, anti-neutrophil cytoplasmic antibody; CYC, cyclophosphamide; ENT, ear, nose and throat; EUVAS, European Vasculitis Study Group; VCRC, Vasculitis Clinical Research Consortium; WGET, Wegener's Granulomatosis Etanercept Trial.

Box 1: Research agenda

- Development and validation of disease assessment tools for all types of PSV
- Evaluation of novel imaging techniques like magnetic resonance imaging or PET in the assessment of disease activity
- Long-term outcome and cohort studies to identify relevant end points for all types of PSV
- Incorporation of the patients' perspective in outcome assessment
- Identification and evaluation of novel biomarkers (genomics, proteomics)
- Systematic evaluation of adverse events in vasculitis
- Research in children and elderly people with vasculitis
- Assessment of disease activity and damage in the ENT region in patients with WG
- RCTs in vasculitides other than AAV

Notes: AAV, anti-neutrophil cytoplasmic antibody-associated vasculitis; ENT, ear, nose and throat; PET, positron emission tomography; PSV, primary systemic vasculitis; RCT, randomised controlled trial; WG, Wegener's granulomatosis.

than one diagnosis. In one series of 99 patients with PSV, it was found that MPA carried a worse prognosis compared with WG or CSS.[72] By contrast, in one large RCT, relapse rates were lower for MPA compared with WG.[2]

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

- Combined outcomes: remission and relapse

  – Generic points to consider and recommendations for AAV

As discussed in the section ''Mortality'' above, mortality is rarely a useful primary end point of clinical trials although it remains an important end point of long-term studies. Therefore, for therapeutic trials, the successful induction and maintenance of remission are the preferred primary end points. Response, as defined in section 1, can be a useful secondary end point, 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 the section ''Defenitions of disease and activity series''.

- 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 end point of therapeutic trials and particularly long-term studies. Damage can be either recorded globally using a quantitative instrument such as the VDI (see the section ''Damage'') 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. Data available from reviewing the available published evidence, are insufficient data to recommend the routine use of imaging procedures such as high-resolution CT of the chest, MRI or positron emission tomography 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 (box 1). 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 has a significant impact on the quality of life and long-term prognosis in patients with AAV. Therefore, we encourage therapeutic trials aimed at reducing

Table 2 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	Re-occurrence or new onset of disease attributable to active vasculitis
Major	Re-occurrence or new onset of potentially organ- or life-threatening disease
Minor	Re-occurrence or new onset of disease which is neither potentially organ- nor life-threatening
Refractory disease	Unchanged or increased disease activity in acute AAV after 4 weeks of treatment with standard therapy in acute AAV, or Lack of response, defined as $\leqslant$50% reduction in the disease activity score, after 6 weeks of treatment, or 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 $\geqslant$12 weeks of treatment
Low-activity disease state	Persistence of minor symptoms (eg, 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 in the current medication

AAV, anti-neutrophil cytoplasmic antibody-associated vasculitis; BVAS, Birmingham Vasculitis Activity Score; BVAS/WG, Birmingham Vasculitis Activity Score for Wegener's granulomatosis; CSS, Chug–Strauss syndrome; GC, glucocorticoid; WG, Wegener's granulomatosis.

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.[79] Renal function should be assessed using the glomerular filtration rate (GFR), and chronic renal disease should be defined as outlined below in the section ''Biomarkers reflecting disease activity''. There are few data on the impact of end organ damage in the ear, nose and throat 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 the section ''Damage'' for definitions and details). There are very few well-conducted studies on long-term outcome in vasculitis which might help to identify clinically relevant end points (eg, 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.

- Use of GC 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 to 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 drugs has been either the primary or the 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 be designed to reduce patients' total exposure to GC or CYC and that the details of the treatment regimens are clearly outlined.

Use of placebo and randomisation

- Generic points to consider

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 (ie, 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 by 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 RCTs that CYC can induce remission in around 90% of patients with AAV.[1–3] In patients with early systemic or limited disease (table 1), MTX is an effective alternative.[1 3] Therefore, in studies of induction therapy, the investigational treatment should be randomised against either CYC or MTX, depending on the disease stage. Alternatively, the investigational agent may be randomised against placebo if both are used as adjuncts to induction therapy with MTX or CYC.[3] In a large study of MTX compared with CYC as induction therapy of vasculitis, relapse rates after complete withdrawal of immunosuppressive therapy were found to be 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 are randomised against standard therapy (ie, azathioprine[2] or MTX[13]) rather than only placebo.

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 randomised together in some previous RCTs (eg, 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 outcomes of WG, MPA and CSS may differ in several aspects. For example, relapse rates are significantly higher in patients with WG compared with patients with MPA.[2] In addition, analysis of features present only in one disease (eg, granulomatous inflammation in WG) may be inconclusive due to the low number of subjects with these 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 end points exist, if identical treatments are used, if disease type is a stratification variable for randomisation, and a subgroup analysis based on diagnosis is performed and reported.

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, a combined analysis of common end points 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 subgroup analyses should be conducted.

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 before trial entry. The wash-out period before entry should be at least 5 half-lives of the previous drug to rule out any interference. This restriction does not apply if this comedication is part of the study protocol (eg, addition of an experimental treatment to the existing immunosuppression in refractory patients) or is given for other reasons (eg, low-dose GC given for asthma in CSS), but the dosage should be stable and should not be changed at least 2 weeks before 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 whether pneumocystis carinii prophylaxis with low-dose trimethoprim–sulphamethoxazole was given as full dosage if this drug 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).

Biomarkers

Biomarkers relating to diagnosis

- Generic points to consider

ANCA directed against PR3 and MPO are diagnostic markers for generalised WG and MPA, respectively. Therefore, determination of ANCA is recommended for classification of patients with medium-and small-vessel vasculitis in clinical trials. Biomarkers that characterise other forms of vasculitis include quantitative tests for hepatitis C virus and circulating cryoglobulins in cryoglobulinaemic vasculitis, and HBV serology in HBV-associated PAN.

- 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 having the typical clinical or histomorphological features of WG.[80] Thus, a diagnosis based solely on the ANCA subtype may lead to misclassification. ANCA should be determined by both indirect immunofluorescence testing and ELISA, since determination with immunofluorescence testing alone is too non-specific and commercially available ELISA kits show large variations in terms of sensitivity and specificity.[81] Given the variations in results of ANCA testing between different laboratories,[82] analysis in a central laboratory is recommended, if this is feasible. Patients with localised WG are ANCA-positive in only 50% of cases. Even patients with generalised WG may be ANCA-negative or may show anti-MPO-ANCA positivity. There is some evidence that these ANCA-negative or anti-MPO/P-ANCA-positive patients represent clinically distinct subtypes[83] 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 are 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 (boxes 2 and 3).

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 3 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 before the first study visit. Although non-specific, an increase in ESR and/or CRP levels in patients reporting new symptoms that may be related to but are not specific for a relapse (eg, 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

Box 2: Recommendations for eligibility criteria for clinical trials in primary systemic vasculitis

- A diagnosis of vasculitis on the basis of a compatible clinical picture and histopathology or surrogate parameters
- Definition of the type of vasculitis according to published criteria by using CHCC definitions and/or ACR classification criteria
- Definition of disease stage(s) of eligible patients (eg, localised/generalised)
- Definition of activity states (eg, refractory or relapsing)
- Definition of other patient characteristics
  - Newly diagnosed or previously treated?
  - Type and duration of previous immunosuppressive therapy (previously treated patients only)
  - Demographic details
  - Serologic status (eg, ANCA +/−, anti-MPO vs anti-PR3)

Notes: ACR, American College of Rheumatology; CHCC, Chapel Hill Consensus Conference; MPO, myeloperoxidase; PR3, proteinase 3.

Box 3: Final set of recommendations for conducting clinical trials in systemic vasculitis based on both evidence and expert opinion

- For clinical trials or studies, patients with vasculitis should be categorised into clearly defined activity states. The following terms are recommended to use: remission, response, refractory disease and relapse; definitions for these activity states are provided (table 2). Grade of recommendation B.
- 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.
- 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 (eg, necrotising vasculitis, granulomatous inflammation, glomerulonephritis) should be listed as an inclusion criterion, but patients without confirmatory biopsy but with compatible clinical picture may also be included if either (1) specific investigations (angiography, MRI/CT imaging, neurophysiology) or surrogate parameters are strongly suggestive of vasculitis, glomerulonephritis and/or granuloma, and/or (2) 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.
- Given the high mortality of untreated systemic vasculitis, the use of placebo must in general be restricted as 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 (eg, WG and MPA) and distinct disease duration (eg, newly diagnosed and relapsing patients) if (1) identical treatment protocols are prescribed, (2) identical end points and outcome measures are used, (3) both combined and subgroup analyses are performed and reported, and (4) sufficient numbers of patients with each individual disease and subgroup are recruited for the relevant analyses. Grade of recommendation B.
- 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 such as 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.

Notes: AAV, anti-neutrophil cytoplasmic antibody-associated vasculitis; ANCA, anti-neutrophil cytoplasmic antibody; ACR, American College of Rheumatology; CHCC, Chapel Hill Consensus Conference; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase 3; WG, Wegener's granulomatosis.

or activity, and must always be interpreted in the clinical context; potential interfering factors such as intercurrent infections and variable dosing of GC before study enrolment must be considered. Despite these limitations, serial determinations of acute-phase reactants are recommended in any study on 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.[84] Considerable differences in study methodology precluded quantitative meta-analytic calculations. In line with previous reviews,[80 85] 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 to obtain more valid data on the prognostic value of serial ANCA measurements. Serial ANCA measurements are particularly important in studies evaluating treatments that directly aim to reduce circulating ANCA levels (eg, anti-B cell treatment, 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 (ie, early glomerular vs tubular proteins) can be a helpful additional surrogate parameter for the serial evaluation of glomerulonephritis.[86] A prospective analysis of 96 patients with AAV and moderate renal involvement has shown that the GFR at baseline is the most potent predictor of renal function apart from histological features.[87] Recently, the Kidney Disease Quality Outcome Initiative (K/DOQI) recommended a consensus definition and classification for chronic kidney disease which is based on the GFR.[88] The K/DOQI defined chronic kidney disease by consensus as a GFR of <60 ml/min/1.73 m for $\geqslant 3$ months.[88] GFR can be estimated from calibrated serum creatinine and estimating equations, such as the Modification of Diet in Renal Disease study equation or the Cockroft–Gault formula.[88 89] 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 are however, data from observational and cohort studies implicating ANCA as a 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

The present recommendations, summarised in box 3 were developed following the EULAR standardised operating procedures for the elaboration, evaluation, dissemination and

implementation of recommendations.[5 6] The steering group intended 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 generalised 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, because even the trials which studied only patients with AAV were heterogeneous in many methodological aspects (eg, 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 summarised in a research agenda (box 1).

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 5 years from publication.

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