Vasculitis and SLE

Why we need guidelines for clinical trials in vasculitis and systemic lupus erythematosus

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The systemic vasculitides and systemic lupus erythematosus (SLE) are uncommon systemic rheumatic diseases. They have attracted increasing clinical trial activity, for which there is a need for international consensus and guidelines on clinical research methodology. There have been a number of relatively small studies of these diseases. Unfortunately, these have had varying design, outcome and assessment measures, thus it is difficult to interpret the evidence or subject it to a meta-analysis, and this has resulted in considerable uncertainty—for example, in deciding the role and dosing of cyclophosphamide in vasculitis or SLE.[1–4] Standardisation of the methodology for conducting clinical trials facilitates recruitment of patients into larger multicentre studies, which are likely to include non-expert centres, because of the low incidence and prevalence of cases. There is increasing involvement by the pharmaceutical industry in clinical trials of SLE and vasculitis. These companies will also need guidelines on which to base their trial protocols. Furthermore, standardisation allows for future inter-trial comparisons and meta-analysis of separately conducted studies. The purpose of this editorial is to highlight the existence of a new set of recommendations to improve the conduct of clinical trials in vasculitis and SLE.

The vasculitis and SLE working groups of the European League Against Rheumatism (EULAR) Standing Committee on International Clinical Studies Including Therapeutic Trials (ESCISIT) have developed guidelines based on current evidence.[5 6] In the absence of evidence, expert consensus has formed the basis of some of the recommendations. In a review of 370 separate clinical studies of antineutrophil cytoplasmic antibody-associated systemic vasculitis (AASV) and polyarteritis nodosa, only 42 had sufficient consistency to allow comparison between trials.[6] These 42 papers were analysed and form the basis for the current guidelines in vasculitis. Each guideline has been reviewed by the ESCICIT committee. The guidelines emphasise the need for collaboration and standardization of terminology and assessment in clinical trials. They also acknowledge the lack of diagnostic criteria in vasculitis and highlight the need for clear definitions of disease states (Table 1). The measurement and documentation of disease activity and disease-related damage should be standardised, using validated assessment tools to compare the efficacy of trial interventions or measure long-term morbidity in observational studies. This is especially important because of the absence of valid biomarkers to reflect disease activity in SLE and AASV. Standardisation of concomitant therapy with steroids or other drugs such as angiotensin-converting enzyme inhibitors and trimethoprim/sulfamethoxazole is important and is highlighted in both sets of guidelines. Many studies of vasculitis include mixed cohorts with different diagnostic subgroupings of vasculitis. Similarly, in SLE, patients may have variable organ involvement. In these circumstances, the recommendations suggest that common endpoints should be identified and that the trial is powered adequately to perform subgroup analyses. Both sets of guidelines stress the importance of long-term observation, as the likelihood of relapse in these diseases can only be appreciated over years rather than months. For example, a follow-up period of 5 years for a remission maintenance study in vasculitis has been recommended, where practical.

The lack of valid biomarkers in vasculitis and SLE mean that clinical assessment tools are relied upon for assessment of disease activity and damage. These clinical tools (eg Birmingham Vasculitis Activity Score (BVAS), BVAS for Wegener's granulomatosis, Vasculitis Damage Index, Systemic Lupus Erythematosus Disease Activity Index, British Isles Lupus Assessment Group Index, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Index), required trained personnel for appropriate use. With increasing recruitment of patients from non-expert centres, such training is desirable before trial recruitment is commenced. It may also be desirable that the recruitment of patients to clinical trials and their assessment should be performed by doctors rather than allied health professionals, as most nurses and physician assistants do not have sufficient experience to differentiate disease activity from other comorbidities such as infection and malignancy.

There is a need to consider pharmacoeconomic outcome measures in clinical trials, especially if biological agents are to be evaluated. The economic cost of the intervention should be balanced against the costs of treating ongoing chronic low-grade morbidity with current (less expensive) treatments that are likely to have lower efficacy and/or greater toxicity than the new intervention. We would encourage future studies to include a pharmacoeconomic aspect so that the use of potentially expensive agents can be justified by demonstrating cost-effective improvements in disease activity, quality of life and lower toxicity. However, we recognise there is little current experience of pharmacoeconomic evaluation in these diseases.

The development of recommendations for clinical trials might be seen as limiting or as forcing a change in practice. Individual groups might perceive the guidance as a way of undermining professional autonomy by making individual

Table 1 Definitions of clinical states of ANCA-associated vasculitis used in EUVAS trials

Clinical subgroup	Definition
Localised	Upper and/or lower respiratory tract disease without any other systemic involvement or constitutional symptoms
Early systemic	Any, without organ-threatening or life-threatening disease
Generalised	Renal or other organ-threatening disease, serum creatinine <500 μmol/l
Severe	Renal or other vital organ failure, serum creatinine >500 μmol/l
Refractory	Progressive disease unresponsive to glucocorticoids and cyclophosphamide

ANCA, antineutrophil cytoplasmic antibody; EUVAS, European Vasculitis study group.

Table 2 Examples of application of standardisation in clinical trials of vasculitis and SLE (this is not an exhaustive list).

Recommendations	Vasculitis	SLE
Classification: apply standard classification criteria	Chapel Hill consensus definitions or ACR classification criteria for vasculitis[8 9]	ARA classification criteria for SLE[10]
Staging/severity/eligibility: apply standardised structured clinical evaluation	BVAS, BVAS/WG, DEI, VDI[11–14]	BILAG Index, SLEDAI , SLICC/ACR Index[15–17]
Outcome measures: clinical evaluation of disease activity and damage, quality of life and economic impact	BVAS, BVAS/WG, DEI, VDI, SF36, QALY assessment[11–14 18]	BILAG Index, SLEDAI, SLICC/ACR Index, SF36, QALY assessment[15–18]
Biomarkers*: serological assessment of disease	ANCA, CRP, renal function	dsDNA, complement, renal function
Relapse/remission/refractory disease definitions: based on standardised clinical evaluation and qualified by use of ongoing therapy	BVAS, BVAS/WG, DEI[12–14]	BILAG Index, SLEDAI[15 16]
Immunosuppressive therapy: standardise	Standard or biological therapy, placebo where indicated	Standard or biological therapy, placebo where indicated
Steroid therapy: standardise	Dose and method of administration	Dose and method of administration
Concomitant therapy: standardise	Trimethoprim/sulfamethoxazole	ACE inhibitors

ACE, angiotensin-converting enzyme; ANCA, antineutrophil cytoplasmic antibody; ARA, American Rheumatism Association; BILAG Index, British Isles Lupus Assessment Group Index; BVAS, Birmingham Vasculitis Activity Score; BVAS/WG, Birmingham Vasculitis Activity Score for Wegener's Granulomatosis; CRP, C reactive protein; DEI, Disease Extent Index; dsDNA, double-stranded DNA; IV, intravenous; QALY, quality-adjusted life year; SF36, Short Form 36; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SLICC/ACR, Systemic Lupus International Collaborating Clinics/American College Of Rheumatology; VDI, Vasculitis Damage Index.
*We recommend that these investigations are performed routinely as part of clinical protocol but cannot be used on their own to guide therapy unless the trial design is aimed at testing the validity of these markers.

researchers accountable for their failure to adhere to the guidelines.[7] In reality, the guidelines are meant to function as a readily available framework, which is based on a firm evidence base or widespread expert consensus, around which a clinical trial could be designed (Table 2). We recognise that many international experts will have not been involved in the formation of these guidelines, and welcome their views and any evidence-based improvements they can make to any future versions of these guidelines. There are numerous barriers to implementing any guideline, including excess paperwork and time, a lack of ownership of the individual guideline and a requirement to change established patterns of practice.

Widespread availability of the EULAR Guidelines through publication in *Annals of the Rheumatic Diseases* and their accompanying editorials will allow access by doctors and academics. This is an important step towards their implementation, and should assist in their subsequent improvement. Uptake of the guidelines will be vital to their development, and we would encourage all health professionals involved in caring for patients and conducting clinical trials to make use of them. It is inevitable that these guidelines will have to be modified with evolving therapies and better quality of evidence. Future trials based on these guidelines will highlight the limitations of the guidelines themselves and in turn lead to an improvement in the standard of the guidelines. We hope that researchers involved in current and future studies of systemic vasculitis and SLE will find the guidelines of use in their everyday practice.

Ann Rheum Dis 2007;**66**:569–570.
doi: 10.1136/ard.2006.065854

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Accepted 6 February 2007

Competing interests: None declared.

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