Disease-specific quality indicators, guidelines, and outcome measures in vasculitis

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Abbreviations:

AAV:	ANCA-associated vasculitis
ANCA:	anti-neutrophil cytoplasm antibody
BVAS:	Birmingham Vasculitis Activity Score
C-ANCA:	cytoplasmic ANCA
CI:	confidence interval
CSS:	Churg-Strauss syndrome
DEI:	disease extent index
EULAR:	European League Against Rheumatism
EUVAS:	European Vasculitis Study group
HR:	hazard ratio
MPA:	microscopic polyangiitis
OR:	odds ratio
PR3:	proteinase 3
RH:	relative hazard
RR:	relative risk
VDI:	vasculitis damage index
WG:	Wegener's granulomatosis

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ABSTRACT

Measuring quality of care in the anti neutrophil cytoplasm antibody (ANCA) associated vasculitides (AAV) has become more complex, because the introduction of immunosuppressive therapy has resulted in a substantial improvement in survival. Early diagnosis remains a problem, because many patients are seen by non-specialists who may not recognize vasculitis or fail to initiate therapy promptly. A comprehensive assessment to determine the pattern and severity of organ involvement allows a specialist to plan a therapeutic regimen, and to manage co-morbidity effectively. Recent guidelines from the European League Against Rheumatism (EULAR) address the conduct of high-quality clinical trials in vasculitis.

Risk factors for poor outcome in vasculitis are probably similar in the different forms of AAV. The risk factors are discussed in the context of failing to achieve remission, relapse, organ failure, and death. Factors indicating a poor prognosis include: the presence of high disease activity at diagnosis (which increases mortality risk even though it is associated with a greater likelihood of response to therapy); the pattern of organ involvement, for example with cardiac features carrying an adverse outcome in Wegener's granulomatosis; significant damage; renal impairment; persistence of ANCA; elderly age at diagnosis; under-use of cyclophosphamide and glucocorticoids in the first 3 months of treatment; persistent nasal carriage of Staphylococcus aureus*; and the increased risk of bladder cancer in patients who are given large amounts of cyclophosphamide.*

Introduction

The vasculitides are a heterogeneous group of conditions united by their capacity to produce inflammation with or without necrosis of the vessel wall, leading to vaso-occlusion, and/or stenosis, and/or aneurysm formation. The primary vasculitides are commonly classified into broad categories based on the size of the smallest caliber of vessel involved (1). The association with antibodies directed against myeloperoxidase or proteinase 3 in neutrophil cytoplasm (ANCA) defines an important sub-group of small vessel vasculitides (2). Management of small vessel vasculitis is based upon clinical trials in ANCA-associated vasculitis (AAV); we will concentrate on Wegener's granulomatosis (WG), microscopic polyangiitis (MPA) and Churg-Strauss Syndrome (CSS) in this chapter.

Defining disease-specific quality indicators and management guidelines for the management of vasculitis has been challenging for several reasons:

1. The incidence of primary systemic vasculitis is 40 to 54 per million per year (3). The incidence of AAV is 9.5 to 17 per million per year (3-5). The rarity of these conditions contributes to delays in diagnosis and has precluded large single-centre clinical trials.
2. Clinical trials have included heterogeneous cohorts, but often without disease-specific sub-analysis. Different vasculitides have been regarded as similar or single entities, rendering data difficult to analyze.
3. Definitions of outcomes in the clinical trials often have been variable, *e.g.*, remission and relapse have meant different things in different clinical trials, often producing substantially different interpretations of results (6, 7).

The above obstacles to producing a quality framework for the care of vasculitis, are being addressed in collaborative clinical trials by the European Vasculitis Study group (EUVAS) (8). We have recently published European League Against Rheumatism (EULAR) guidelines on the conduct of clinical

trials in vasculitis, and their application should improve comparison across clinical trials (9). The British Society for Rheumatology and EULAR are independently engaged in the production of guidelines for management of the primary systemic vasculitides, which may become the benchmarks for the quality of care in vasculitis.

Quality control is an important aspect of all interventions and management of complex multi-system disease, especially if potentially toxic immunosuppression is used. Some of the issues are summarized in Table I.

This paper reviews disease-specific data concerning quality indicators, guidelines and outcome measures in vasculitis.

Current status of clinical outcomes and factors affecting them

Remission

Remission of disease activity is achievable for most patients with current therapeutic regimens. The lack of uniformity in the definition of remission does not allow comparison across studies (Table II). The EULAR/EUVAS group has defined remission and other disease states for use in future clinical trials and studies (9)

Disease-specific remission rates in AAV are variable, as shown in Figure 1, but remission can be achieved in up to 90% of patients. Some factors influencing the rate of remission are as follows:

1. Variation in the definition of remission (Table II): With a stringent definition (absence of disease activity for 6 months without maintenance glucocorticoid therapy), the remission rate was 30% (6). When remission was defined as being sustained for 3 months without needing to stop maintenance glucocorticoid therapy, the remission rate was 54% (7).
2. Cohort inclusion or exclusion criteria: The methotrexate arm of a randomized controlled trial (RCT) comparing methotrexate to cyclophosphamide for remission induction in WG achieved a remission rate of 90% (16). This trial excluded patients with a serum creatinine >150 μmol/l (1.69 mg/dl). An open-label study using the combination of methotrexate and glucocorticoid in patients with WG, including active renal disease (serum creatinine up to 2.5 mg/dl), recorded a remission rate of 71% (11). These results cannot be compared directly and highlight the importance of disease staging, which must be considered when comparing results (21).
3. Disease-related factors
   (a) High disease activity: When stratified for disease activity, as measured by the Birmingham Vasculitis Activity Score (BVAS) (22), high disease activity (BVAS >23) was associated with an increased likelihood of remission [relative hazard (RH) 2.94; 95% confidence interval (CI) 1.48 to 5.85] (15). This may be due to the increased responsiveness of active disease to treatment. High disease activity is also associated with poor survival (22, 23). These two findings are not mutually incompatible; for example, renal involvement is more likely to result in mortality than nasal involvement, but is more amenable to treatment.
   (b) The presence of damage, as measured by the vasculitis damage index (VDI), reduces the likelihood of remission [odds ratio (OR) 1.53; 95% CI 1.03 to 2.27] (15). Damage may reduce responsiveness to treatment; equally, it might confound the accurate assessment of disease activity. For example, the presence of a chronic non-healing ulcer for more than 3 months should be considered as damage, but may be misconstrued as active disease even in the absence of other evidence of activity.

Relapse

Relapse is common in AAV. Disease-specific relapse rates from various studies are shown in Figure 2; different remission maintenance regimens were used in each study (10-12, 15, 20, 24-35). The graph shows a general trend of increasing relapse with time. This supports the prolonged use of a remission maintenance regimen. Long-term use of cyclophosphamide has been associated with substantial drug toxicity, especially the development of bladder carcinoma (36). With safer remission maintenance regimens including azathioprine, methotrexate, leflunomide and mycophenolate mofetil, long-term remission maintenance therapy is possible (29, 30, 37, 38). Figure 2 suggests that patients with WG may have a higher relapse rate than those with MPA. In a prospective RCT, patients with WG relapsed more frequently than those with MPA (18% *vs.* 4%, respectively; $p = 0.03$) at 18 months (30).

In WG, several factors predispose to an earlier relapse. Awareness of some of these risk factors may have therapeutic utility.

1. Treatment: Using high dose cyclophosphamide (> 10 g as compared with ≤ 10 g) in the first 6 months is associated with an increased likelihood of relapse [relative risk (RR) 2.83; 95% CI 1.33 to 6.02] (15). Short-term use of high-dose glucocorticoid therapy (prednisolone >20 mg/day for a period of less than 12 weeks as compared with ≥ 12 weeks) increased the risk of a subsequent relapse (RH 2.41; 95% CI 1.12 to 5.21) (15). Both of these findings support the current practice of initial high-intensity therapy.

   The use of trimethoprim/sulfamethoxazole as adjunctive remission maintenance therapy is associated with protection against relapse (RR

Table I. Quality of care issues in systemic vasculitis.

- Is the diagnosis being made early and correctly?
- Are patients being evaluated in a standardized way?
- Is the most appropriate regimen being offered?
- Are complications being managed?
- Is co-morbidity being screened for?
- Is drug monitoring being performed?
- Are patients receiving appropriate counseling and education?
- Is the functional outcome and/or patient satisfaction being assessed?
- Is the management being conducted at, or in collaboration with, expert centers?
- Are physicians maintaining their expertise?

Table II. Definitions of remission used in studies of WG, as qualified by the use of a clinical assessment tool, the sustaining of remission over time, and the prednisolone dose.

Study	Definition	Clinical tool	Time factor	Prednisolone dose
Hoffman 1992 (10)	Absence of active disease	None	Unrestricted	Unrestricted
Reinhold-Keller 1994 (6)	Absence of clinical, serologic, and radiologic (including MRI) evidence of disease activity. These conditions had to be sustained for at least 6 months after the discontinuation of pulse CYC treatment, without further immunosuppressive therapy, including withdrawal of prednisolone.	DEI	6 months	0 mg
Sneller 1995 (11)	Absence of active disease	None	Unrestricted	Unrestricted
Guillevin 1997 (12)	When the patient's general condition improved, no new manifestations of WG appeared, and the ESR returned to normal.	None	Unrestricted	Unrestricted
Aasarod 2000 (13)	A state with no sign of active vasculitic disease and complete resolution of pulmonary infiltrates, improvement of renal function, and resolution of extra-renal manifestations of vasculitis.	None	Unrestricted	Unrestricted
Reinhold-Keller 2000 (7)	Absence of pathologic findings, irrespective of ANCA titer	DEI	3 months	Unrestricted
Koldingsnes 2003 (15)	Absence of active disease, complete resolution of pulmonary infiltrates or evidence of stable scarring, absence of systemic inflammatory disease such as serositis and fever, and stabilization or improvement in renal function without active urinary sediment.	None	1 month	Unrestricted
De Groot 2005 (16)	Absence of new or worse clinical activity; minor persistent activity allowed	BVAS 1 = 0; BVAS 2 ≤ 2	Unrestricted	Unrestricted

BVAS: Birmingham Vasculitis Activity Score; CYC: cyclophosphamide; DEI: Disease Extent Index; ESR: erythrocyte sedimentation rate; WG: Wegener's granulomatosis.

0.32; 95% CI 0.13 to 0.79) (25). The use of trimethoprim/sulfamethoxazole as monotherapy for remission maintenance compares unfavorably with the current standard of azathioprine (24, 30).

2. ANCA: The presence of ANCA at diagnosis confers an increased risk of relapse in WG (RR 2.89; 95% CI 1.12 to 7.45) (25). A 4-fold rise in cytoplasmic (C)/proteinase 3 (PR3) ANCA is the strongest known predictor of subsequent relapse (RR 42.5; 95% CI 9.48 to 180.8) (27). The persistence or reappearance of ANCA should be considered when deciding the longevity of remission maintenance therapy, although this remains controversial (39).
3. Other disease-specific risk factors for relapse of WG: Cardiac involvement increases the risk of relapse (RH 2.87; 95% CI 1.09 to 7.58; $p = 0.03$) (15). A creatinine clearance >60 ml/min is associated with an increased risk of relapse (RR 2.94; 95% CI 1.27 to 6.67; $p = 0.01$) (40). This may be due to a predominance of relapse in patients without renal involvement, who are towards the granulomatous end of the disease spectrum. Chronic nasal carriage of *Staphylococcus aureus* is an independent risk factor for relapse (RR 7.16; 95% CI 1.63 to 31.50; $p = 0.009$) (40). The presence of low-grade infection and inflammation, as provided by nasal carriage of *S. aureus*, may present a nidus for PR3 ANCA activation, as suggested in animal models (41).

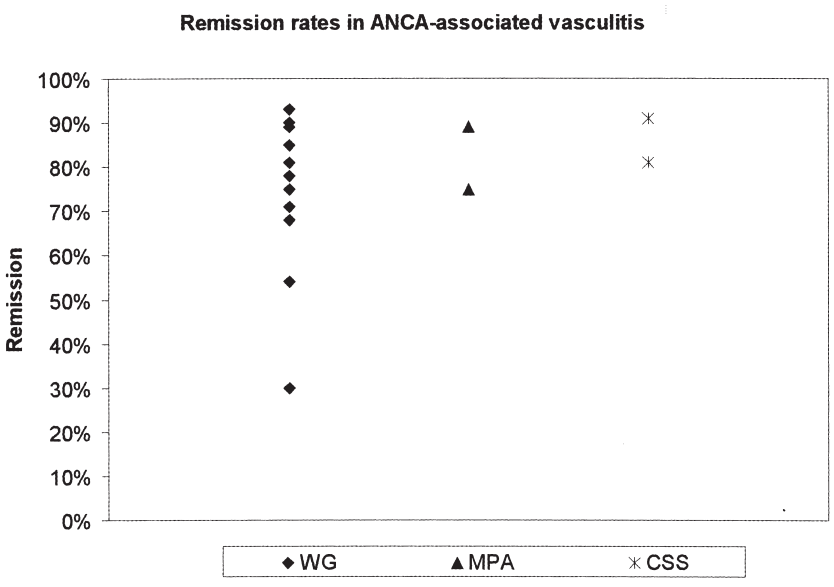

Fig. 1. Remission rates in ANCA-associated vasculitis (AAV) (6, 7, 10-20).
(CSS: Churg-Strauss syndrome; MPA: microscopic polyangiitis; WG: Wegener's granulomatosis).

Renal involvement

Renal involvement is more common in WG (54%) and MPA (79%) than in CSS (26%) (7, 20, 33). The 5-year renal survival in WG is 14% to 25% (13, 42). Renal involvement predicts poor survival in all three AAV (7, 20, 43, 44). Patients with WG have a better survival as compared to MPA until the onset of renal failure (45-47). Factors that appear to predict poor renal survival in WG are increasing age at presentation [Hazard Ratio (HR) 1.47 for every decade rise; 95% CI 0.95 to 2.24; $p = 0.08$] and impaired renal function, defined as: dialysis dependence at diagnosis (RR 3.3; 95% CI 1.3 to 8.8; $p = 0.001$), a rise in serum creatinine of 100 μmol/l (HR 1.35; 95% CI 1.11 to 1.49; $p = 0.001$) or a rise in 24-hour urinary proteinuria of 1 g (HR 1.50; 95% CI 1.08 to 2.07; $p = 0.02$) (13, 42). It may seem obvious that poor renal function predicts subsequent renal outcome, but it serves to stress the importance of early diagnosis and therapy before significant kidney disease becomes established.

Malignancy

The use of cyclophosphamide is associated with a high risk of developing bladder cancer (7, 36, 48). Recent data suggest a higher risk of bladder neoplasm and other solid tumors prior to the diagnosis of WG and use of cyclophosphamide (49, 50). A retrospective study in the UK demonstrated a 6-fold rise in the risk of developing any cancer within 6 months of diagnosis of WG/MPA (51).

Damage

Damage is the irreversible burden of disease that does not respond to treatment. Damage has been an outcome in clinical trials of vasculitis, but never a primary outcome (30, 52). Damage accumulation can start early, and in WG increasing VDI increases the resistance to treatment and worsens survival (15, 42, 53). In two trials that have collected damage data as measured by the VDI, the mean score at baseline was 1.3 in both (30, 52). Also, in both trials the VDI rose: to 1.8 (mean) at 12 months in one trial (30) and to 2.5 (mean) at 18 months in the second (52).

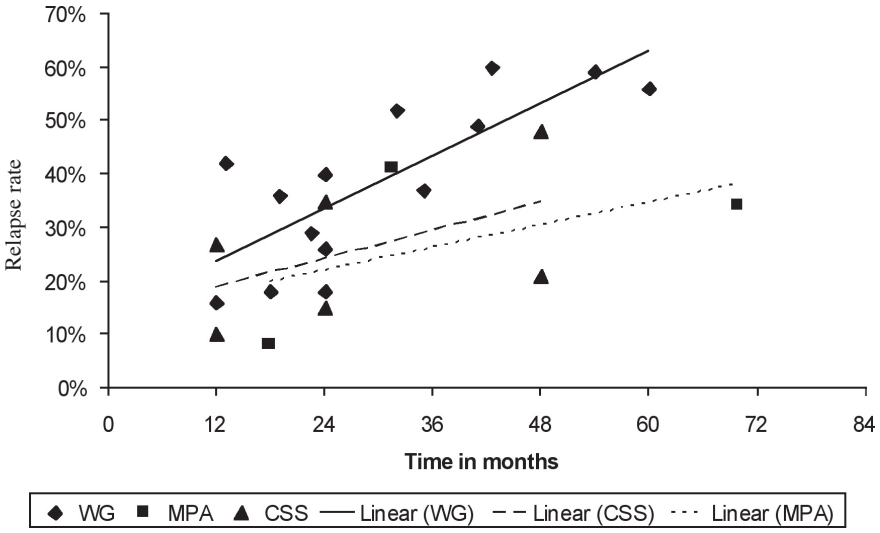

Fig. 2. Disease-specific relapse rates for WG, MPA and CSS. The time (months) on the x-axis corresponds to the follow-up of the cohort, not the mean time to relapse (10-12, 15, 20, 24-35). The three trend lines are based on the data from sepa.rate studies and cannot be compared.

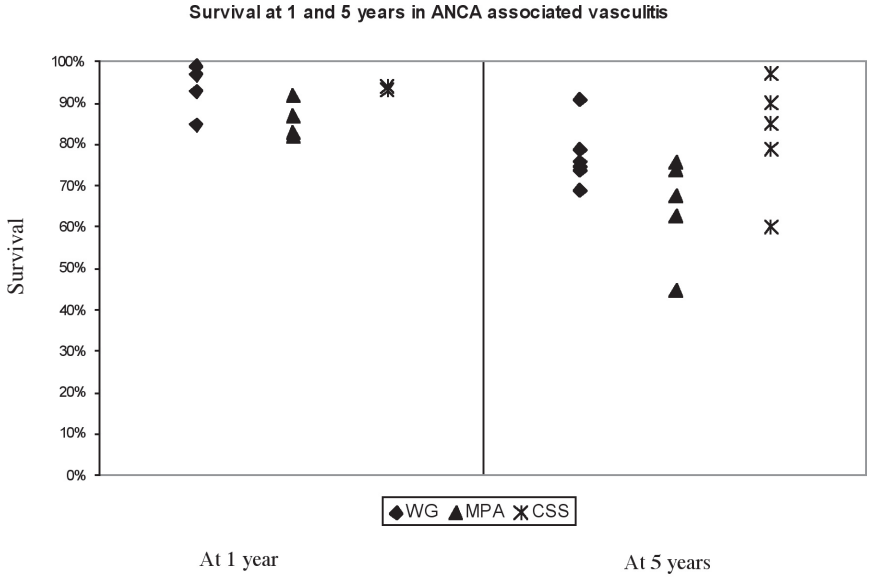

Fig. 3. Survival at 1 and 5 years in ANCA-associated vasculitis. WG: 1-year data from 4 studies including 398 patients, published between 1989–2002 (7, 14, 42, 57); 5-year data from 7 studies including 484 patients, published between 1989–2006 (13, 42, 43, 46, 47, 57, 58). MPA: 1-year data from 4 studies including 252 patients, published between 2000–2006 (34, 44, 46, 47); 5-year data from 5 studies including 217 patients, published between 1999–2006 (33, 34, 46, 47, 58). CSS: 1-year data from 2 studies including 165 patients, published in 2001 and 2005 (19, 44); 5-year data from 5 studies including 187 patients, published between 1998–2002 (19, 20, 59-61).

Survival

The short-term outlook for untreated primary systemic vasculitis is poor. Untreated WG has a mortality of 83% at 1 year (54). WG is associated with a 4-fold higher mortality rate as compared to the general population (13). Similar data are not available for MPA and CSS, but patients with MPA seem to be more likely to die than patients with WG. In two separate studies, the 5-year survival in patients with WG was better than in MPA: 76% *vs.* 45% ($p = 0.02$) and 91.5% *vs.* 63% ($p < 0.01$) (46, 47). In a third study, patients with WG had higher mortality than patients with MPA, with a relative risk of 1.917 (95% CI 1.075 to 3.419; $p = 0.025$) (55). Survival in primary systemic vasculitis has improved as a re-

sult of better therapeutic regimens, the most important change being the use of cyclophosphamide and glucocorticoid combination therapy for remission induction (56). The disease-specific survival of ANCA-associated vasculitis is shown in Figure 3.

Disease-specific data for WG indicate several factors associated with higher mortality:

1. Age: Rising age increases the risk of WG-related mortality (42). In two separate studies, older age at disease onset was an independent risk factor for death: >50 years, HR 3.4 (95% CI 1.03 to 11.21; $p = 0.04$); and >52 years, HR 5.73 (95% CI 2.07 to 15.85) (7, 43). These studies did not include a control group.
2. Target organ involvement
   (a) Renal disease: The need for dialysis at diagnosis (HR 8.2; 95% CI 2.03 to 33.11; $p = 0.003$), the presence of impaired renal function (HR 5.10; 95% CI 1.59 to 10.16), and any renal involvement (HR 4.45; 95% CI 1.48 to 13.65) are associated with adverse survival (7, 42).
   (b) The presence of lung involvement may be an independent risk factor for mortality, but there are contradictory data (7, 43). A possible explanation for this discrepancy could be the type of lung disease in each study. In the report of Reinhold-Keller *et al*. (7), two-thirds of the patients with lung involvement had infiltrates and were at an increased risk of dying (HR 3.58; 95% CI 1.15 to 11.11). In contrast, Bligny *et al*. (43) reported that most patients with pulmonary involvement had either nodules or pneumonic consolidation and there was no association between lung involvement and mortality. If infiltrates represent the vasculitic end of the spectrum of WG and round shadows represent the granulomatous end, then this discrepancy can be explained. Vasculitis is more likely to be acute in presentation, and life-threatening, but more amenable to treatment. Granulomatous disease is more likely to be indolent in its presentation, "grumbling" and more likely to relapse (62). The presence of upper respiratory tract involvement in WG is associated with protection against mortality (HR 0.31; 95% CI 0.11 to 0.84; $p = 0.02$) (43).
3. Damage: In a retrospective study, the presence of even minimal damage, defined as VDI >1, substantially increased the risk of mortality (HR 5.54; 95% CI 1.28 to 24.05; $p = 0.022$) (42, 63).

Renal insufficiency is a risk factor for mortality in MPA (HR 3.69, 95% CI 1.006 to 13.4), and in CSS it is included in the five-factor score (FFS) for poor prognosis (44, 64). The components of the FFS are: proteinuria >1 g/day; serum creatinine >1.58 mg/dl; gastrointestinal involvement; cardiomyopathy; and neurological involvement. FFS >2 is associated with an increased risk of mortality in CSS (RR 1.36; 95% CI 1.10 to 1.62; $p < 0.001$) and, conversely the absence of poor prognostic markers (FFS = 0) confers a better prognosis (RR 0.52; 95% CI 0.42 to 0.62; $p < 0.03$) (20). Cardiomyopathy is independently validated as a poor prognostic marker for CSS (HR 3.39; 95% CI 1.6 to 7.3) (44).

Identified factors affecting survival are derived from cohort studies, many of which are retrospective. The data have been subjected to multivariate analysis, but it is important to test their replication in prospective cohort studies.

Disease-specific quality indicators

Diagnosis

In the presence of vasculitis-related symptoms such as purpura, mononeuritis multiplex, ulcer, or upper respiratory involvement, pattern recognition is important for characterizing the vasculitis. In the absence of diagnostic criteria, classification criteria have been used to make the diagnosis (65). It is important to recognize the limitations of classification criteria; an absence of some criteria does not rule out a diagnosis of vasculitis (66). Early diagnosis and treatment of vasculitis is important in order to limit the amount of irreversible damage, which can often commence early in the disease (53). When possible, histological evidence of vasculitis should be sought prior to the onset of treatment.

Clinical evaluation

In small vessel vasculitis, the myriad of manifestations indicates the multi-system nature of the disease and the patient may present to any number of different specialists. A structured physical examination must be performed at each evaluation. It is possible for new organ systems to be involved late in the disease, and multidisciplinary input over a prolonged period of time will allow the early recognition of new organ-system involvement (7). The BVAS form is a list of all the important features of systemic vasculitis, and is widely used in clinical trials. While the list may seem daunting at first glance, it contains a distillation of expert knowledge in the clinical care of patients with vasculitis, and is particularly helpful to those with less experience in managing vasculitis. It is a valuable *aide memoire* of items to be assessed at each visit.

Choice and timing of therapy

There is strong evidence in favor of using a combination of cyclophosphamide and glucocorticoid to induce remission in WG (10, 12). Treatment for MPA and CSS is based on evidence from clinical trials of WG and other trials including mixed cohorts (Table II). In patients who do not have organ- or life-threatening disease, methotrexate is a suitable alternative to cyclophosphamide, with the caveat that it may take longer to induce remission (16). Azathioprine or methotrexate are suitable options for the maintenance of immunosuppression following induction of remission (29, 30). The exact regimens are discussed below.

Therapy should be commenced as early as possible after the diagnosis has been established. Patients must be counselled prior to commencing immunosuppression, especially with regard to the risk of bladder complications and sterility in the case of cyclophosphamide, and osteoporosis in the case of glucocorticoid therapy. When appropriate, sperm storage should be organized prior to the commencement of cyclophosphamide.

Adjunctive therapy

Prophylaxis against *Pneumocystis jiroveci*: Although no RCTs have been reported to date, prophylaxis against *P. jiroveci* is widely practiced using trimethoprim/sulfamethoxazole (800/160 mg three times a week) for the duration of cyclophosphamide treatment (16, 30). An economic analysis in an artificial neural network suggests that it is cost-effective to use TMP/SMX in the above dose (67). In this analysis, a hypothetical cohort of patients with WG was followed up over their lifetimes. Three treatment strategies were employed consisting of: no prophylaxis; TMP/SMX 800/160 mg three times a week (stopped in the event of an adverse drug reaction); or the same treatment regimen of TMP/SMX but replaced with monthly aerosolized pentamidine 300 mg in the event of an adverse drug reaction. No prophylaxis resulted in a life expectancy of 13.36 quality-adjusted life years (QALY) at an average discounted lifetime cost of US$ 4,538. Prophylaxis with TMP/SMX alone increased the QALY to 13.54 and saved US$ 1,234. The addition of pentamidine marginally increased the life expectancy to 13.61 QALY, but at a further lifetime cost of US$ 2,890. Compared with TMP/SMX alone, TMP/SMX followed by pentamidine increased the QALY by 0.07 at an incremental cost of $58,037 per QALY (67).

Nasal *S. aureus* eradication: Chronic nasal carriage of *S. aureus* is thought to increase the risk of relapse (40), leading to the use of empirical therapy with topical mupirocin by some experts.

Bone protection: Many patients will continue on a long-term maintenance dose of glucocorticoids (30). Local guidelines regarding bone protection should be followed (68, 69).

Renal protection: Renal involvement is predictive of poor survival, as is progression to end stage renal failure (7, 20, 43, 44). Empirical renal protection with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers has been advocated, and we would support this practice.

Urothelial protection: The urothelial toxicity of cyclophosphamide is due to local irritation of the mucosa by metabolites of cyclophosphamide, which have the potential to cause haemorrhagic cystitis in the short and medium term and transitional cell carcinoma in the long term (36, 48). Mesna [2-Mercaptonethanesulfonate sodium (Na)] binds to the metabolites, converting them into harmless substances, and should be administered to all patients using the pulsed regimen of cyclophosphamide. Other simpler measures to protect the urothelium include ensuring adequate water intake on the day of the pulse, thus diluting the toxic metabolites.

Other quality indicators

Co-morbidity screening: Patients with systemic vasculitis should be screened for co-morbidities including hypertension, type 2 diabetes mellitus, osteoporosis, malignancy and cardiovascular disease (52, 53).

Drug monitoring: Immunomodulatory drugs require regular blood test monitoring for early detection of cytopaenia, liver and renal toxicity. In addition, all patients on cyclophosphamide must have urine analysis to detect non-glomerular haematuria, which may be due to cystitis.

Patient education and counselling: All patients undergoing treatment should receive education and counselling about the condition and the drugs being used. Issues such as sperm storage and family planning should also be addressed when relevant.

Centres of excellence: Patients should be managed in close collaboration with expert centres, and patients with refractory disease or needing specialist procedures (subglottic stenosis dilatation, arterial bypass grafting for Takayasu arteritis, etc.) should be referred to specialist centres. Development of standardized protocols and care pathways is to be encouraged and makes it easier for non-specialist centres to treat patients with vasculitis.

Continuing education of physicians: Physicians treating vasculitis have an obligation to maintain their expertise.

Feedback: Patient satisfaction surveys and assessment of the quality of life of patients have not been discussed in detail, but are being increasingly considered as a way of improving the clinical care for patients with vasculitis (70).

Management

Remission induction

There is good evidence for remission induction in WG. The evidence for the management of MPA and CSS is derived from heterogeneous cohorts without disease-specific sub-analysis, as well as extrapolation of our knowledge concerning WG. Remission induction with oral or intravenous cyclophosphamide combined with glucocorticoids is the standard of care in WG, and by default in MPA and CSS (56, 71). Controversies remain regarding the choice for the route of administration and the exact treatment regimen.

1. Cyclophosphamide
   (a) Oral *vs*. intravenous. Since the 1980s oral cyclophosphamide 2 mg/kg has been commonly used to induce remission in WG (56). In a RCT comparing pulsed high dose with continuous lower dose cyclophosphamide in WG, pulse therapy was at least as good for inducing remission as continuous therapy (12). The advantages of pulsed therapy include a lower incidence of adverse effects and a lower cumulative dose of cyclophosphamide. A meta-analysis comparing the two regimens, which included patients with MPA and WG, arrived at a similar conclusion (71).
   (b) Regimen for intravenous pulsed cyclophosphamide. In a RCT comparing intravenous cyclophosphamide (0.7 mg/m^2 three times per week) *vs*. oral therapy (2 mg/kg/day), the pulsed regimen had the same efficacy as the oral regimen, but an increased risk of relapse (12). This problem may be overcome by increasing the total dose administered in the first 6 months (15). Results of a RCT of oral *vs*. 2 to 3 weekly intravenous pulses will shortly be available (72).
   (c) Monitoring. Routine practice is to check blood and urine tests prior to pulse therapy; the dose is then adjusted downward or delayed in the event of neutropenia or haematuria. In the case of oral cyclophosphamide, monitoring should

be more intense in the initial stages of the treatment (weekly to bi-weekly) and then monthly. In the event of neutropenia or macroscopic haematuria, the dose must be either scaled down or withheld until the neutropenia is resolved and/or the cause of macroscopic haematuria is ascertained. All patients who have ever taken cyclophosphamide should have regular lifelong checks of their urine cytology, as bladder cancers can occur long after the discontinuation of therapy (36).

2. Glucocorticoids. Initially as monotherapy, and later in combination with immunosuppressive agents, glucocorticoids have been used to induce remission in WG since the 1950s (73).
   (a) Method of administration. Glucocorticoids have been used in three ways: initial intravenous pulsed methylprednisolone followed by tapering oral doses; oral therapy alone; and oral therapy punctuated by intervening intravenous pulsed therapy (usually at the same time as intravenous cyclophosphamide therapy). There is no evidence to suggest the superiority of one method over another.
   (b) Dose. Clinical trials have used prednisolone orally at a dose of 1 mg/kg for remission induction (16, 30, 31); Intravenous pulses have been given at a dose of 10 mg/kg. There is evidence that maintaining a high initial dose of prednisolone (>20 mg/day) for at least 12 weeks reduces the risk of relapse in WG (15). The maintenance dose of prednisolone following the onset of remission should be ≤10 mg/day (30). There are no data for the use of long-term low-dose glucocorticoids. In some instances, it may not be possible to wean patients off glucocorticoids completely, either due to the resurgence of vasculitic symptoms or due to suppression of the hypothalamo-pituitary axis.
3. Methotrexate. The use of methotrexate has previously been restricted to patients who did not have immediately life-threatening disease (11). In a recent trial, methotrexate (20 to 25 mg/kg/week) has been shown to be equal to cyclophosphamide (2 mg/kg/day orally) in its ability to induce remission in patients without significant renal involvement (16). The use of methotrexate in patients with severe renal disease is precluded by the nephrotoxicity of the drug (74).
4. Refractory disease. Patients who fail to respond to cyclophosphamide and methotrexate should be referred to centres with expertise in managing vasculitis. Alternative immunomodulatory treatments include 15-deoxyspergualin, infliximab, intravenous immunoglobulin, mycophenolate mofetil, plasma exchange and rituximab (75-80). A trial comparing plasma exchange *vs*. pulsed methyl prednisolone (in addition to cyclophosphamide and corticosteroid) in patients with severe renal involvement demonstrates the benefit of plasma exchange over methylprednisolone in improving renal survival in AAV (72).

Remission maintenance

The toxicity and neoplastic potential of cyclophosphamide has encouraged clinical investigation into safer remission maintenance therapies.

1. Azathioprine. In a RCT of azathioprine 2 mg/kg/day *vs*. oral cyclophosphamide 1.5 mg/kg/day, equal efficacy with lower adverse effects was demonstrated in the azathioprine arm (30). Azathioprine does not carry the neoplastic potential of cyclophosphamide, and can be used long-term for the maintenance of remission in AAV.
2. Alternative remission maintenance agents
   (a) Leflunomide. A RCT of leflunomide 30 mg/day *vs*. oral methotrexate shows a higher relapse rate with methotrexate than leflunomide (38).
   (b) Methotrexate. In an open-label follow-up study of patients with WG, the relapse rate of 52% at 32 months with oral methotrexate 20-25 mg/week appears to be comparable with other studies (29) (Fig. 2).
3. Length of remission maintenance therapy. Long-term remission maintenance therapy in other rheumatic disorders has not generally been a cause of concern. The use of a potentially carcinogenic drug in cyclophosphamide has meant that, traditionally, treatment has been stopped at some point of time after remission maintenance. The CYCAZAREM trial continued for 18 months, and the low relapse rates in that trial (18% for WG and 8% for MPA at 18 months) suggest that treatment should be continued for at least 18 months following the onset of remission, if not longer (30).

In this review, we have mainly discussed WG, because disease-specific evidence is lacking for MPA and CSS. There have been several RCTs that included patients with MPA and CSS, but disease-specific interpretation of the results has been difficult (Table III). There is evidence from cohort studies of the benefits of immunosuppression in MPA and CSS (20, 33).

Standards for clinical trials

The evidence base for the management of vasculitis remains unsatisfactory, due to the lack of standardized outcomes and conduct of clinical trials. Recently published guidelines (9) suggest the following points to consider in designing future clinical trials and studies in vasculitis:

1. Standardized definition of disease category, *e.g*., localized *vs*. generalised.
2. Standardized definition of disease state, *e.g*., remission as defined by a specified score on a validated clinical assessment tool, below a specified dose of prednisolone and maintained for a specified length of time.
3. Uniform method of clinical assessment with a validated clinical assessment tool, *e.g*., BVAS.
4. Performance of disease-specific subanalysis when the cohort contains a heterogeneous population.
5. Adequate testing of biomarkers, *e.g*., ANCA, at regular time points and at remission and relapse.

Table III. RCTs of MPA and CSS.

Trial	Patients	Intervention	Outcome	Conclusion
Jayne 2003 (30)	MPA – 60	AZA 2 mg/kg/day	Relapse rate 15.5 % at 18 months	The difference was not statistically significant. There was no disease-specific sub-analysis for each arm, but for the whole cohort the relapse rate was lower for MPA (8%) than for WG (18%) [p = 0.03].
	WG – 95	CYC 1.5 mg/kg/day	Relapse rate 13.7% at 18 months	
Guillevin 2003 (17)	PAN – 12 MPA – 19 (FFS > 0)	IV CYC 2 weekly for a month, then 4 weekly, for 6 pulses; no remission maintenance therapy (N = 31)	74% remission in MPA, 22% relapse at 3 years	There was no difference in the remission induction potential of 6 vs. 12 pulses [P = 0.73]. The relapse rate was higher in patients who were treated for less time [P = 0.02]. The dose of CYC was not specified.
	PAN – 6 MPA – 28 (FFS > 0)	IV CYC 2 weekly for a month, then 4 weekly, for 12 pulses; no remission maintenance therapy (N = 34)	86% remission in MPA, 66% relapse at 3 years	
Gayraud 1997 (81)	PAN + MPA (N = 6) CSS (N = 6) (FFS = 0)	Prednisolone 1 mg/kg/day + oral CYC 2 mg/kg/day for 12 months	75% sustained remission for 18 months at 61 months	Long-term sustained remission was possible with both therapies. No disease-specific subanalysis. For CSS the number of patients was too small to make any meaningful conclusions.
	PAN + MPA (N = 11) CSS (N = 2) (FFS = 0)	Prednisolone 1 mg/kg/day + intravenous CYC 0.6 g/m^2 monthly for 12 months	77% sustained remission for 18 months at 60 months	
Guillevin 1995 (82)	PAN, MPA, CSS (N = 28) (FFS > 0)	Prednisolone 1 mg/kg/day + intravenous CYC 0.6 g/m^2 for 12 months	57% sustained remission for 18 months	Both combinations could produce sustained remissions in this subset of patients. As survival at 5 years was equal in both groups, PE has no survival benefit over a combination of prednisolone and CYC. No disease-specific sub-analysis.
	PAN, MPA, CSS (N = 34) (FFS > 0)	Prednisolone 1 mg/kg/day + intravenous CYC 0.6 g/m^2 + PE for 12 months	65% sustained remission for 18 months	
Guillevin 1992 (83)	PAN, MPA, CSS (N = 36)	Prednisolone 1 mg/kg/day + PE	78% remission, 36% relapse	PE had no advantage as first-line therapy in comparison with glucocorticoid monotherapy in this subset of patients. No disease-specific sub-analysis.
	PAN, MPA, CSS (N = 42)	Prednisolone 1 mg/kg/day	83% remission, 23% relapse	
Guillevin 1991 (84)	PAN + HBV, MPA, CSS (N = 39)	Prednisolone 1 mg/kg/day + PE for 12 months	90% remission, 43% relapse	In this subset of patients the addition of CYC produced a significant reduction in relapse rates. No disease-specific sub-analysis.
	PAN + HBV, MPA, CSS (N = 32)	Prednisolone 1 mg/kg/day + PE + CYC 2 mg/kg/day for 12 months	94% remission, 10% relapse	

AZA: azathioprine; CSS: Churg-Strauss syndrome; CYC: cyclophosphamide; FFS: five-factor score; HBV: hepatitis B virus; IV: intravenous; MPA: microscopic polyangiitis; PAN: polyarteritis nodosa; PE: plasma exchange; WG: Wegener's granulomatosis.

Conclusions

Modern management of AAV has resulted in significantly improved survival; remission is achieved in 90% of all patients. There is a robust evidence base for the management of WG, but in light of the differences in the behaviour of WG and MPA, future trials should attempt disease-specific sub-analysis. Cyclophosphamide or methotrexate, each in combination with glucocorticoids, form the first-line therapy in patients with AAV, depending on the presence or absence of organ- or life-threatening disease. For patients who are refractory to these therapies, early referral should be considered to specialist centres for the possibility of enrolling them into clinical trials. The ongoing monitoring of patients is perhaps as important, if not more important, than the initial quick recognition and treatment of the disease. Relapse is an unfortunate reality of these conditions and the early recognition of relapsing disease is important to prevent morbidity and the accumulation of damage.

Structured clinical examination and a multidisciplinary assessment of these patients will assist in the early recognition of relapsing disease as well as complications of therapy, *e.g.*, osteoporosis, type 2 diabetes mellitus, etc. Patients treated with cyclophosphamide have developed bladder cancer many years after the cessation of therapy, and

urinary cytology monitoring is mandatory for these patients in the long term. With improving data emerging from collaborative clinical trials, these recommendations and quality benchmarks will require regular updating.

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