EDITOR'S CHOICE

Outcomes from studies of antineutrophil cytoplasm antibody associated vasculitis: a systematic review by the European League Against Rheumatism systemic vasculitis task force

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ABSTRACT

Objectives: We undertook a systematic literature review as a background to the European League Against Rheumatism (EULAR) recommendations for conducting clinical trials in anti-neutrophil cytoplasm antibody associated vasculitis (AAV), and to assess the quality of evidence for outcome measures in AAV.

Methods: Using a systematic Medline search, we categorised the identified studies according to diagnoses. Factors affecting remission, relapse, renal function and overall survival were identified.

Results: A total of 44 papers were reviewed from 502 identified by our search criteria. There was considerable inconsistency in definitions of end points. Remission rates varied from 30% to 93% in Wegener granulomatosis (WG), 75% to 89% in microscopic polyangiitis (MPA) and 81% to 91% in Churg–Strauss syndrome (CSS). The 5-year survival for WG, MPA and CSS was 74–91%, 45–76% and 60–97%. Relapse (variably defined) was common in the first 2 years but the frequency varied: 18% to 60% in WG, 8% in MPA, and 35% in CSS. The rate of renal survival in WG varied from 23% at 15 months to 23% at 120 months. Methods used to assess morbidity varied between studies. Ignoring the variations in definitions of the stage of disease, factors influencing remission, relapse, renal and overall survival included immunosuppressive therapy used, type of organ involvement, presence of ANCA, older age and male gender.

Conclusions: Factors influencing remission, relapse, renal and overall survival include the type of immunosuppressive therapy used, pattern of organ involvement, presence of ANCA, older age and male gender. Methodological variations between studies highlight the need for a consensus on terminology and definitions for future conduct of clinical studies in AAV.

Outcome measures in primary small vessel vasculitis help to describe the natural history of treated disease. Cyclophosphamide and glucocorticoids have reduced mortality in antineutrophil cytoplasm antibody (ANCA) associated vasculitides (AAV), although cure remains uncommon.[1] The 5-year survival of treated AAV is over 70%,[2–5] but relapse and low grade persistent disease result in poor quality survival.[4 6–8] There is an increased focus on preserving target organ function.[3 9 10]

Terms used to describe and quantify different disease states have been inconsistent. Methodological agreement is important to enable inter-study comparison, and enable uniform management in future studies.

We undertook a systematic literature review to define disease specific outcomes in primary systemic vasculitis, and the factors affecting them. We concentrated on remission, relapse, renal survival and mortality. This systematic review forms the basis of recently published recommendations for conducting clinical studies in vasculitis.[11]

METHODS

Search methods

We identified the following medical subject headings (MeSH) in the indexing database of Medline through PubMed to construct our search: "Antibodies, Antineutrophil cytoplasmic", "Vasculitis", "Wegener Granulomatosis" (WG), "Churg–Strauss Syndrome" (CSS), "Epidemiologic Study Characteristics", "Evaluation Studies" and "Study characteristics". "Microscopic polyangiitis" (MPA) is not a MeSH term, therefore it was used as a free text phrase to be used in "all fields". The search identified 832 citations, excluding case reports. These were limited by the terms "Adult" and "Abstracts" to 502 results, but there were no limits by time or language. A search of the Cochrane library did not produce any additional papers. No manual searching of papers was performed.

Selection criteria

From 502 papers identified, 44 were selected using the following criteria:

- >20 patients per cohort/arm of a study.
- Disease specific subanalysis in heterogeneous cohorts (one paper did not meet this criterion, but was included because the cohort had 94% homogeneity).[12] Papers were ignored if the patient population was defined by their serological status only, without a specific diagnosis.
- Relevant outcome data.
- Multivariate analysis for risk factors affecting the outcomes.
- Elimination of duplicate data.

Data analysis

Patients were classified as WG, MPA and CSS as described in the articles. The identified risk factors for outcomes have been awarded a level of evidence according to European League Against Rheumatism (EULAR) standardised operating procedures.[13] We discussed the variability in terminology, outcomes and risk factors affecting the outcomes.

RESULTS

Methodological quality of the studies

A total of 44 papers met the selection criteria; 25 were retrospective studies. Of the 19 prospective studies, 6 were randomised controlled trials.[12 14–18] Three of these trials had heterogeneous cohorts,[12 14 18] and only one had disease specific analysis.[18]

Wegener granulomatosis

Remission

The remission rate for WG (table 1) ranges from 30% to 93% depending on the definition of remission and remission induction therapy.[1 3 12 15 19–23] The definition of remission varied from "commencement of clinical improvement", to "complete absence of disease manifestations for at least 6 months". In most studies, the time to achieve remission (where stated) is less than 6 months. The heterogeneity of remission induction therapy and the definition of remission make this data difficult to interpret.

Factors affecting remission

Two main factors affected remission. Firstly, in a retrospective study, severe disease as defined by a Birmingham Vasculitis Activity Score (BVAS) of >23, was associated with an increased likelihood of achieving remission independent of treatment intensity; relative hazard (RH) 2.94, 95% CI 1.48 to 5.85, level of evidence = 3.[23] This finding may reflect increased responsiveness of severe disease to immunosuppression. Patients with higher activity have poorer survival.[24 25] It is possible to have life threatening disease, responsive to treatment. Subsequent studies have not re-examined this relationship.

Secondly, in a retrospective cohort, each 1-point increase in the Vasculitis Damage Index (VDI) score increased treatment resistance; odds ratio (OR) 1.53 (95% CI 1.03 to 2.27), level of evidence = 3.[23] Damage occurred early in disease,[26] and its presence may have influenced the definition of remission in this study, but it is likely that damage makes disease less responsive to therapy.

Relapse

Relapse was common in WG (table 2). The rate (18–40% at 24 months) and time to first relapse (15 to 29 months) varied.[1 14–17 20 23 27–32] This variability may be spurious (due to differing definitions of relapse) or genuinely due to differing remission maintenance therapies or the presence or absence of risk factors for relapse (table 3).

Factors associated with relapse

Three factors were associated with relapse. The first was treatment; receiving <10 g (compared to ⩾10 g) of cyclophosphamide in the first 6 months was associated with an increased relapse rate (relative risk (RR) 2.83, 95% CI 1.33 to 6.02) despite maintenance of immunosuppression.[23] Patients who tolerated oral cyclophosphamide 2 mg/kg/day received >10 g in 6 months (10 g in 6 months = 55 mg/day). For intravenous therapy, three regimens have been used in trials: (a) 15 mg/kg/pulse, first three pulses twice weekly, then every 3 weeks;[34] (b) 0.7 g/m^2 thrice weekly;[15] and (c) 0.75 g/m^2/month.[35]

At a maximum of 1 g/pulse, only regimen (a) can deliver 10 g of cyclophosphamide in 6 months. This regimen is being validated in a prospective study.[36]

Maintaining a high dose of prednisolone (>20 mg/day) for less than 2.75 months increases risk of relapse (RH 2.41, 95% CI 1.12 to 5.21). This supports the current use of intensive initial therapy.

The use of adjunctive trimethoprim/sulfamethoxazole 160/800 mg twice daily, maintained remission for longer (RR 0.32, 95% CI 0.13 to 0.79),[16] but resulted in a withdrawal rate of 20%.[16] However, trimethoprim/sulfamethoxazole as monotherapy for remission maintenance had a higher relapse rate in

Table 1 Rates of remission from studies of Wegener granulomatosis (WG) with definitions of remission and the remission induction therapy

Author	Study	Size (n)	Remission rate (%)	Time to remission	Remission induction therapy	Definition of remission
Hoffman *et al* 1992[1]	P	133	75	NA	Oral daily CYC (2 mg/kg/day) + Pred (1 mg/kg/day, tapered after 2–4 weeks)	Complete absence of disease
Reinhold-Keller *et al* 1994[19]	P	43	30	NA	CYC iv (mean 667 mg/m^2/month) + iv Pred 100 mg +/– oral Pred	Complete absence of disease for 6 months
Sneller *et al* 1995[20]	P	42	71	4.2 months (median)	MTX (20–25 mg/week) + Pred 1 mg/kg/day	Complete absence of disease
Guillevin *et al* 1997[15]	P	27	89	6 months	CYC iv (0.7 g/m^2 thrice weekly) + Pred 1 mg/kg/day	Clinical improvement
		23	78	6 months	Oral daily CYC (2 mg/kg) + Pred 1 mg/kg/day	
Aasarod *et al* 2000[3]	R	108	81	4 months (median)	Heterogeneous regimens	Complete absence of disease
Reinhold-Keller *et al* 2000[21]	P	155	54	NA	Heterogeneous regimens	Complete absence of disease for 3 months
Bolley *et al* 2000[22]	R	38	68	NA	Heterogeneous regimens	Undefined
Koldingsnes and Nossent 2003[23]	R	52	85	NA	Heterogeneous regimens	Complete absence of disease
De Groot *et al* 2005*[12]	P	49	90	3 months (median)	MTX (20–25 mg/week) + Pred 1 mg/kg/day	BVAS 1 = 0 and BVAS 2<2
		46	93	2 months (median)	Oral CYC 2 mg/kg/day + Pred 1 mg/kg/day	

*There were six patients with MPA in this cohort, divided between the two arms.
BVAS, Birmingham Vasculitis Activity Score (score 1 is for active disease and score 2 is for persistent disease); CYC, cyclophosphamide; iv, intravenous; MPA, microscopic polyangiitis; MTX, methotrexate; P, prospective; Pred, prednisolone; R, retrospective.

Table 2 Incidence of relapse from studies of Wegener granulomatosis (WG) with definition of relapse and the remission maintenance regimen

Author	Study	Size (n)	Relapse rate	Time to relapse	Maintenance regimen	Definition of relapse
Hoffman *et al* 1992[1]	P	98	56% at 60 months	NA	Heterogeneous regimen	Undefined
Sneller *et al* 1995[20]	P	30	36% at 29 months	29 months	MTX 20–25 mg/week + tapering Pred	Reappearance of disease
Reinhold-Keller *et al* 1996[27]	P	24	42% at 13 months	NA	TMP + SMX (2×960 mg/day)	Undefined
		21	29% at 23 months	NA	None	
Stegeman *et al* 1996*	P	41	18% at 24 months	NA	TMP/SMX (2×960 mg/day) + standard therapy	Reappearance of disease
		40	40% at 24 months	NA	Placebo + standard therapy	
Guillevin *et al* 1997[15]	P	24	59% at 54 months	NA	CYC iv (0.7 g/m^2 thrice weekly) + tapering Pred	Reappearance of major disease manifestation
Haubitz *et al* 1998[28]	R	35 (with ESRD)	49% at 41 months	NA	Heterogeneous regimens	Reappearance of disease
Boomsma *et al* 2000[29]	P	100	37% at 35 months	NA	Heterogeneous regimens	Undefined
Fauchais *et al* 2001[30]	R	35	60% at 39 months	NA	Heterogeneous regimens	Undefined
Koldingsnes and Nossent 2003[23]	R	52	60% at 42.5 months	18 months	Heterogeneous regimens	Reappearance of disease after complete or partial remission
Langford *et al* 2003[31]	P	42	52% at 32 months	15 months	MTX 20–25 mg/week	Reappearance of disease
Jayne *et al* 2003[14]	P	92	18% at 18 months	NA	AZA 2 mg/kg OR CYC 1.5 mg/kg + Pred 10 mg/day	Reappearance of one major or three minor BVAS items
WGET 2005†[17]	P	89	30% at 25 months	NA	Eta 25 mg s/c twice weekly + standard therapy	Reappearance of an item on the BVAS/WG
		85	25% at 19 months	NA	Placebo + standard therapy	
Pavone *et al* 2006[32]	R	36	16% at 12 months	NA	Heterogeneous regimens	Reappearance of disease requiring immunosuppressive therapy
		36	26% at 24 months			

Where defined, relapse was considered only after achievement of remission.
*Standard therapy was cyclophosphamide and/or prednisolone. It was not offered to all patients, there were no differences in the number of patients on standard therapy in each arm. †Standard therapy was methotrexate or azathioprine depending on renal function, for 12 months following remission.
AZA, azathioprine; BVAS, Birmingham Vasculitis Activity Score (Score 1 is for active disease and score 2 is for persistent disease); BVAS/WG, BVAS for Wegener granulomatosis; CYC, cyclophosphamide; ESRD, end-stage renal disease; Eta, etanercept; iv, intravenous; MTX, methotrexate; NA, not available; P, prospective; Pred, prednisolone; R, retrospective; s/c, subcutaneous; TMP + SMX, trimethoprim + sulphamethoxazole.

comparison to conventional remission maintenance therapy (18% at 18 months with CYC 1.5 mg/kg/day or AZA 2 mg/kg/day in combination with prednisolone 10 mg/kg/day; 42% at 23 months with trimethoprim/sulphamethoxazole monotherapy).[14 27]

The second factor was ANCA; presence of ANCA at diagnosis conferred an increased risk of relapse (RR 2.89, 95% CI 1.12 to 7.45).[16] ANCA are likely to be important in the pathogenesis of disease;[37 38] absence may represent a milder disease less prone to relapse.

In patients who had been positive for ANCA, a fourfold rise in cytoplasmic (C)/proteinase 3 (PR3) ANCA predicted subsequent relapse (RR 42.5, 95% CI 9.48 to 180.8).[29] However, about a third of patients did not suffer a relapse.[29] Aggressive treatment solely on the basis of a rise in ANCA titres would expose patients to unnecessary cytotoxic therapy. Persistence of ANCA at the onset of remission has been associated with a high risk of relapse in mixed cohorts.[39] Serial ANCA testing for guiding therapy remains controversial; a meta-analysis of 22 studies could not reach a conclusion about the value of serial ANCA testing due to the heterogeneity in the assay methodologies.[40]

The final factor was target organ involvement. Cardiac involvement increased risk of relapse (RH 2.87, 95% CI 1.09 to 7.58; p = 0.03).[23] A creatinine clearance >60 ml/min was associated with an increased risk of relapse (RR 2.94, 95% CI 1.27 to 6.67; p = 0.01);[33] perhaps due to non-renal, granulomatous disease (for example otolaryngological involvement), which is more prone to relapse.[41] Chronic nasal carriage of *Staphylococcus aureus* was an independent risk factor for relapse (RR 7.16; 95% CI 1.63 to 31.50; p = 0.009).[33] The presence of *S aureus* may provide a nidus of inflammation required by ANCA to produce an inflammatory response.[38]

Table 3 Factors associated with Wegener granulomatosis (WG) relapse with level of evidence

Risk factor	Risk of relapse	Level of evidence	Reference
A fourfold rise in C ANCA/PR3 ANCA titre	RR 42.5 (95% CI 9.48 to 180.8)	3	Boomsma *et al* 2000[29]
Chronic nasal carriage of *Staphylococcus aureus**	RR 7.16 (95% CI 1.63 to 31.50); p = 0.009	2B	Stegeman *et al* 1994[33]
Creatinine clearance >60 ml/min	RR 2.94 (95% CI 1.27 to 6.67); p = 0.01	3	Stegeman *et al* 1994[33]
The presence of ANCA at diagnosis	RR 2.89 (95% CI 1.12 to 7.45)	1B	Stegeman *et al* 1996[16]
Cardiac involvement at diagnosis	RH 2.87 (95% CI 1.09 to 7.58); p = 0.03	3	Koldingsnes and Nossent 2003[23]
Cumulative cyclophosphamide dose <10 g in the first 6 months	RH 2.83 (95% CI 1.33 to 6.02); p = 0.007	3	Koldingsnes and Nossent 2003[23]
Prednisolone ⩾20 mg/day for <2.75 months	RH 2.41 (95% CI 1.12 to 5.21); p = 0.03	3	Koldingsnes and Nossent 2003[23]
Co-trimoxazole as adjuvant to remission maintenance therapy	RR 0.32 (95% CI 0.13 to 0.79)	1B	Stegeman *et al* 1996[16]

*Nasal carriage of *Staphylococcus aureus* tended to decrease the relapse rate in Pavone *et al*;[32] this was not statistically significant.
ANCA, antineutrophil cytoplasm antibody; C, cytoplasmic; PR3, proteinase 3; RH, relative hazard; RR, relative risk.

The presence of these risk factors cannot be used to justify treatment decisions.

Relapses have been classified according to severity in some clinical trials, but there have been methodological differences.[14 17] In one study,[14] a major relapse was defined as the appearance of at least one major (eg, haematuria) item; minor relapse required the presence of three minor (eg, myalgia, arthritis, nasal crusting) BVAS items. By contrast, in the Wegener's Granulomatosis Etanercept Trial (WGET), relapses were classified as limited or severe depending on the need for cyclophosphamide and/or reappearance of specific organ involvement.[17] The qualification of relapses is useful in comparing interventions since it may make an intervention with a higher overall relapse rate superior, if it lowers the incidence of severe, life-threatening relapse.

Renal survival in WG

There is a progressive rise in renal mortality over time in patients with WG. In a retrospective cohort, 7% of patients developed end stage renal disease at 12 months; increasing to 14% at 5 years and 23% at 10 years.[9] In two other studies, end stage renal disease occurred in 19% at 38 months, and 23% at 15 months.[3 10] Factors predicting progression to end stage renal disease were as follows. Renal factors: dialysis dependence at diagnosis (RR 3.3 (95% CI 1.3 to 8.8), p = 0.001,[3] HR 4.78 (95% CI 1.27 to 17.86), p = 0.02,[9] level of evidence = 3). A rise in serum creatinine of 100 μmol/litre (HR 1.35 (95% CI 1.11 to 1.49), p = 0.001,[9] level of evidence = 3). A rise in the 24 h urinary protein of 1 g (HR 1.50 (95% CI 1.08 to 2.07), p = 0.02,[9] level of evidence = 3.

Other factors: a fall in haemoglobin of 1 g/dl (HR 1.64 (95% CI 1.05 to 2.57), p = 0.03,[9] level of evidence 3). An increase in age of 10 years (HR 1.47 (95% CI 0.95 to 2.24), p = 0.08,[9] level of evidence = 3).

Survival

WG is associated with higher mortality compared to the general population (mortality risk ratio (MRR) 3.8 (95% CI 2.6 to 5.6), MRR 4.0 for men (95% CI 2.5 to 6.3), MRR 3.4 for women (95% CI 1.6 to 7.2)).[3] The mean survival for untreated WG is 5 months and the 2-year mortality is 93%.[42] Immunosuppressive therapy has changed the outlook. In a historical cohort of 265 patients, the median survival of 27 patients not receiving any initial immunosuppression was 4.2 years;[43] however, 57 patients treated with azathioprine +/− prednisolone and 74 patients treated with oral cyclophosphamide +/− prednisolone had a median survival of 7.3 years and 8.5 years, respectively.[43] A median survival of 21.7 years was recorded in a series of 155 treated patients.[21]

Table 4 Survival in antineutrophil cytoplasm antibody associated vasculitides (AAV)

Time	WG	MPA	CSS
12 months	85–97% (data from six studies including 398 patients)[9 21 22 44–46]	82–92% (data from four studies including 252 patients)[45–48]	93–94% (data from two studies including 155 patients)[48 49]
24 months	86–97% (data from two studies including 263 patients)[21 50]	NA	NA
60 months	69–91% (data from seven studies including 427 patients)[5 9 44–46 50 51]	45–76% (data from five studies including 217 patients)[4 45–47 51]	60–97% (data from five studies including 187 patients)[2 49 52–54]
120 months	75–88% (data from two studies including 211 patients)[9 21]	NA	NA

CSS, Churg–Strauss syndrome; MPA, microscopic polyangiitis; NA, not available; WG, Wegener granulomatosis.

Factors affecting survival

There are three main factors that affect survival (table 5). They are as follows. Age: a rise of each decade in age increases the risk of death in patients with WG (HR 2.18, 95% CI 1.38 to 3.42, p<0.001).[9] Over the age of 52 years, the older population has a poorer survival (HR 3.4, 95% CI 1.03 to 11.21, p = 0.04).[5] Two other studies, which stratified patients at 50 and 60 years, respectively, found similar results.[21 55] Patients aged >50 had a HR of 5.73 (95% CI 2.07 to 15.85) for death in a calendar year when compared to younger patients.[21] There was no control group to prove that the increasing risk of death was not simply a function of increasing mortality in an older sub-group.

The second factor is target organ damage. WG has vasculitic and granulomatous components, each of which may respond to different treatment.[56] Upper respiratory tract involvement is the granulomatous end of the spectrum and renal involvement is the pure vasculitis manifestation. Upper respiratory tract involvement is associated with better survival (HR 0.31, 95% CI 0.11 to 0.84, p = 0.02) and renal involvement with poorer survival (HR 4.45, 95% CI 1.48 to 13.65).[5 21] This would fit with the clinical observation that vasculitic manifestations are more acute and life-threatening than granulomatous manifestations, which are more likely to be indolent. The presence of lung involvement may be a risk factor for mortality (HR 3.74, 95% CI 1.26 to 11.13),[21] but this is disputed[5] and can only be resolved by larger prospective studies.

The third factor is damage. The presence of even minimal damage is associated with a higher risk of mortality.[9] This observation would correlate with data from the original VDI validation exercise, where a comparison of 12 non-survivors vs 47 survivors revealed that the median VDI score

Table 5 Factors affecting survival

Risk factor	Risk of death (95% CI)	Level of evidence	Reference
Dialysis dependence at diagnosis	HR 8.2 (2.03 to 33.11) p = 0.003	3	Koldingsnes and Nossent 2002[9]
VDI ⩾1 at diagnosis	HR 5.54 (1.28 to 24.05) p = 0.022	3	Koldingsnes and Nossent 2002[9]
Impaired renal function at diagnosis	HR 5.10 (1.59–10.16)	3	Reinhold-Keller *et al* 2000[21]
A serum albumin level of ⩽30 g/litre at diagnosis	RR 4.5 (1.3 to 16)	3	Aasarod *et al* 2000[3]
Renal involvement at diagnosis*	HR 4.45 (1.48 to 13.65)	3	Reinhold-Keller *et al* 2000[21]
Lung involvement at diagnosis†	HR 3.74 (1.26 to 11.13)	3	Reinhold-Keller *et al* 2000[21]
Age >52	HR 3.4 (1.03 to 11.21), p = 0.04	3	Bligny *et al* 2004[5]
Age (rise of 10 years)	HR 2.18 (1.38 to 3.42), p<0.001	3	Koldingsnes and Nossent 2002[9]
Upper respiratory tract involvement at diagnosis‡	HR 0.31 (0.11 to 0.84), p = 0.02	3	Bligny *et al* 2004[5]

*Affected only univariate analysis, not multivariate analysis.[5] †Did not affect survival.[5]
‡Affected only univariate analysis, not multivariate analysis.[9]
HR, hazard ratio; RR, relative risk; VDI, Vasculitis Damage Index.

for non-survivors was significantly higher that that for survivors (7 vs 4).[57]

Microscopic polyangiitis

There are very few studies of MPA due to the absence of a definition until the Chapel Hill consensus conference.[58] It is possible that previously published studies of WG may have inadvertently included patients with MPA. These are limitations of classification and we have excluded those papers that do not describe MPA as a separate entity. We have also excluded cohorts with renal limited vasculitis because they have the potential to differentiate into either WG or MPA.

Remission

In two studies, remission rates for MPA were 75% and 89%.[18 41] Objective inter-study comparison and with WG (table 1) cannot be made due to differences in defining remission and variable remission induction regimens.

Relapse

The relapse rates in MPA from three studies are 34% at 70 months (mean time to relapse 43 months),[4] 41% at 32 months (mean time to relapse 22.5 months)[47] and 8% at 18 months.[14] The latter was directly compared to the relapse rate in WG (18% at 18 months), demonstrating that WG has a higher rate of relapse than MPA (level of evidence = 2B.[14] Variations in trial methodology (treatment, baseline characteristics for the cohort and definition of outcomes) hamper inter-trial comparison.

Survival

The 1-year survival in MPA is 82–92%,[45–48] and the 5-year survival estimates are between 45% and 76%,[4 45–47 51] which is worse than in WG (RR 1.917, 1.075–3.419, p = 0.025) (table 4).[59] In two separate studies, the 1-year (83% vs 85%, p = not significant and 87% vs 97%, p<0.01) and 5-year (45% vs 76%, p = 0.02 and 63% vs 91.5%, p<0.01) survival of MPA was lower than WG.[45 46] The survival advantage of WG may be lost following the onset of end stage renal disease.[60]

The presence of significant renal insufficiency at diagnosis is an adverse survival marker in MPA (HR 3.69, 95% CI 1.006 to 13.4) (level of evidence = 3).[48]

Churg–Strauss syndrome

Remission

The search yielded only two papers where Churg–Strauss syndrome (CSS) was studied as a distinct diagnosis.[2 49] Disease specific sub-analysis for CSS was not available in other studies. The remission rate for CSS is 81–91%.[2 49]

Relapse

Relapse rates in CSS increase with time; 10%, 15% and 21% at 1, 2 and 4 years in one study,[2] and 27% and 35% at 1 and 2 years in another.[32] The relapse rate of CSS maybe lower than MPA (20% vs 34%), as seen in a prospective cohort (which also included polyarteritis nodosa (PAN)).[25] Intravenous methotrexate (0.3 mg/kg/week) and low dose prednisolone as remission maintenance therapy resulted in a relapse rate of 48% after 4 years.[6] The median time to relapse was 9 months.[6] The variable definition of relapse has an affect on the relapse rate. For example, when defined as "reappearance of disease except asthma and eosinophilia", the relapse rate was lower than in comparison with a definition of relapse "...requiring immunosuppression".[2 32] Gastrointestinal involvement is a risk factor for relapse in CSS (HR 6.75, 95% CI 1.55 to 29.52; p = 0.011) (level of evidence = 3).[32]

Survival

Patient survival in CSS is 93–94% at 1 year[48 49] and 60–97% at 5 years (table 4).[2 49 52–54] The five factor score (proteinuria >1 g/day, creatinine >1.58 mg/dl, gastrointestinal involvement, cardiomyopathy, neurological involvement) was validated in a heterogeneous cohort of CSS and PAN (which may have included MPA),[61] but did not include a CSS specific sub-analysis. The score was indirectly validated in a later study.[2] The absence of any of the five factors carries a good prognosis (RR 0.52, 95% CI 0.42 to 0.62; p<0.03) and the presence of two or more of the factors increases the risk of mortality (RR 1.36, 95% CI 1.10 to 1.62; p<0.001) (level of evidence = 3).[2] Of the five factors, cardiomyopathy is an independent risk factor in CSS (HR 3.39, 95% CI 1.6 to 7.3) (level of evidence = 3)[48] Proteinuria >1 g/day was not associated with adverse survival in a prospective cohort.[2]

CONCLUSIONS

This literature review summarises the clinical outcomes and the factors influencing them in studies of AAV. A small number of manuscripts met our selection criteria, indicating a lack of good quality research for outcome measures in AAV. There have only been six randomised controlled trials in AAV, and only one had disease-specific analysis. There is limited data available from structured clinical studies for specific diseases. From the identified papers, it is difficult to compare outcomes due to the variation in trial regimen and differing definitions of clinical states. The identification of risk factors was restricted to multivariate analysis. However, most risk factors are derived from descriptive cohorts and there have been no controlled studies to validate them. Definitions used for inclusion of patients varied considerably. In some instances, the data was published prior to any international classification scheme. The use of the Chapel Hill Consensus Conference definition[58] has helped identify a homogeneous group of patients with MPA. The variation in methodology of the studies reviewed in this paper formed the basis of the recommendations by EULAR/EUVAS for conduct of studies in AAV.[11] The differences between outcomes in the studies we have discussed may be genuine (dependent on stage of disease, organ involvement, therapy and so on) or perceived (due to a variation in the definition of the outcome). Future trial design should address this variation when calculating sample sizes by stratifying patients according to identified risk factors. The outcome measures and results in this paper may require updating in future when data emerges from new studies. Currently, the recommendations and the literature search are restricted to AAV, primarily because the majority of controlled trials and long-term observational studies have focussed on these forms of vasculitis. A similar approach would apply to other forms of primary small vessel vasculitis and may lead to the development and implementation of recommendations in these diseases in future. Disease related damage and the quality of life of patients with these chronic debilitating diseases are measures of prognostic and economic importance.[8 62 63] We have not concentrated on those outcomes, but they are discussed elsewhere.[64]

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