Risks of treatments and long-term outcomes of systemic ANCA-associated vasculitis

Oliver Flossmann

Royal Berkshire Hospital, Department of Nephrology, London Road, Reading, Berkshire, RG15AN, United Kingdom

olflossmann@doctors.org.uk

Summary

Patients with ANCA-associated vasculitis (AAV) have an increased risk of premature death and organ failure. Treatment strategies with immune-suppressive drugs need to balance disease control and prevention of relapse against the risk of side effects in particular infection and malignancy. The longer-term outcome of patients with AAV who participated in several randomised controlled trials has been published in recent years. The results of these and other newer studies will be the focus of this review.

ANCA-associated vasculitis (AAV) is the most common form of small vessel vasculitis and comprises granulomatosis with polyangiitis (previously known as Wegener's granulomatosis) (GPA), microscopic polyangiitis (MPA) and the much rarer eosinophilic granulomatosis with polyangiitis (formerly known as Churg-Strauss angiitis) (EGPA) [1]. Most of these patients have detectable antibodies against either proteinase 3 (PR3-ANCA) or myeloperoxidase (MPO-ANCA). There are important differences in genetic susceptibility, demographic features, clinical presentation and prognosis between patients with either antibody specificity [2].

Since the introduction of immune-suppressive therapy with cyclophosphamide and high dose glucocorticoids in the 1960s, patient survival has improved dramatically and remission is achieved in 79%–93% of patients [3]. Both cyclophosphamide and glucocorticoids have well recognised toxicity in particular when used in high doses and over prolonged periods. Remission is however no cure and relapses are common, requiring prolonged remission maintenance therapy for the majority of patients. The main focus of randomised controlled trials, in the last 25 years, has been to evaluate treatment protocols allowing a safe reduction in cumulative cyclophosphamide dose or possible alternatives to cyclophosphamide. The European Vasculitis Study Group (EUVAS) undertook a long-term follow-up of four randomised controlled trials reporting on the outcome of 535 newly diagnosed patients after a median follow-up of 5.2 years spanning almost the entire disease activity spectrum, although it is likely that both the mildest and most severe forms were underrepresented. The French Vasculitis Study Group, who
pioneered randomised controlled trials in systemic vasculitis, also recently reported the longer-term outcomes of several of their studies.

I will review the main findings of these and other outcome studies published in the last five years.

Survival

Reported survival rates depend to a large extent on demographic and clinical characteristics of included patients. There are important differences in e.g. patient age, severity of renal involvement, ANCA specificity among recently reported randomised controlled trials and observational cohorts limiting the comparability between studies (see table I).

One report from a single centre in Germany suggests that there has been a steady decline in the mortality of GPA over four decades. Standardised mortality ratios (SMR) were 2.1, 1.41 and 1.03 in three cohorts from 1966–1993, 1994–1998 and 1998–2002 in patients with similar organ manifestations. This was attributed to an earlier diagnosis with the median time between onset of symptoms and diagnosis halving from 8 to 4 months and progressive reduction in the median cumulative dose of cyclophosphamide from 67 g in the earliest to 24 g in the latest cohort [4]. Similar findings have been reported from a Dutch registry of patients with renal vasculitis [5].

Patient survival in the EUVAS cohort of 535 newly diagnosed patients with AAV who participated in four randomised controlled trials spanning most of the disease severity spectrum at 1, 2 and 5 years was 88%, 85% and 78%, respectively. Compared to an age-, sex- and country-matched general population, the risk of death was increased by 2.6 (95%, confidence interval [CI] 2.2–3.1). Multivariable analysis showed advancing age, a higher disease activity as measured by the BirminghamVasculitis Activity Score (BVAS) and severely impaired kidney function with an estimated glomerular filtration rate (eGFR) of 15 ml/min to be predictors of death at presentation. The main causes of death within the first year of diagnosis were infections (48%) and active vasculitis (19%) whereas after the first year cardiovascular events (26%), malignancy (22%) and infection (20%) were the leading causes of death [6]. Eighty-seven percent of patients in the EUVAS cohort had renal and only 53% ear-nose-and-throat involvement suggesting that patients with milder disease were underrepresented. On the other hand, patients with life-threatening alveolar haemorrhage at presentation were excluded.

The Five Factor Score (FFS) has been used to enrol patients with good or poor prognosis to different clinical trials by the French Vasculitis Study Group [7]. The five- and eight-year survival in patients with polyarteritis nodosa (PAN) and microscopic polyangiitis without poor prognostic factors was 93% and 86% [8]. A study using a primary care database of over 6 million patients representative of the general population of the United Kingdom identified 255 patients with a new diagnosis of GPA between 1989 and 2004. Compared to an age-, sex- and practice-matched control group they had an especially high excess mortality in the first year after diagnosis with a hazard ratio (HR) of 9.0 and after 10 to 15 years with an HR of 4.4. The mortality in the intervening years was still elevated but less marked with a HR of 1.68 and 2.41 1 to 5 and 5 to 10 years after diagnosis, respectively. The cause of the late excess mortality was unclear [9].

Compared to MPA and GPA, the prognosis for patients with EGPA appears to be better. Long-term follow-up of 118 patients from two French studies of patients with or without poor prognostic factors on the Five Factor Score showed that survival was 90% at seven year with only age greater than 65 years being an independent risk factor of death [10]. A retrospective analysis of 383 patients with EGPA diagnosed between 1957 and 2009 by the French Vasculitis Study Group showed a five- and ten-year survival of 88.9% and 78.6%. Independent predictors of death were cardiomyopathy at diagnosis, older age and diagnosis prior to 1996 [11].

Organ failure

Renal involvement is common in patients with AAV. A population-based study of all newly presenting patients with AAV showed that 85% of patients positive for MPO-ANCA and 68% of those with PR3-ANCA had renal involvement at presentation. Thirty-eight percent of the MPO-ANCA patients developed end-stage renal failure (ESRF) whereas only 15%
of PR3-ANCA patients did so. The hazard ratio for ESRF was 2.64 (95% CI 1.25–5.58) for MPO-ANCA compared to PR3-ANCA even after adjustment for age, sex, and serum creatinine at presentation [12].

Severe renal failure or dialysis dependency at presentation are major predictors of a poor outcome in patients with AAV. After a median follow-up of 3.95 years of 137 patients recruited into a trial comparing adjunctive therapy with either methylprednisolone or plasma exchange in patients presenting with a creatinine of more than 500 μmol/L or dialysis dependency, 70 (51%) patients had died and 56 (41%) had developed ESRF. There was no significant difference in the composite outcome of death or ESRF between the treatment arms. The median creatinine at five years in the 37 patients alive and not on dialysis was 167 μmol/L [13].

Similarly poor outcomes were described in a Dutch study of 48 patients requiring dialysis at presentation between 1990 and 1997; 11 (23%) died within six months and 14 (29%) remained dialysis dependent. Of 23 patients who recovered independent renal function seven only did so temporarily before needing to restart renal replacement therapy [14].

Immunosuppressive therapy even in elderly patients is likely to lead to better renal and overall survival as a retrospective study from the United States on 78 patients aged greater than 80 years showed. After two years, the risk of death (HR 0.33; 95% CI 0.11–0.97) or death or ESRF (HR 0.16; 95% CI 0.06–0.42) was considerably lower in patients treated with immune-suppression than in untreated patients [15].

A classification scheme for renal biopsy findings in AAV, which has recently been proposed by an international working group of histopathologists, holds promise as predictor of renal outcome. Renal survival at five years in the different groups dependent on glomerular lesions was 93% for focal, 76% for crescentic, 61% for mixed and 50% for sclerotic, respectively [16]. These findings have been confirmed in other cohorts as well [17,18].

The outcome of patients with AAV who receive a kidney transplant is good and the relapse rate low [19,20] although registry data from New Zealand and Australia suggest that patients with MPO-ANCA have worse graft and overall survival compared to non-vasculitic patients whereas patients with PR3-ANCA had comparable outcomes [21].

The survival of patients with AAV on dialysis is similar to dialysis patients without vasculitis but infection may be more common [21,22].

Pulmonary fibrosis as manifestation of AAV has only recently received closer attention. Outcome data were limited to small case series, however, the French Vasculitis Study Group has now published a retrospective series of 49 patients with AAV associated pulmonary fibrosis, 43 (88%) of whom had MPO-ANCA. After a median follow-up of 48 months, 18 (37%) of patients had died, 11 due to respiratory insufficiency. Factors predictive of

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### Table I

**Overview on long-term outcome of patients with AAV: duration of follow-up, patient characteristics, relapse rate, patient survival, induction treatment**

<table>
<thead>
<tr>
<th>Author/ year of publication</th>
<th>Period years</th>
<th>Number of patients Diagnosis Cohort</th>
<th>Follow-up (months)</th>
<th>Age (years)</th>
<th>Renal involvement/ serum creatinine at baseline (μmol/L)</th>
<th>ANCA positivity at baseline (% positive)</th>
<th>Relapse Prop. of patients</th>
<th>Patient survival % at follow-up</th>
<th>Induction treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flossmann/ 2011 [6]</td>
<td>1993-2001</td>
<td>535; GPA MPA RCT prospective</td>
<td>62</td>
<td>61</td>
<td>92% CKD 2-5 203μmol/L</td>
<td>PR3 67</td>
<td>38%</td>
<td>75%: cumulative survival at 1 and 5 years 88%-78%</td>
<td>Cyc/CS</td>
</tr>
<tr>
<td>Samson/ 2014 [8]</td>
<td>1993-2005</td>
<td>58 PAN; 66 MPA RCT prospective</td>
<td>98</td>
<td>56.5</td>
<td>9% microscopic haematuria 82 μmol/L</td>
<td>ND</td>
<td>53%</td>
<td>93%-5 years 86%-8 years</td>
<td>MTX/CS</td>
</tr>
<tr>
<td>Samson/ 2013 [10]</td>
<td>1994-2005</td>
<td>118 EGPA RCT prospective</td>
<td>81</td>
<td>52</td>
<td>27% 89.9 μmol/L</td>
<td>ND</td>
<td>41%</td>
<td>98%-1 year 92%-5 years 90%-7 years</td>
<td>MTX/CS</td>
</tr>
</tbody>
</table>

CS: corticosteroids; Cyc: cyclophosphamide; EGPA: eosinophilic granulomatosis with polyangiitis; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; MTX: methotrexate; ND: not done or no information given in manuscript; PE: plasma exchange; RCT: randomised controlled trial; TMP: trimethoprim/sulfamethoxazole.
mortality were chronic respiratory insufficiency (HR 7.44; 95% CI 1.6-34.5), induction therapy with glucocorticoids only instead of combination with cyclophosphamide or rituximab (HR 2.94; 95% CI 1.05-8.33) and initial weight loss (HR 2.83; 95% CI 1.05-7.65). The three-year survival in patients treated with a combination of either cyclophosphamide or rituximab with glucocorticoids was 94% but only 64% in patients treated with glucocorticoids only [23].

Treatment toxicity

The most common cause of death in the first year after diagnosis of AAV is infection rather than active vasculitis [6,24]. A review of data from four European trials including 524 patients with newly diagnosed AAV showed that 59% of deaths within one year of diagnosis were caused by adverse events associated with therapy compared to only 14% due to active vasculitis. In multivariable Cox Regression Infection Score, adverse event score, leukopaenia score and eGFR were independent predictors of mortality [25].

Relapse

The risk of relapse was found to be between 38% and 54% in data from the French Vasculitis Study Group (434 patients), the Glomerular Disease Network based in Chapel Hill, USA (347 patients) and the long-term follow-up of four EUVAS trials [26,27]. Patients with PR3-ANCA were found to have an increased risk of relapse in all three cohorts with a HR between 1.62-1.77. The pattern of organ involvement appears to influence the relapse risk with a higher risk of relapse in patients with lung and/or ENT involvement in the French and American cohorts [27] whereas cardiovascular involvement in the EUVAS group [26]. The latter has also been found in a French cohort of patients with GPA [28]. Poorer kidney function at presentation was associated with a reduced risk of relapse in the EUVAS cohort [26]. Cyclophosphamide sparing strategies through reducing duration of cyclophosphamide therapy, substituting intravenous pulse or methotrexate for daily oral administration appear to increase the risk of relapse as long-term follow-up data from three EUVAS trials show [29-31]. This risk has to be balanced however with the well-established risks of high cyclophosphamide exposure as there are now alternatives to cyclophosphamide with in particular rituximab being at least as effective in relapsing patients [32]. Patients with EGPA participating in two French trials who were treated with either cyclophosphamide and glucocorticoids if they had risk factors for a poor outcome or glucocorticoids only in patients without risk factors had a 41% risk of relapse after a mean follow-up of 8.13 months. Patients who were positive for MPO-ANCA were at increased risk of relapse whereas patients with an initial eosinophil count > 3000/mm³ were at reduced risk [10].

Malignancy

Historically the treatment of AAV was associated with an increased risk of malignancy, in particular haematological malignancies, bladder cancer [33] and non-melanoma skin cancer [34]. In a Danish cohort of patients with GPA diagnosed between 1973 and 1999, the risk of cancer was increased (Standard Incidence Rate [SIR] of cancer 2.1, 95% CI 1.5-2.7) in patients who had received more than a cumulative dose of 36 g of cyclophosphamide but not for those who had never received cyclophosphamide or less than 36 g cumulative dose [34]. A large proportion of the excess cancer risk occurred after a long latency period. The risk of non-melanoma skin cancer increased from the second year of follow-up and after more than 20 years of follow-up the SIR was 7 (95% CI 2.3-16). For bladder cancer, the incidence was increased after 5-9 years follow-up with an SIR 5.3 (95% CI 5.3-31) and a SIR of 10.5 (95% CI 1.2-38) after 15-19 years [35]. During 2650 person-years of follow-up in the long-term EUVAS study, 50 new cancers were observed, with a SIR of 1.58 (95% CI 1.17-2.08) for cancers at all sites but a SIR 1.30 (95% CI 0.90-1.80) excluding non-melanoma skin cancer. The standardised incidence rate was higher in patients with GPA compared to MPA. Thus, there was an increased risk for non-melanoma skin cancer, SIR 2.8 (95% CI 1.6-4.6), but not for other types of cancer [36]. A recent German study also did not find an increased incidence of cancer in patients with AAV [4]. This may reflect a reduced exposure to cyclophosphamide in more recent years.

Cardiovascular

In common with other chronic inflammatory diseases, patients with AAV appear to be at increased risk of cardiovascular morbidity and mortality. The rate of ischemic heart disease was increased early (less than five years) (observed to expected ratio 2.1 [95% CI 1.4-3.0]) after diagnosis and late (more than 10 years after diagnosis) (observed to expected ratio 2.2 [95% CI 1.3-3.4]) in a Danish cohort of GPA. The risk was particularly high for acute myocardial infarction. Patients who were either male, older than 50 years and/or had a high cyclophosphamide exposure were at particular risk [37]. In contrast the risk of cerebrovascular disease was not increased after a median follow-up of 7.2 years in 180 Danish GPA patients diagnosed between 1993-2011 [38]. However, the Incidence Rate Ratio (IRR) for deep vein thrombosis (DVT) and pulmonary embolism (PE) was substantially increased within the first two years of diagnosis with an IRR of 25.7 (95% CI 6.9-96) for PE and 20.3 (95% CI 5.1-81) for DVT in the same cohort. Seventy percent of thrombo-embolic events occurred during episodes of active vasculitis [38].
In the long-term follow-up of four EUVAS trials, 74 (13.8%) of 535 patients suffered at least one cardiovascular event within five years of diagnosis. Older age and diastolic hypertension were found to confer a higher risk whereas patients with PR3-ANCA had a reduced risk compared to patients with MPO-ANCA or ANCA negative patients [39].

**Infection**

Patients with AAV are at high risk of infection, at five year follow-up 30% of patients from four EUVAS trials required hospital treatment for infections and infections were the leading cause of death [6,40]. A Canadian retrospective study identified lower initial GFR, longer duration of corticosteroid treatment and presence of lymphocytopenia as risk factors. Patients with severe (lymphocyte count \( \leq 0.3 \times 10^9/L \) lymphocytopenia had a rate of severe infections of 1.00 per person-year compared to 0.08 for patients with moderate (lymphocyte count \( 0.3-1.0 \times 10^9/L \)) and 0.10 for patients without lymphocytopenia [41].

The initial hope that the substitution of cyclophosphamide or azathioprine with rituximab as remission induction or remission maintenance agent would lead to a lower rate of infection has not been borne out in randomised controlled trials[32,42,43]. A possible cause for this is the contribution of high dose corticosteroids to the overall infection risk.

**Damage**

Damage refers to irreversible scarring which does not respond to immune-suppressive therapy. Long-term data from four EUVAS trial show that after a mean of 7.3 year follow-up only 7.9% of patients had no item of damage whereas 34.4% had accumulated at least five items. The most common potentially treatable organ failure, relapsing disease and other adverse outcomes. Early diagnosis is important to avoid irreversible organ damage such as end-stage renal failure. The intensity and duration of immune-suppressive therapy needs to be chosen carefully in order to balance rapid disease control and avoidance of relapse against the risk of infection and malignancy.

**Conclusion**

The prognosis of patients with AAV appears to have improved over the last decades. But patients still remain at increased risk of premature death, particularly in the first year after diagnosis, organ failure, relapsing disease and other adverse outcomes. Early diagnosis is important to avoid irreversible organ damage such as end-stage renal failure. The intensity and duration of immune-suppressive therapy needs to be chosen carefully in order to balance rapid disease control and avoidance of relapse against the risk of infection and malignancy.

The optimal form and duration of remission maintenance therapy to achieve this goal are currently unclear.

**Disclosure of interest:** the author declares that he has no conflicts of interest concerning this article.

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O. Flossmann


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