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The long term outcomes of systemic vasculitis

Key words; Relapse, patient survival, renal outcomes, malignancy, cardio-vascular disease

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ABSTRACT

Patients with generalized ANCA-associated small vessel vasculitis (AAV) have a very poor outcome if the ANCA-associated vasculitis is not diagnosed, evaluated and treated properly. The introduction of treatment with immunosuppressive therapy has improved patient survival dramatically but with considerable side effects. Besides, almost 50 % of surviving patients experience a relapse of vasculitis. Since 1995 the European Vasculitis Society (EUVAS) has designed and conducted several clinical trials on patients with AAV independently of pharmaceutical companies. The studies included patients with newly diagnosed AAV and were stratified according to renal function and generalized vs more localized forms.

As the immediate patient survival has improved the longer term outcome has become more important. There are several reports on outcome of patients with ANCA-associated vasculitis, but the patient groups were heterogeneous regarding diagnosis as well as treatment and follow-up. Therefore EUVAS decided to further evaluate the effect and possible adverse events of the original randomized trials. This review presents an overview on long-term follow-up of patients with ANCA-associated vasculitis, with focus on relapse rate, patient and renal survival, development of cardiovascular disease and malignancy.

INTRODUCTION

It is well known today that patients with generalized ANCA-associated small vessel vasculitis (AAV) have a very poor outcome(1) if not diagnosed, evaluated and treated properly. Since 1995 the European Vasculitis Society (EUVAS) has designed and conducted several clinical trials on patients with AAV independently of pharmaceutical companies. The studies included patients with newly diagnosed AAV and were stratified according to renal function and generalized vs more localized forms.

The introduction of treatment with corticosteroids in the 1950's lead to an improved outcome, with a 5-year patient survival of 48 % (2). Further improvement was gained by the introduction of the combination of corticosteroids and cyclophosphamide as induction therapy in AAV since the 1960's (3) after which patient survival improved dramatically from 20 to over 80% at two-years. However, longer follow-up revealed abundant side-effects of prolonged therapy with cyclophosphamide together with a high relapse rate (4). For this reason EUVAS designed therapeutic trials to test efficacious but less toxic therapeutic regimens. Thus, three prospective randomized trials, NORAM, CYCAZAREM and MEPEX, were launched in the mid 1990'ies, and two further, CYCLOPS and IMPROVE, some years later, all of which have been successfully completed.

As the immediate patient survival has improved the longer term outcome has become more important and therefore EUVAS decided to further evaluate the effect of the original first four randomized controlled trials by a five-year follow-up, including 535 patients with a median age of 61 years at time of the diagnosis of AAV(5). Although the EUVAS cohort of patients comprised a wide spectrum of small vessel vasculitis, there was a bias towards renal involvement, which possibly led to worse outcomes. Thus, patients with milder forms of AAV may have been under-represented in the EUVAS trials, on the other hand patients with the most severe, immediately life threatening, disease are also likely to have been excluded.

PATIENT SURVIVAL

Several reports have been published on patient survival, and an overview of reports with a follow-up of at least 24 months is presented in Table 1. However, the diagnostic criteria for GPA and MPA differ and there is abundant variation as to the subsets of patients and pharmacological treatments given. Naturally the length of follow-up is of importance for survival, as well as the age of the patients and the severity of disease at recruitment. As shown in Table 1, patient survival has been reported to be approximately 70% at 5 years of follow-up in cohorts comprising GPA and MPA, while in cohorts with exclusively GPA it is approximately 79%. Many studies have documented a worse outcome for elderly patients and those with renal insufficiency at time of diagnosis of AAV, Table 1.

The patient survival at 1, 2 and 5 years within the five-year follow-up of the EUVAS cohort was 88% (95% CI 86-91%), 85% (95% CI 82-88%) and 78% (95% CI 75-82%), respectively(5). AAV-patients had a 2.6 (95% CI 2.2-3.1) fold increased risk of death compared to a matched general population. Multivariable analysis revealed advanced age, a severely decreased glomerular filtration rate (eGFR<15ml/min) and a high Birmingham Vasculitis Score (BVAS) at entry as significant predictors of mortality as had been reported earlier by others (6-10). When analyzing the cohort into age quartiles we found that unsurprisingly the patient survival at 5 years for those aged 50-60 years at time of diagnosis was higher; nearly 90 % while those aged > 70 years had a survival rate of only 55 % (11). Although younger patients commonly have a good outcome, their survival is worse than in a age, sex and country matched general population cohort in a multivariable Cox regression model (5) Others have reported a worse outcome for patients with AAV and pulmonary involvement at presentation (12), low serum albumin (13, 14) and high levels of PR3-ANCA measured by capture ELISA (15).

The main causes of death within the first year of follow-up were infection and active vasculitis, while cardiovascular events, malignancy and infection after that (5).

There are indications that patient survival has improved during the last decades, and in GPA it has been reported to be as high as 95% at 47 months of follow-up in a recent publication (16), possibly this reflects earlier diagnosis, more individually tailored therapy and more accurate follow-up of patients.

A separate entity regarding patient outcome comprises patients with the most severe and life-threatening presentations of AAV such as pulmonary haemorrhage. A recent report of patients with AAV (36 with PR3-ANCA and 17 with MPO-ANCA) presenting with pulmonary haemorrhage and ,except for one patient, renal involvement (53% dialysis dependent on entry) of which the majority (76%) were treated with adjunctive plasma exchange, revealed a patient survival of 83% at 3 months and 58% at 49 months of follow-up (17). Dialysis dependency or age> 65 years at entry were associated with higher mortality (17).

It is still not known if a prolonged treatment may result in less mortality, however analysing an earlier Swedish cohort we found that patients surviving the first year, remission maintaining therapy with azathioprine for longer than 12 months was associated with improved patient survival (15).

RELAPSE

Relapse is common in AAV with several reports indicating that approximately 50% of patients will have a relapse (10, 12, 18), Table 1. Within the five-year follow-up of the EUVAS cohort, 201 (38 %) of patients had at least one relapse during 1,804 patient-years of time at risk. PR3-ANCA and cardiovascular involvement at entry were independently associated with

a higher relapse risk, while renal function was inversely related i.e. renal insufficiency was associated with a lower risk for relapse (19). Others have found an association of increased risk for relapse in patients with GPA compared to those with MPA (10, 20), and in some series patients with initial involvement of the respiratory system are more prone to relapses (12, 21). The relapse may involve the same organ system as at the initial presentation but any organ may be affected. The role of ANCA, particularly a raised level of PR3-ANCA, is still under evaluation. Please, see the review written by *Rasmussen and Jayne.*
However, a Dutch study has indicated that patients who have a detectable level of PR3-ANCA (c-ANCA) at time of switch from induction to remission maintenance therapy have a higher relapse rate compared to those who have no detectable ANCA at switch (22).
Results from the five-year follow-up of EUVAS patients have shown that cyclophosphamide sparing strategies either by using pulsed intravenous cyclophosphamide or methotrexate compared to daily oral cyclophosphamide as induction therapy, although achieving comparable response, may be associated with a higher relapse rate of vasculitis in the long term perspective (23)(24). This effect is particularly observed in patients with PR3-ANCA. The observation is in agreement with earlier studies indicating a higher risk for relapse among patients treated with pulse cyclophosphamide (13, 25) and a German study which showed that the relapse-free survival correlated with the initial duration of induction therapy; the longer the treatment period the longer the relapse-free survival (9). The role of glucocorticoid therapy for relapse prevention is debatable, but a meta-analysis found that studies with longer courses of glucocorticoids were associated with fewer relapses (26).
In the Glomerular Disease Collaboration Network 42% of the 258 patients attaining remission relapsed during a follow-up of 49 months (median), and PR3-ANCA positivity, disease of the lung or upper respiratory tract were all associated with an increased risk for relapse (12). This report also documented that treatment resistance affected 23% of patients, particularly female, black patients and those presenting with severe kidney disease. Although, induction therapy was not standardized as in randomized controlled trials, it included corticosteroids and cyclophosphamide either as intravenous pulse or daily oral, and remission maintenance therapy with either azathioprine, mycophenolate mofetil or cyclosporine.
The long-term experience of newer therapeutic strategies is limited. Alberici et al., presented (abstract) at the 2013 EDTA meeting in Istanbul a 43% relapse rate after rituximab therapy for treating relapsing AAV, predominantly GPA, during a further 22 months of follow-up.
Thus, we still have no cure for AAV, at least not for the 50% of patients who are relapsing. Furthermore, we have no solid data at present regarding the optimal duration and type of remission maintenance therapy. We hope that at least some answers will be provided by the REMAIN trial which is currently undergoing data analyses.

RENAL OUTCOMES
The renal survival, i.e. survival without the need for renal replacement therapy, in patients with AAV has been reported to be as low as 57% at 30 months (11) up to 82% at 57 months (27). However, the reports on renal survival show great variation regarding the degree of renal involvement and renal function at entry, age of patients and type of ANCA.
As presented above, elderly people have an increased risk of death, and this may be at least partially caused by a decreased renal function of the elderly, as presented by Harper et al (14).

Table 2 shows the results of renal survival of patients with AAV presenting with renal involvement at diagnosis and with at least a follow-up of 24 months. Patients presenting with renal insufficiency, i.e. serum creatinine > 500µmol/L or dialysis dependency, at time of diagnosis have a worse outcome for renal as well as for patient survival. The EUVAS study on this subgroup of patients with AAV, the MEPEX trial, showed a high mortality, a finding in accordance with others (28). Recently a Dutch study showed that 23% of patients with dialysis dependency at presentation died within six months of follow-up, and another 29% continued on dialysis (29).
Patients with end stage renal failure treated by a kidney transplant do well (30), and the relapse rate among them has been reported as 0.01 per patient per year (30) or 17% (31). The relapse rate may be higher in patients with GPA and PR3-ANCA at time of transplantation vs those with MPA and MPO-ANCA. A retrospective analysis of a cohort of 36,884 patients with AAV with ESRD from New Zeeland and Australia demonstrated a comparable outcome on dialysis, as for patients with GPA and a kidney transplant, while patients with MPA and a kidney transplant had a higher risk for graft failure and death compared to those with non-AAV (32).
Please, see also the review by Bajema et al.

CARDIOVASCULAR DISEASE
It may not be surprising that AAV is associated with an increased risk for cardiovascular death, primarily involving the blood vessels and also commonly associated with renal involvement and renal insufficiency, further contributing to an increased risk of cardiovascular morbidity and mortality. Patients with AAV have a two- to fourfold increased risk of coronary heart disease compared to control subjects, (33, 34).Suppiah et al. presented (35) a logistic regression model to predict the risk of a cardiovascular (CV) event. Out of the 535 patients analyzed 74 (14%) had at least one CV event within the first five years of follow-up; 12% of the patients with GPA and 16% with MPA, respectively. There were 32 (6%) CV deaths, 25 (5%) non-fatal strokes and 42 (8%) had a non-fatal myocardial infarction or coronary intervention. Older age was associated with higher risk for a CV (OR 1.45 (95%CI 1.11-1.90)) while those with a PR3-ANCA showed a reduced risk for CV compared to those with a MPO-ANCA (OR 0.39 95%CI 0.20-0.74).
Arterial hypertension was diagnosed during the five-year follow-up in 17% of patients, and diabetes mellitus in 4% (35) This may be less than expected, comparing with patients with a kidney transplant in whom new onset diabetes develops in 5-50% (36)

MALIGNANCY
One of the main objectives launching new therapeutic trials within EUVAS was to reduce the risk for development of a malignancy. The report by Hoffman revealed an overall increased risk for cancer SIR (standardized incidence ratio) of 2.4 with a 33- fold increased risk for urinary bladder cancer and an 11 -fold increased risk for lymphoma (37). Similar findings of a SIR of 1.6-3.8 for all sites of cancer have later been published (10, 38-40). From the transplant field it is known that long-term immunosuppressive therapy is associated with an increased risk of cancer, particularly post transplant lymphoproliferative disorders (PTLD) and squamous cell carcinoma (41). However, for patients with AAV treatment with cyclophosphamide has particularly been associated with an increased risk for haemorrhagic cystitis with a subsequent risk for bladder cancer (42, 43), the latter often after a considerable latency period (38).

During 2,650 person years of follow-up in the long-term EUVAS study 50 new cancers were observed, with an SIR of 1.58 (95% CI 1.17-2.08) for cancers at all sites but an SIR 1.30 (95% CI 0.90-1.80) excluding non-melanoma skin cancer (44). 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. Previous reports have documented an SIR of 4.7-10.4 for non-melanoma skin cancer (15, 38, 39). A recent report from Germany in 2011 revealed no increased risk (SIR of 0.8 (95%CI 0.5-1.4)) of cancer at all sites among patients with AAV (16). This may reflect a less toxic therapy such as a less exposure to cyclophosphamide for example if administered as intravenous pulses instead of continuous oral and improvement of care regarding hydration and elimination of acrolein during administration of cyclophosphamide. However, it may be the total burden of immunosuppressive therapy that leads to an increased risk for cancer. Even the duration of azathioprine and corticosteroid use has been associated with an increased risk for skin cancer. Azathioprine for at least 12 months and a latency period of at least 60 months for developing a cancer gave a SIR of 24.7 (95% CI 6.7-63.2) for skin cancer, and corticosteroids for > 48 months a SIR for 20.8 (95% CI 5.7-53.3) (10).
The promising results obtained from the five-year follow-up of EUVAS patients as well as the German report could be the result of a smaller burden of immunosuppressive therapy. Alternatively, the lower incidence of cancer could be the result of a too short follow-up period. Therefore a longer follow-up study seems to be necessary. In view of the increased risk for non-melanoma skin cancer it may be advisable to regularly screen patients with AAV treated with immunosuppressive therapy for more than a year.
Another aspect is that there may be an association of cancer and AAV, as for cutaneous leukocytoclastic vasculitis or polyarteritis nodosa. Analyzing cohorts with AAV, approximately 8-10 % of patients have a cancer preceding the diagnosis of AAV by several years (15, 40).

CONCLUSIONS

Patients with a PR3- or MPO-ANCA associated vasculitis seem to have a more favorable long-term outcome today. But a lot still needs to be achieved and in particular the goal of finding a cure remains elusive. Early diagnosis is important in particular before end-stage renal failure is reached. Older patients have a worse outcome but younger patients should nevertheless be monitored carefully. The intensity of immune-suppression should be chosen to be sufficient to control disease manifestations and prevent relapse but also to avoid infection and malignancy. The optimal duration of remission maintenance therapy to achieve this goal is currently unclear.

CONFLICT OF INTEREST STATEMENT

KW, OF and GG None declared

TABLE 1 Overview on long-term outcome of patients with AAV; duration of follow-up, patient characteristics, relapse rate, patient and renal survival, induction treatment

Author / year of publication	**Period years**	**Numbers of patients Diagnosis Cohort**	**Follow-up** (months)	**Age** (years)	**Renal involvement / serum creatinine at baseline** (µmol/L)	**ANCA positivity at baseline** (% positive) **PR3**	**MPO**	**Relapse** Prop.of patients	**Patient survival** % at- months follow-up	**Induction treatment**
Andrassy / 1991 (45)	1980-89	25 GPA prospective	36	52	100 %	95[1]			96 % -36 months	Cyc SM
Hoffman /1992 (4)	1967-90	158 GPA prospective	96 (> 6 months)	41	18%	88[1]	-	50%	Approx. 80%	Cyc CS
Franssen / 1995 (46)	1985-93	92 GPA+MPA consecutive	24	59	75 %	50	50		86 % PR3-, 78 % MP0-ANCA	Cyc CS
Matteson /1996 (47)	1982-87	77 GPA	85	45	73 %	ND		ND	64 % - 85 months	Cyc CS Aza
Hogan /1996 (11)	1980-90'ies	107 MPA prospective	30	58	100 % 400	36[1]	64		85 % - 30 months	Cyc CS
Brijker / 1999 (48)	1993-96	32 GPA+MPA consecutive	25	58	-	38	62	-	88 % - 24 months	Cyc CS
Reinhold-Keller /2000 (7)	1966-93	155 GPA Consecutive retrospective	84	48	54 %	84	-	64 %	88 % - 60 months	Cyc CS MTX T/S
Aasaröd / 2000 (13)	1988-98	108 GPA Consecutive retrospective	42	55	100 % 250	88[1]	8		75 % - 60 months	Cyc CS
Cohen / 2000 (49)	1984-98	75 Consecutive retrospective	33	59	100 % 440	77*		23 %	87 % - 33 months	Cyc CS (PE)
Mahr / 2001 (6)	1990-95	49 GPA prospective	22	57	100 %	76[1]	8		67 % - 24 months	Cyc CS (PE)
Koldingsness/ 2002 (27)	1984-	56 GPA retrospective	57	50	80 % 168	87[2]			79 % - 60 months	Cyc CS PE TMP
Booth/ 2003 (20)	1995-00	246 GPA+MPA retrospective	37	66	100 % 450	92[2]		34 % (13 mo)	76 % - 60 months	Cyc CS (SM, PE)
Weidner/ 2004 (9)	1986-01	80 GPA+MPA retrospective	47	63	100 % 385	54	39		74 % - 47 months	Cyc CS (SM, PE)
Harper/ 2005 (14)	1990-00	229 GPA+MPA retrospective		65	100 % 550	95[2]		26 % (17mo)	60%	Cyc CS (SM, PE)

Rihova/ 2005 (50)	1986-97	61 GPA+MPA Consecutive retrospective	90	54	100 % 221	48	37	45 %	62 % - 120 months	Cyc CS
Westman / 2003 (15)	1971-93	117 GPA+MPA consecutive	92	62	100 % 288	61	33	56 %	52 % - 120 months	Cyc CS (SM, PE)
Bligny/2004 (51)	1984-99	93 GPA Retrospective	54	52	62 % 124	84	13	45 %	74 % -60 months	Cyc CS MtX, PE, others
Flossmann / 2011 (5)	1993-01	535; GPA MPA RCT prospective	62	61	92 % CKD 2—5 203	67	26	38 %	75%: cumulative survival at 1 and 5 years 88% - 78%	Cyc CS MTX PE SM
Holle /2011 (16)	1999-02	167 GPA (the third latest cohort 1999-2002)	47	55	ND	78	5	35 %	95% (159/167)	Cyc CS MTX TMP
Nakaya /2013 (52)	2000-01	64 MPA consecutive	40	69	> 90 % 203µmol/L	11	83	ND	66 % - 40 months	Cyc CS

*77% out of 66 patient sera tested, 75 patients were followed-up

[1] ANCA analysis by IIF only

[2] ANCA by IIF, c- and p-ANCA

GPA Granulomatosis with polyangiitis

MPA Microscopic polyangiitis

AAV ANCA-associated vasculitis

Cyc cyclophosphamide CS corticosteroids SM solumedrol PE plasma exchange Aza azathioprine MTX methotrexate TMP TrimetoprimSulpha

ND Not Done or No information given in manuscript

TABLE 2 Overview on renal survival of patients with a renal involvement at time of diagnosis of the ANCA-associated vasculitis, age and serum creatinine at baseline, induction treatment, and duration of follow-up, renal survival and predictors for renal survival

Numbers of patients Diagnosis	**Age** (years)	**Serum creatinine at baseline** (µmol/L)	**Induction treatment**	**Follow-up** (months)	**Renal survival** Proportion of patients without need for renal replacement therapy (%)-at time of follow-up (month)	**Predictors renal survival**	**Reference**
25 GPA Prospective	52	530	Cyc SM	36	75 % -36 months	Oboloscent glomeruli, tubulointerstitial lesions Relapse	(45)
107 AAV (69 MPA) Prospective	58	400	Cyc CS	30	57 % -30months	Serum creatinine at entry Age Race (African American worse vs Caucasians) Arterial sclerosis in renal biopsy	(11)
108 GPA Consecutive retrospective	55	250	Cyc CS (PE)	42	75 % - 60months	Serum creatinine at entry	(13)
75 AAV Consecutive retrospective	59	440	Cyc CS (PE)	33	50 % - 33months		(49)
246 GPA+MPA Retrospective	66	450	Cyc CS (SM, PE)	37	72 % - 37months		(20)
80 GPA+MPA Retrospective	63	385	Cyc CS (SM, PE)	47	77 % - 47months		(9)
61 GPA+MPA Consecutive retrospective	54	221	Cyc CS	90	69% - 60 months 56 % - 120 months		(50)
117 GPA+MPA Consecutive	62	288	Cyc CS (SM, PE)	92	67 % - 92months	PR3-ANCA>550U capture ELISA RR 2.2 (1.1-4.4) Serum creatinine ≥ 500 µmol/l RR 4.4 (1.2-15.7)	(15)
181 AAV renal Consecutive	60	395	Cyc CS (PE, IvMeP)	>37 months	Estimated 5 year renal survival 54%; not censored for death		(53)
212 GPA+MPA	58	321	Cyc CS (PE)	88	93% of those without DD, 33% of DD		(29)

GPA Granulomatosis with polyangiitis MPA Microscopic polyangiitis AAV ANCA-associated vasculitis DD Dialysis dependent
Cyc cyclophosphamide CS corticosteroids SM solumedrol PE plasma exchange Aza azathioprine MTX methotrexate T/S TrimetoprimSulpha
ND Not Done or No information given in manuscript

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