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Title

Outcome and treatment of elderly patients with anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis

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Running title

Treatment of ANCA-vasculitis in the elderly

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Abstract

Background and objectives ANCA-associated vasculitis is commonly found in elderly patients, but there are few data concerning outcome and treatment in the highest age groups.

Design, setting, participants and measurements Consecutive patients (n=151) presenting between 1997 and 2009 were retrospectively included from local registries in six centers in Sweden, United Kingdom and Czech Republic if diagnosed with microscopic polyangiitis or granulomatosis with polyangiitis at an age ≥75 years during the study period. Patients were followed until 2 years from diagnosis or death. Data on survival and renal function were analyzed with respect to age, sex, ANCA specificity, renal function, C-reactive protein, comorbidities and Birmingham Vasculitis Activity Score at diagnosis as well as treatment during the first month.

Results Median follow-up was 730 days (IQR 244-730). Overall 1-year survival was 71.5 % and 2-year survival 64.6 %. Older age, higher creatinine and lower Birmingham Vasculitis Activity Score were associated with higher mortality in multivariable analysis. Patients who were not treated with standard immunosuppressive therapy had significantly worse survival. Renal survival was 74.8 % at 1 year. No new cases of ESRD occurred during the second year. High creatinine at diagnosis was the only significant predictor of renal survival in multivariable analysis.

Conclusions ANCA-associated vasculitis is a disease with substantial mortality and morbidity among elderly patients. This study showed a better prognosis for those who received immunosuppressive treatment and those who were diagnosed before having developed advanced renal insufficiency.

Introduction

The ANCA-associated vasculitides (AAV) comprise microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA; Wegener's) and eosinophilic granulomatosis with polyangiitis (EGPA; Churg-Strauss).(1, 2) AAV are predominantly diseases of older patients, and the incidence increases with age.(3, 4) Several studies have shown that the risk of death and ESRD is higher in older patients but their response to treatment differs between studies.(5, 6) Because of an increased risk of adverse events,(7) dose adjustments of cyclophosphamide have been made for age in clinical trials(8) and are recommended in guidelines.(9) Despite the fact that AAV commonly affect older patients, the outcome of MPA and GPA in the elderly population is largely unknown.(10) Many randomized trials exclude patients aged >75 years and there are few observational studies focusing on elderly patients.(11, 12) The aim of this study was to investigate demographic factors, treatment and outcome in patients aged ≥75 years presenting with MPA or GPA.

Materials and Methods

Case retrieval and classification

Consecutive patients presenting at six centers in Sweden, United Kingdom and Czech Republic between 1997 and 2009 were included. Inclusion criteria were age ≥75 years at diagnosis and a clinical diagnosis of MPA or GPA according to the European Medicines Agency algorithm during the study period.(13) Patients classified as having eosinophilic granulomatosis with polyangiitis and polyarteritis nodosa were excluded, along with secondary vasculitis, drug-induced vasculitis and anti-glomerular basement membrane disease in accordance with the exclusion criteria in the European Medicines Agency algorithm.(13) Diagnosis was confirmed by review of patient charts. The project was approved by the Ethical Review Board in Lund, Sweden.

Participating centers

The Swedish cohort was recruited from local vasculitis databases at the Nephrology and Rheumatology Departments at Linköping University Hospital (catchment area 430 000 inhabitants)(14), the Nephrology and Rheumatology Departments at Skåne University Hospital in Lund and Malmö (700 000 inhabitants)(3) and the Nephrology Department at Karolinska University Hospital (1.5 million inhabitants).

The English cohort was recruited from a local database at the Imperial College Renal and Transplant Centre (2 million inhabitants) and from vasculitis and renal pathology databases at the Nephrology Department at Royal Free Hospital (1.4 million inhabitants) in London.

The Czech cohort was recruited from the Department of Nephrology at General University Hospital in Prague (tertiary national referral center with catchment area for vasculitis about 5 million inhabitants), using a local database transferred into a nationwide registry in 2009.

Data collection

The following data were collected retrospectively from time of diagnosis: date of diagnosis, age, sex, diagnosis type (MPA/GPA), ANCA specificity, C-reactive protein, creatinine (at diagnosis or before start of dialysis in patients dialysis dependent at diagnosis), dialysis dependency, disease activity according to Birmingham Vasculitis Activity Score (BVAS)(15) and major comorbidities. Data on outcome up to 2 years from diagnosis included day of death and ESRD. Data on treatment during the first 3 months from diagnosis included cumulative dose of pulse steroids, oral steroids and cyclophosphamide, treatment with rituximab or other cytotoxic agents, and use of plasma exchange. Based on the treatment issued during the first month, patients surviving that point were divided into groups. Patients were assigned to the rituximab group if they were receiving any dose of rituximab. Patients were assigned to the

oral cyclophosphamide group or the intravenous cyclophosphamide group if they were issued a minimum cumulative dose of 2000 mg oral or 1500 mg intravenous cyclophosphamide, respectively, during the first 3 months. Patients who were given less cyclophosphamide or treated with azathioprine, mycophenolate or methotrexate were assigned to "other regimens" group, whereas patients were assigned to the "steroids only" group if they were given a daily dosage of ≥30 mg of prednisolone. The remaining patients were placed in the "untreated" group. For each group, the proportion of patients given pulse steroids (cumulative dose ≥250 mg) or plasma exchange was recorded. The effect of treatment on survival and renal survival was estimated using an intention-to-treat approach starting on day 30.

Date of diagnosis was defined as follows: start of treatment with prednisolone ≥30 mg/day, plasma exchange or cyclophosphamide; if never treated, the day of biopsy; and if no biopsy, the day of the first positive ANCA test result. A dipstick value of ≥2 was taken as representative of hematuria equal to 10 red blood cells per high-power field when assessing BVAS. Indirect immunofluorescence or antigen-specific ELISA was used to detect ANCA. ESRD was defined as need for dialysis for >90 days. Comorbidities were registered essentially as described by Davies et al[16] with 1 point each given for malignancy, ischemic heart disease, peripheral vascular disease, heart failure, diabetes, systemic inflammatory disease (excluding AAV), pulmonary disease and cirrhosis.

Statistical analyses

Statistical analysis was performed using SPSS Statistics for Windows software (version 21.0; IBM Corp., Armonk, NY). P-values <0.05 were considered significant. Double-positive patients were designated as having either myeloperoxidase-ANCA (MPO-ANCA)/perinuclear ANCA (P-ANCA) or proteinase-3-ANCA (PR3-ANCA)/cytoplasmic ANCA (C-ANCA) depending on the highest titer. Differences between groups were analyzed

using the Mann-Whitney or Kruskal-Wallis test for non-parametric data and the chi-squared or Fisher's exact test for categorical data. All analyses exclude missing data. The Kaplan-Meier method was used to estimate overall and renal survival, and the log-rank test used to evaluate differences between groups. Censoring was performed at the day of loss to or completion of follow-up. Estimates of renal survival were censored for death. In analysis of treatment, patients who died within the first 30 days after diagnosis were excluded. Cox proportional hazards models were used to analyze variables at diagnosis and their association with overall survival and renal survival. Variables included were age, sex, ANCA specificity, BVAS, creatinine, C-reactive protein and comorbidity index. In a second model, a treatment variable was included. Patients in the intravenous cyclophosphamide/oral cyclophosphamide and rituximab groups were considered to have received standard immunosuppressive therapy and were compared with those who had not received such treatment. The standardized mortality ratio (SMR) was calculated for the group aged 75-84 years comparing the observed death rates in the Swedish cohorts with expected death rates in the general Swedish population matched for age and calendar year. The death rate for the general population was calculated using life tables from 2004 provided by Statistics Sweden (http://www.scb.se).

Results

Baseline patient characteristics

A total of 151 patients were included in this study, and their characteristics at diagnosis are shown in Table 1. Median age at diagnosis was 79 years (interquartile range [IQR] 77-82). MPA was diagnosed in 70% of the patients and GPA in 30%. MPO-ANCA/P-ANCA-positivity was seen in 60%, PR3-ANCA/C-ANCA-positivity in 36%, double-positivity in 1% and ANCA negativity in 3%. Renal involvement (according to BVAS) was seen in 92% of the patients, more commonly in patients with MPA (P<0.001). Biopsy was performed in 113

patients (76.4%; data missing in three patients), of these 96 (85.0%) were renal biopsies. Most parameters showed no significant differences between the three participating countries. However, dialysis dependency at diagnosis was seen in 16% in the Swedish cohort, compared to 44% in the English cohort and 60% in the Czech cohort (P<0.001). Comorbidities were more common in Czech patients; only 16% had no comorbidities compared to 47% and 40% of the Swedish and English patients, respectively (P<0.001). Median BVAS was 12 (IQR 9-12) in patients with renal-limited disease and 16 (IQR 13-19) in patients with more than one organ system involved (P<0.001).

Treatment

In total, seven patients died during the first month, and an additional 14 were excluded because of insufficient treatment data, leaving 130 patients for analysis of treatment. Characteristics for the different treatment groups are shown in Table 2. There were no significant differences between patients receiving standard immunosuppressive therapy (oral cyclophosphamide, intravenous cyclophosphamide, and rituximab groups) and those not receiving such therapy (other regimens, steroids only, or untreated groups) with regard to creatinine, BVAS, proportion of dialysis dependency, or proportion of patients with at least one comorbid condition at diagnosis. Likewise, there were no significant differences between the participating countries (Supplemental Table S1). The median cumulative dose of intravenous cyclophosphamide during the first 3 months in the standard treatment group was 3000 mg (IQR 2100-4500) and the corresponding figure for oral cyclophosphamide was 5270 mg (IQR 3100-6950).

Survival

Patients were followed until 2 years after diagnosis or death. Six patients (all from England) were lost to follow-up, within a median time of 69 days (IQR 34-140). One-year overall survival was 71.5% and 2-year survival 64.6%. During the first 3 months after diagnosis 22 patients (14.6%) died. Older age, higher creatinine and lower BVAS at diagnosis were independent factors associated with higher mortality by univariable (Figure 1; Supplemental Table S2) as well as multivariable analysis (Table 3). Two-year survival was 36.0% in the Czech Republic, 66.7% in Sweden and 80.2% in the United Kingdom (P=0.001). Dialysis at diagnosis was not significantly associated with survival (hazard ratio [HR], 1.57 95% confidence interval [CI], 0.90 to 2.74, P=0.12). Out of the 37 patients who developed ESRD, 18 (48.6%) died during follow-up compared to 34 of the 114 patients (29.8%) who did not develop ESRD. The SMR in patients aged 75-84 years in the Swedish cohort was 3.69 (95% CI 2.45 to 5.55) after 2 years. The SMR was 5.04 (95% CI, 3.13 to 8.11) in the first year and 1.86 (95% CI, 0.77 to 4.47) in the second year. Survival was significantly worse in patients not treated with standard immunosuppressive therapy compared to patients treated with either cyclophosphamide or rituximab (Figure 2). Two-year survival was 72.9% for patients treated with oral cyclophosphamide, 72.5% for intravenous cyclophosphamide, 81.3% for rituximab and 45.0% for no/other treatment. When including treatment in the survival analysis, age, creatinine and treatment remained significant predictors of mortality in both univariable and multivariable analyses, but BVAS lost its significance in the multivariable analysis (Table 4, Supplemental Table S3). The results remained essentially unchanged when including patients with lower cumulative doses of cyclophosphamide in the cyclophosphamide treatment group (HR, 0.30; 95% CI, 0.11 to 0.80; P=0.02).

Renal function

Dialysis was needed in 45 patients (30.6%) at the time of diagnosis. Twelve of these (26.7%) recovered independent renal function during follow-up. By the end of the first year, a total of 37 patients (24.5%) had developed ESRD. No new cases of ESRD occurred during the second year. Renal survival censored for death was 74.8%. It was 35.2% for the Czech cohort, 88.2% for the Swedish cohort and 71.1% for the English cohort (P<0.001). In multivariable analysis, creatinine level at diagnosis was the only significant predictor of renal survival (HR, 4.10; 95% CI, 2.25 to 7.49 per quartile increase in serum creatinine; P<0.001; Figure 3), whereas treatment was not significantly associated with renal outcome (HR, 1.88; 95% CI, 0.61 to 5.77; P=0.27). In the subgroup of patients dialysis dependent at diagnosis, nine of the 11 (81.8%) who recovered renal function were treated with plasma exchange, as compared with 14 of the 26 (53.8%) who did not recover renal function (P=0.15).

Discussion

In this study, we show that AAV in older patients is a severe condition with high mortality and morbidity during the first year after diagnosis. Despite the significant burden of disease, we found a relatively favorable outcome for those who survive the first year. To our knowledge, this is the largest study of patients ≥75 years with AAV.

We found older age, high creatinine and low BVAS to be predictors of worse survival. High age and impaired renal function have previously been shown to predict mortality in younger age groups as well.(6, 11, 14, 17-20) The inverse relationship between BVAS and survival is intriguing and opposite of some previous findings.(11, 18) Because the vast majority of patients in our study had renal involvement at diagnosis, patients with a high BVAS had both renal and extrarenal symptoms, whereas those with renal-limited disease fell in the low BVAS group. It is possible that patients with few extra-renal symptoms are diagnosed at a

later stage with more irreversible renal damage and worse survival. However, this association needs to be confirmed in other studies and the cause remains to be elucidated.

Survival was significantly worse in those not treated with standard doses of cyclophosphamide or rituximab. There is a risk of confounding by indication when analyzing treatment data in retrospective studies (in this case, that frail patients receive less treatment), and we did not have data on the detailed clinical context including the goals and preferences of patients or the treating physician's motive for therapy decisions. To reduce this effect we did not include deaths occurring during the first month and used an intention-to-treat approach, reasoning that standard therapy given during the first month was intended to continue according to modern guidelines,(9, 21) whereas this was not the case when such therapy was not issued during the first month. It is, however, difficult to rule out the possibility that some patients who originally received immunosuppressive treatment developed complications and that therapy was stopped. The worse prognosis in these patients would thus be caused by early adverse events. However, also when considering all cyclophosphamide use as intention-to-treat with standard therapy, there was a clear survival benefit for standard therapy. The unfavorable prognosis in those treated less aggressively cannot readily be explained by more comorbidities, worse renal function or differences in disease activity at diagnosis, because these parameters did not differ significantly between the groups. However, this does not exclude the possibility that some patients were still considered frail and not suitable for immunosuppressive therapy. The best survival was seen in patients treated with rituximab; however the number of patients was rather small and no rituximab was given in the Czech cohort with the worst survival rate. Hence, this result should be interpreted with care

The survival differences between countries may, at least partly, be explained by selection bias. The Department of Nephrology in Prague is a tertiary referral center receiving the most

severe cases of AAV. Additionally, the Czech patients had more comorbidities and more often had advanced renal insufficiency at diagnosis. Opposite to our results, others have reported dialysis at diagnosis to be an independent factor for survival(20) and it is possible that our analysis did not fully compensate for this factor. Comorbidities were not associated with mortality in the entire cohort, but reached borderline significance in the analysis including treatment. In our cohort, 15% of the patients had a previous malignancy before the diagnosis of AAV. This is similar to other studies showing a frequency of malignancies of 8-16%.(17, 22) The life expectancy at birth was 75.3 years in the Czech Republic in 2003, compared to 78.3 years in the United Kingdom and 80.2 years in Sweden.(23) The effect of differences in life expectancies in the general population when comparing the survival of AAV is difficult to discern.

One-year survival was 72% and 2-year survival was 65% in this study compared with 82-88% and 82-85%, respectively in previous studies.(2, 17, 18) We also show that survival in the Swedish cohort was significantly worse compared to the background population during the first year after diagnosis, but was not significantly worse during the second year. Together with the fact that no new cases of ESRD occurred during the second year, this implies a fairly good prognosis if patients survive the first year.

Importantly, we found that elderly patients usually present with significant renal involvement and a predominance of clinical MPA and MPO-ANCA/P-ANCA positivity. This is consistent with the finding that patients with MPA are older than patients with GPA and that patients with MPO/P-ANCA are older than patients with PR3/C-ANCA.(5, 6, 11, 18, 24, 25) Results showing that older patients with GPA have more renal insufficiency and less upper airway symptoms(26) add to this picture. We found a higher proportion of MPO/P-ANCA positive GPA as compared to two large studies in Caucasian patients. In our cohort, 24% of patients with GPA were positive for MPO/P-ANCA compared with 9% and 10%, respectively, in a

follow-up of patients from four European Vasculitis Study Group trials and a large genetic study in Europe.(18, 27)

High creatinine at presentation is a well-known risk factor for impaired renal survival(2, 12, 17, 28, 29), and we confirmed this in older patients. High creatinine at diagnosis was the only significant predictor of renal survival in multivariable analysis, and treatment with immunosuppressive agents was not significantly associated with renal survival. Most patients reaching ESRD were dialysis dependent at presentation and conceivably already had irreversible renal damage at the time of diagnosis. Increased awareness of these conditions in the elderly and early recognition is probably important for improved renal survival. Plasma exchange has been shown to reduce the risk of progression to ESRD in patients with severe renal impairment at diagnosis.(30) In accordance with this, we found a tendency towards better renal survival in those treated with plasma exchange in the subgroup of patients who were dialysis dependent at diagnosis.

Our study has several limitations. The greatest limitation is the retrospective nature of the data and the risk of introducing bias related to this, as discussed above. A possible limitation is that the centers in Linköping and Lund received both rheumatology and nephrology patients, whereas London received relatively more nephrology patients and Stockholm and Prague almost exclusively received patients with renal involvement. However, referral bias cannot explain the large proportion of patients with MPA and renal involvement because this did not differ significantly between countries. Because of the heterogeneity of referral patterns in the participating centers, our results are difficult to generalize to sites with different patient characteristics. We did not have any data on renal histology, so we could not analyze whether this was predictive of outcome.

In conclusion, we demonstrate in a large cohort of elderly patients with AAV that survival is significantly better in patients who are treated with adequate doses of cyclophosphamide or rituximab at diagnosis compared with patients who receive less aggressive treatment.

Disclosures

None.

Acknowledgements

References

1. Jennette JC, Falk RJ, Hu P, Xiao H: Pathogenesis of antineutrophil cytoplasmic autoantibody-associated small-vessel vasculitis. *Annu Rev Pathol* 8**:** 139-160, 2013

2. Booth AD, Almond MK, Burns A, Ellis P, Gaskin G, Neild GH, Plaisance M, Pusey CD, Jayne DR: Outcome of ANCA-associated renal vasculitis: a 5-year retrospective study. *Am J Kidney Dis* 41**:** 776-784, 2003

3. Mohammad AJ, Jacobsson LT, Westman KW, Sturfelt G, Segelmark M: Incidence and survival rates in Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome and polyarteritis nodosa. *Rheumatology (Oxford)* 48**:** 1560-1565, 2009

4. Ntatsaki E, Watts RA, Scott DG: Epidemiology of ANCA-associated vasculitis. *Rheum Dis Clin North Am* 36**:** 447-461, 2010

5. Harper L, Savage CO: ANCA-associated renal vasculitis at the end of the twentieth century--a disease of older patients. *Rheumatology (Oxford)* 44**:** 495-501, 2005

6. Chen M, Yu F, Zhang Y, Zhao MH: Antineutrophil cytoplasmic autoantibody-associated vasculitis in older patients. *Medicine (Baltimore)* 87**:** 203-209, 2008

7. Little MA, Nightingale P, Verburgh CA, Hauser T, De Groot K, Savage C, Jayne D, Harper L: Early mortality in systemic vasculitis: relative contribution of adverse events and active vasculitis. *Ann Rheum Dis* 69**:** 1036-1043, 2010

8. Harper L, Morgan MD, Walsh M, Hoglund P, Westman K, Flossmann O, Tesar V, Vanhille P, de Groot K, Luqmani R, Flores-Suarez LF, Watts R, Pusey C, Bruchfeld A, Rasmussen N, Blockmans D, Savage CO, Jayne D: Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up. *Ann Rheum Dis* 71**:** 955-960, 2012

9. Mukhtyar C, Guillevin L, Cid MC, Dasgupta B, de Groot K, Gross W, Hauser T, Hellmich B, Jayne D, Kallenberg CG, Merkel PA, Raspe H, Salvarani C, Scott DG, Stegeman C, Watts

R, Westman K, Witter J, Yazici H, Luqmani R: EULAR recommendations for the management of primary small and medium vessel vasculitis. *Ann Rheum Dis* 68**:** 310-317, 2009

10. Tarzi RM, Pusey CD: Vasculitis: Risks and rewards of treating elderly patients with vasculitis. *Nat Rev Nephrol* 7**:** 253-255, 2011

11. Hoganson DD, From AM, Michet CJ: ANCA vasculitis in the elderly. *J Clin Rheumatol* 14**:** 78-81, 2008

12. Bomback AS, Appel GB, Radhakrishnan J, Shirazian S, Herlitz LC, Stokes B, D'Agati VD, Markowitz GS: ANCA-associated glomerulonephritis in the very elderly. *Kidney Int* 79**:** 757-764, 2011

13. Watts R, Lane S, Hanslik T, Hauser T, Hellmich B, Koldingsnes W, Mahr A, Segelmark M, Cohen-Tervaert JW, Scott D: Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. *Ann Rheum Dis* 66**:** 222-227, 2007

14. Eriksson P, Jacobsson L, Lindell A, Nilsson JA, Skogh T: Improved outcome in Wegener's granulomatosis and microscopic polyangiitis? A retrospective analysis of 95 cases in two cohorts. *J Intern Med* 265**:** 496-506, 2009

15. Flossmann O, Bacon P, de Groot K, Jayne D, Rasmussen N, Seo P, Westman K, Luqmani R: Development of comprehensive disease assessment in systemic vasculitis. *Ann Rheum Dis* 66**:** 283-292, 2007

16. Davies SJ, Russell L, Bryan J, Phillips L, Russell GI: Comorbidity, urea kinetics, and appetite in continuous ambulatory peritoneal dialysis patients: their interrelationship and prediction of survival. *Am J Kidney Dis* 26**:** 353-361, 1995

17. Westman KW, Selga D, Isberg PE, Bladstrom A, Olsson H: High proteinase 3-anti-neutrophil cytoplasmic antibody (ANCA) level measured by the capture enzyme-linked

immunosorbent assay method is associated with decreased patient survival in ANCA-associated vasculitis with renal involvement. *J Am Soc Nephrol* 14**:** 2926-2933, 2003

18. Flossmann O, Berden A, de Groot K, Hagen C, Harper L, Heijl C, Hoglund P, Jayne D, Luqmani R, Mahr A, Mukhtyar C, Pusey C, Rasmussen N, Stegeman C, Walsh M, Westman K: Long-term patient survival in ANCA-associated vasculitis. *Ann Rheum Dis* 70**:** 488-494, 2011

19. Mukhtyar C, Flossmann O, Hellmich B, Bacon P, Cid M, Cohen-Tervaert JW, Gross WL, Guillevin L, Jayne D, Mahr A, Merkel PA, Raspe H, Scott D, Witter J, Yazici H, Luqmani RA: Outcomes from studies of antineutrophil cytoplasm antibody associated vasculitis: a systematic review by the European League Against Rheumatism systemic vasculitis task force. *Ann Rheum Dis* 67**:** 1004-1010, 2008

20. Slot MC, Tervaert JW, Franssen CF, Stegeman CA: Renal survival and prognostic factors in patients with PR3-ANCA associated vasculitis with renal involvement. *Kidney Int* 63**:** 670-677, 2003

21. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, Kallenberg CG, St Clair EW, Turkiewicz A, Tchao NK, Webber L, Ding L, Sejismundo LP, Mieras K, Weitzenkamp D, Ikle D, Seyfert-Margolis V, Mueller M, Brunetta P, Allen NB, Fervenza FC, Geetha D, Keogh KA, Kissin EY, Monach PA, Peikert T, Stegeman C, Ytterberg SR, Specks U: Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 363**:** 221-232, 2010

22. Silva F, Seo P, Schroeder DR, Stone JH, Merkel PA, Hoffman GS, Spiera R, Sebastian JK, Davis JC, Jr., St Clair EW, Allen NB, McCune WJ, Ytterberg SR, Specks U: Solid malignancies among etanercept-treated patients with granulomatosis with polyangiitis (Wegener's): long-term followup of a multicenter longitudinal cohort. *Arthritis Rheum* 63**:** 2495-2503, 2011

23. OECD. Life expectancy at birth, total population. Health: Key Tables from OECD 2010. No. 11.doi: 10.1787/20758480-2009-table8

24. Mahr A, Katsahian S, Varet H, Guillevin L, Hagen EC, Hoglund P, Merkel PA, Pagnoux C, Rasmussen N, Westman K, Jayne DR: Revisiting the classification of clinical phenotypes of anti-neutrophil cytoplasmic antibody-associated vasculitis: a cluster analysis. *Ann Rheum Dis* 72**:** 1003-1010, 2013

25. de Joode AA, Sanders JS, Stegeman CA: Renal survival in proteinase 3 and myeloperoxidase ANCA-associated systemic vasculitis. *Clin J Am Soc Nephrol* 8**:** 1709-1717, 2013

26. Krafcik SS, Covin RB, Lynch JP, 3rd, Sitrin RG: Wegener's granulomatosis in the elderly. *Chest* 109**:** 430-437, 1996

27. Lyons PA, Rayner TF, Trivedi S, Holle JU, Watts RA, Jayne DR, Baslund B, Brenchley P, Bruchfeld A, Chaudhry AN, Cohen Tervaert JW, Deloukas P, Feighery C, Gross WL, Guillevin L, Gunnarsson I, Harper L, Hruskova Z, Little MA, Martorana D, Neumann T, Ohlsson S, Padmanabhan S, Pusey CD, Salama AD, Sanders JS, Savage CO, Segelmark M, Stegeman CA, Tesar V, Vaglio A, Wieczorek S, Wilde B, Zwerina J, Rees AJ, Clayton DG, Smith KG: Genetically distinct subsets within ANCA-associated vasculitis. *N Engl J Med* 367**:** 214-223, 2012

28. Kaplan-Pavlovcic S, Cerk K, Kveder R, Lindic J, Vizjak A: Clinical prognostic factors of renal outcome in anti-neutrophil cytoplasmic autoantibody (ANCA)-associated glomerulonephritis in elderly patients. *Nephrol Dial Transplant* 18 Suppl 5**:** v5-7, 2003

29. Hogan SL, Nachman PH, Wilkman AS, Jennette JC, Falk RJ: Prognostic markers in patients with antineutrophil cytoplasmic autoantibody-associated microscopic polyangiitis and glomerulonephritis. *J Am Soc Nephrol* 7**:** 23-32, 1996

30. Jayne DR, Gaskin G, Rasmussen N, Abramowicz D, Ferrario F, Guillevin L, Mirapeix E, Savage CO, Sinico RA, Stegeman CA, Westman KW, van der Woude FJ, de Lind van Wijngaarden RA, Pusey CD: Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. *J Am Soc Nephrol* 18**:** 2180-2188, 2007

Tables

Table 1. Demographic factors at the time of diagnosis divided according to country and diagnosis type.

Variables	All n=151	Sweden 58% (n=87)	United Kingdom 26% (n=39)	Czech Republic 16% (n=25)	P value	MPA 70% (n=105)	GPA 30% (n=46)	P value
Sex								
Male	50% (76)	55% (48)	54% (21)	28% (7)	0.05	47% (49)	59% (27)	0.17
Female	50% (75)	45% (39)	46% (18)	72% (18)		53% (56)	41% (19)	
Age (median)	79 (77-82)	79 (77-83)	78 (77-82)	78 (77-82)	0.69	79 (77-82)	78 (76-81)	0.16
Age								
<80 years	54% (82)	52% (45)	56% (22)	60% (15)	0.73	51% (54)	61% (28)	0.28
≥80 years	46% (69)	48% (42)	44% (17)	40% (10)		49% (51)	39% (18)	
ANCA[1]								
MPO/P-ANCA	60% (89)	58% (50)	58% (22)	71% (17)	0.48	75% (78)	24% (11)	<0.001
PR3/C-ANCA	36% (53)	39% (34)	32% (12)	29% (7)	0.56	18% (19)	76% (34)	<0.001
Double-positive	1% (2)	2% (2)	0% (0)	0% (0)	>0.99	2% (2)	0% (0)	>0.99
Negative	3% (5)	1% (1)	10% (4)	0% (0)	0.02	5% (5)	0% (0)	0.32
Creatinine *mg/dL*[2]	3.20 (1.72-5.18)	2.93 (1.57-4.54)	4.33 (2.43-5.85)	4.47 (2.71-5.66)	0.06	3.76 (2.74-5.69)	2.04 (0.97-3.25)	<0.001
CRP *mg/L*[3]	75 (18-134)	99 (27-139)	38 (8-124)	68 (22-120)	0.07	62 (15-123)	119 (50-156)	<0.001
BVAS[4]	15 (12-19)	16 (13-20)	12 (9-14)	14 (13-17)	<0.001	14 (12-18)	17 (13-21)	0.02
Organ involvement[5]								
General	63% (82)	76% (66)	21% (4)	48% (12)	<0.001	62% (56)	65% (26)	0.71
Cutaneous	9% (12)	7% (6)	11% (2)	16% (4)	0.27	10% (9)	8% (3)	0.76
Mucous/eyes	5% (7)	5% (4)	11% (2)	4% (1)	0.43	0% (0)	18% (7)	<0.001
ENT	15% (20)	20% (17)	5% (1)	8% (2)	0.22	3% (3)	43% (17)	<0.001
Chest	34% (44)	36% (31)	11% (2)	44% (11)	0.05	25% (23)	53% (21)	0.002
Cardiovascular	5% (7)	8% (7)	0% (0)	0% (0)	0.30	4% (4)	8% (3)	0.44
Abdominal	3% (4)	5% (4)	0% (0)	0% (0)	0.77	3% (3)	3% (1)	>0.99
Renal	92% (121)	90% (78)	100% (19)	96% (24)	0.23	98% (89)	80% (32)	<0.001
Nervous system	16% (21)	22% (19)	0% (0)	8% (2)	0.02	15% (14)	18% (7)	0.76
Dialysis dependency[6]	31% (45)	16% (14)	44% (16)	60% (15)	<0.001	34% (35)	22% (10)	0.14
Comorbidity score								
0	40% (61)	47% (41)	40% (16)	16% (4)	0.02	36% (38)	50% (28)	0.11

1	35% (53)	29% (25)	44% (17)	44% (11)	0.16	35% (37)	35% (16)	0.96
2	19% (29)	17% (15)	13% (5)	36% (9)	0.06	22% (23)	13% (6)	0.20
3-4	5% (8)	7% (6)	3% (1)	4% (1)	0.62	7% (7)	2% (1)	0.44
Comorbidities								
Hypertension	46% (70)	36% (31)	39% (15)	96% (24)	<0.001	49% (51)	41% (19)	0.41
Heart failure	8% (12)	14% (12)	0% (0)	0% (0)	0.01	10% (11)	2% (1)	0.11
Diabetes	15% (22)	8% (7)	18% (7)	32% (8)	0.01	14% (15)	15% (7)	0.88
IHD	19% (28)	13% (11)	15% (6)	44% (11)	0.004	23% (24)	9% (4)	0.04
Stroke	13% (20)	17% (15)	5% (2)	12% (3)	0.16	14% (15)	11% (5)	0.57
Malignancy	15% (22)	16% (14)	10% (4)	16% (4)	0.77	12% (13)	20% (9)	0.25
Pulmonary disease	12% (18)	9% (8)	18% (7)	12% (3)	0.34	16% (17)	2% (1)	0.01

Values are presented as % (n) or median (interquartile range) and exclude missing data. [1]Data missing in two patients; [2]data missing in nine patients; [3]data missing in six patients; [4]data missing in four patients; [5]data missing in 20 patients; [6]data missing in four patients. MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; ANCA, anti-neutrophil cytoplasm antibodies; MPO, myeloperoxidase; PR3, proteinase-3; CRP, C-reactive protein; BVAS, Birmingham Vasculitis Activity Score; ENT, ear-nose-throat; IHD, ischemic heart disease

Table 2. Groups of patients based on the treatment given during the first month after diagnosis: Contribution to the treatment groups by the participating countries (A), baseline characteristics (B) and additional therapy (C).

	CYC oral 35.4% (n=46)	CYC iv 30.8% (n=40)	Rituximab 12.3% (n=16)	Steroids only 1.5% (n=2)	Other[4] 14.6% (n=19)	Untreated 5.4% (n=7)
A. Countries						
Sweden (n=81)	30.9% (25/81)	35.8% (29/81)	8.6% (7/81)	2.5% (2/81)	14.8% (12/81)	7.4% (6/81)
United Kingdom (n=25)	52.0% (13/25)	0.0% (0/25)	36.0% (9/25)	0.0% (0/25)	12.0% (3/25)	0.0% (0/25)
Czech Republic (n=24)	33.3% (8/24)	45.8% (11/24)	0.0% (0/24)	0.0% (0/24)	16.7% (4/24)	4.2% (1/24)
B. Clinical variables						
Age	79 (77-81)	78 (77-81)	79 (78-81)	78 (76-79)	83 (78-85)	80 (77-81)
MPO[1]	76.1% (35/46)	59.0% (23/39)	37.5% (6/16)	100% (2/2)	47.4% (9/19)	85.7% (6/7)
PR3[1]	21.7% (10/46)	41.0% (16/39)	56.3% (9/16)	0.0% (0/2)	52.6% (10/19)	14.3% (1/7)
Creatinine mg/dL[2]	4.04 (2.68-4.92)	2.00 (1.13-3.69)	3.01 (2.00-4.28)	8.89 (2.29-15.49)	4.02 (2.69-5.96)	2.99 (2.05-6.24)
Dialysis[1]	37.8% (17/45)	17.5% (7/40)	31.3% (5/16)	50.0% (1/2)	26.3% (5/19)	28.6% (2/7)
VAS[1]	14 (12-19)	15 (14-20)	14 (9-21)	15 (14-15)	16 (13-19)	12 (5-17)
Comorbidities[3]	71.7% (33/46)	57.5% (23/40)	50.0% (8/16)	0.0% (0/2)	63.2% (12/19)	71.4% (5/7)
C. Treatment variables						
Pulse steroids	28.3% (13/46)	55.0% (22/40)	56.3% (9/16)	0.0% (0/2)	31.6% (6/19)	0.0% (0/7)
Plasma exchange[1]	26.1% (12/46)	27.5% (11/40)	46.7% (7/15)	50.0% (1/2)	26.3% (5/19)	14.3% (1/7)

Values are presented as % (n) or median (interquartile range) and exclude missing data. [1]Data missing in one patient; [2]data missing in six patients; [3]patients with ≥ 1 comorbid condition at diagnosis; [4]other cytotoxic agents or cumulative cyclophosphamide dose <2000 mg oral cyclophosphamide/<1500 mg intravenous cyclophosphamide during the first 3 months.

CYC, cyclophosphamide MPO, myeloperoxidase; PR3, proteinase-3; BVAS, Birmingham

Vasculitis Activity Score

Table 3. Multivariable Cox regression analysis of overall 2-year survival in the entire cohort[1].

Variable	Hazard ratio (95% CI)	*P* value
Age (per year)	1.13 (1.06-1.21)	<0.001
Male sex	1.20 (0.65-2.18)	0.56
BVAS (per point)	0.92 (0.86-0.98)	0.01
MPO/P-ANCA	0.67 (0.37-1.24)	0.20
CRP (per quartile)	1.13 (0.85-1.51)	0.39
Creatinine (per quartile)	1.35 (1.03-1.76)	0.03
Comorbidity score (per point)	1.22 (0.84-1.78)	0.30

[1]Individual data missing in 15 patients, analysis performed on a total of 136 patients.

CI, confidence interval; BVAS, Birmingham Vasculitis Activity Score; MPO, myeloperoxidase; P-ANCA, perinuclear anti-neutrophil cytoplasm antibodies; CRP, C-reactive protein

Table 4. Multivariable Cox regression analysis of overall 2-year survival in patients with complete treatment data available[1].

Variables	Hazard ratio (95% CI)	*P* value
Age (per year)	1.13 (1.04-1.23)	0.003
Male sex	1.37 (0.69-2.73)	0.37
BVAS (per point)	0.94 (0.88-1.01)	0.09
MPO/P-ANCA	0.74 (0.36-1.51)	0.41
CRP (per quartile)	1.01 (0.72-1.42)	0.95
Creatinine (per quartile)	1.40 (1.02-1.92)	0.04
Comorbidity score (per point)	1.48 (0.97-2.26)	0.07
Treatment[2]	0.40 (0.19-0.87)	0.02

[1]Individual data missing in 11 patients, analysis performed on a total of 119 patients. [2] Rituximab or cyclophosphamide at minimum dose 2000 mg oral/1500 mg intravenous during the first 3 months.

CI, confidence interval; BVAS, Birmingham Vasculitis Activity Score; MPO, myeloperoxidase; P-ANCA, perinuclear anti-neutrophil cytoplasm antibodies; CRP, C-reactive protein
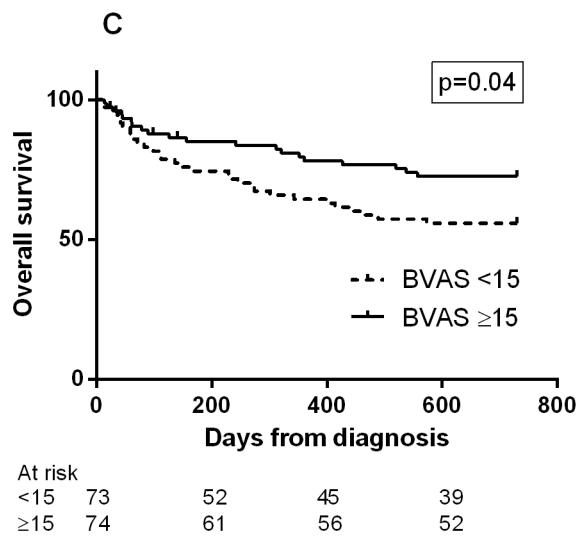
Figure legends

Figure 1. Patient survival
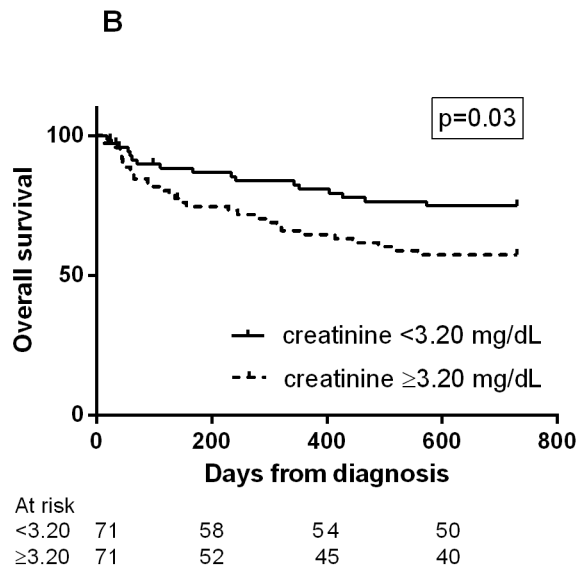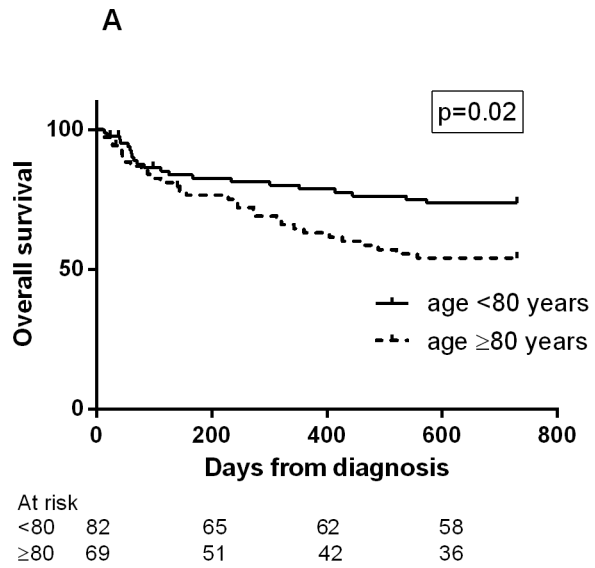
Kaplan-Meier plot depicting overall 2-year survival divided according to age, creatinine level, and BVAS. (A) Age at diagnosis ≥80 years (n=69) vs. <80 years (n=82); (B) Creatinine level at diagnosis equal to/above median (≥3.20 mg/dL) (n=71) vs. creatinine below median (<3.20 mg/dL) (n=71); (C) BVAS at diagnosis ≥15 (n=74) vs. BVAS <15 (n=73). BVAS, Birmingham Vasculitis Activity Score.
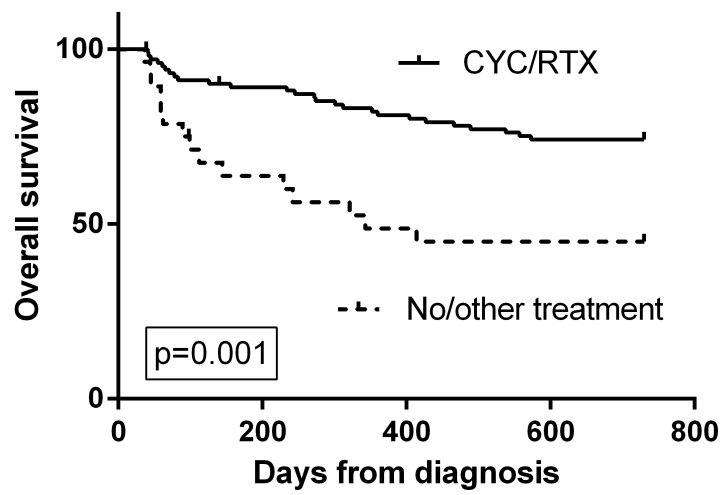
Figure 2. Treatment

Kaplan-Meier plot depicting overall 2-year survival divided according to the treatment given during the first month after diagnosis. CYC/RTX indicates rituximab or cyclophosphamide at minimum dose 2000 mg oral/1500 mg inytravenous during the first 3 months (n=102), whereas no/other treatment indicates other regimens, steroids only or untreated (n=28). Number at risk starting on day 30.
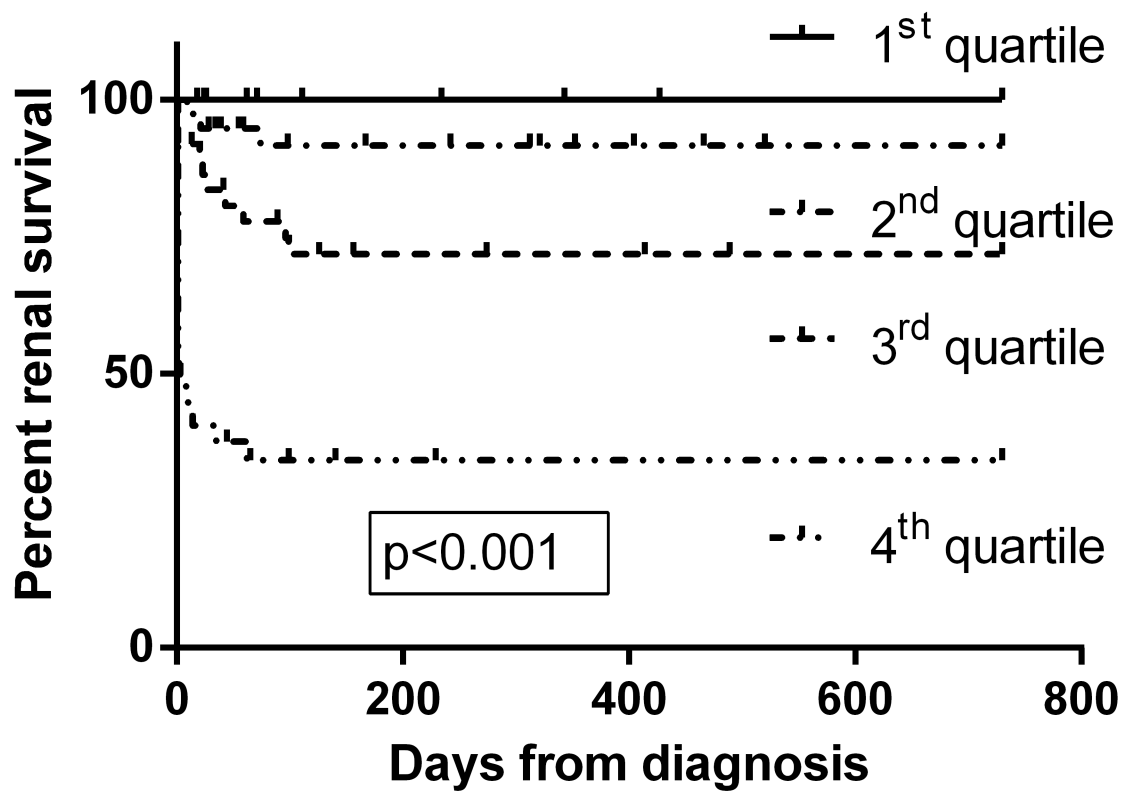
Figure 3. Renal survival

Kaplan-Meier plot depicting renal survival censored for death divided according to serum creatinine at diagnosis. First quartile 0.69-1.73 mg/dL (n=37); second quartile 1.74-3.34 mg/dL (n=38); third quartile 3.35-5.67 mg/dL (n=37); fourth quartile 5.68 mg/dL-dialysis dependency (n=37).

A

p=0.02

Overall survival

100

50

0

age <80 years
age ≥80 years

0   200   400   600   800

Days from diagnosis

At risk
<80   82   65   62   58
≥80   69   51   42   36

B

p=0.03

Overall survival

100

50

0

creatinine <3.20 mg/dL
creatinine ≥3.20 mg/dL

0   200   400   600   800

Days from diagnosis

At risk
<3.20   71   58   5 4   50
≥3.20   71   52   45   40

C

p=0.04

Overall survival

100

50

0

BVAS <15
BVAS ≥15

0   200   400   600   800

Days from diagnosis

At risk
<15   73   52   45   39
≥15   74   61   56   52

At risk

CYC/RTX	102	89	81	74
No/other	28	17	13	12