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# Renal transplantation in systemic vasculitis: when is it safe?

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## Abstract

**Background.** There are no clear guidelines on renal transplantation in patients with antineutrophil cytoplasmic antibody (ANCA)-positive vasculitis.

**Methods.** We undertook a survey of transplant centres across Europe to assess whether there was consensus about how to manage transplantation in patients with vasculitis. We then identified 107 renal allograft recipients whose primary disease was systemic vasculitis and assessed their outcome post-transplant.

**Results.** All questionnaire respondents felt that vasculitis should be in remission at transplantation, 16% believed that ANCA should be negative pre-transplant and 40% felt that one should wait >12 months after remission before transplanting. Remission was defined by all as an absence of clinical symptoms of vasculitis, but three respondents (13%) also required a negative ANCA test. Overall graft survival was 70% after 10 years (95% C.I. 58–82). A total of 30 (41% of those with known ANCA status) were ANCA-positive peri-transplantation, while 15 (14%) were transplanted <1 year post-remission. Severe vasculopathy occurred more frequently in ANCA-positive recipients (odds ratio 4.4, 95% C.I. 1.1–16.8, $P < 0.05$), although causation cannot be determined from this study. Vasculopathy significantly reduced 10-year graft survival to 47% ($P < 0.05$). However, ANCA status *per se* was not significantly associated with graft failure. The strongest predictor of death was transplantation <1 year post-vasculitis remission on both univariate and multivariate analysis (hazard ratio 2.3, $P < 0.05$).

**Conclusions.** In conclusion, circulating ANCA at transplant was associated with the development of vascular lesions in the graft but was not significantly correlated with graft survival. Most grafts were lost due to patient death, which was more likely if transplantation occurred <12 months following induction of remission of ANCA-positive vasculitis.

**Keywords:** ANCA; survey; transplantation; vasculitis; vasculopathy

## Introduction

Glomerulonephritis secondary to renal vasculitis results in end-stage renal disease in ∼20–40% of patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AASV) [1–3]. Renal transplantation is often a viable option in these patients, with allograft survival at least as good as that following transplantation for other causes of inflammatory renal disease [4–7]. Data from small case series indicate that vasculitis recurrence is infrequent post-transplantation and rarely is associated with graft loss [8,9], while relapse rates are well below those reported in the pre-transplant population [10].

However, the available published evidence, limited as it is to small single-centre case series, is insufficient to guide physicians caring for patients with AASV who present for transplantation. For example, there are no agreed guidelines on how long to wait after induction of remission before transplanting, whether or not to transplant in the face of a positive ANCA test or whether circulating ANCA have any impact on the occurrence of transplant vascular injury. With respect to the latter point, several published reports suggest that, in the context of solid organ transplantation, the development of autoantibodies (for example, against the intermediate filament protein, vimentin in cardiac transplants [11–13]) or donor-specific alloantibodies are associated with vascular changes in the graft. Although it is likely that there are several divergent mechanisms at play in the generation of allograft vascular injury, it is possible that ANCA (or coexistent anti-endothelial antibodies) have more subtle effects on progression of allograft vasculopathy. In support of this hypothesis, it has been found that reduplication of the elastic lamina of allograft peri-tubular capillaries is associated with AASV as the original cause of renal failure [14].

Addressing these questions requires a much larger number of cases than that published previously. Therefore, we adopted a broad approach in an attempt to, firstly, assess whether there was a consensus among physicians as to how

to manage these patients and, secondly, to identify as many cases of transplantation in patients with AASV as possible with a view to identifying factors (including ANCA status peri-transplantation) independently associated with mortality post-transplant, graft loss and vascular disease in the graft.

## Materials and methods

*Questionnaire assessing physician attitudes to transplanting patients with AASV*

We designed a questionnaire to assess whether there was consensus among physicians as to how to approach renal transplantation in these patients (supplemental online material 1). This was sent to transplant units in the UK, Ireland and across Europe [via the European Vasculitis Study group (EUVAS) network]. UK Transplant, the national body overseeing renal transplantation in the UK (www.uktransplant.org.uk) was approached for a list of those renal transplant units that had returned data on patients with an EDTA code of 74, indicating a diagnosis of Wegener's granulomatosis (WG) ($N = 74$). As transplantation in Ireland falls under a different remit, these physicians were contacted directly. To maximize the response, questionnaire packs were followed up with telephone and/or email contact. The respondent was asked to try and provide answers that reflected the policy of the unit as a whole. If there was more than one view in a given unit, multiple returns were encouraged.

*Identification of patient population*

To ensure patient anonymization and to make it as simple as possible for participating units, we arranged for UK Transplant to send a list of transplanted patients with EDTA code 74 (WG) separately to each unit. In the questionnaire pack, we included a second questionnaire pertaining to patients on this list. We also asked each participating unit to attempt to identify transplanted patients with AASV that had been omitted from the UK Transplant list, or that had forms of AASV other than WG, as defined by the Chapel Hill consensus conference (microscopic polyangiitis, renal-limited vasculitis and Churg-Strauss syndrome). In the event of failure to return data, those units that were listed as having transplanted four or more patients with AASV were targeted with follow-up telephone calls and email.

Full approval for the study was obtained from the National Research Ethics Service of the UK (NRES) and from local ethics bodies in Birmingham.

*Clinical data*

On each patient identified, we sought to obtain data on the following variables: age, gender, date of diagnosis, date of remission induction [as defined by the absence of clinical evidence of active ongoing vasculitis/Birmingham vasculitis activity score (BVAS) = 0–1], date of transplant, type of AASV, date of death, date of transplant failure, cause of graft failure, ANCA status at the time of transplantation and at intervals for the first post-transplant year (as reported by each centre), anti-myeloperoxidase/proteinase-3 ELISA results at the time of transplant (defined by local reporting practices), evidence of recurrent vasculitis and data regarding all transplant biopsies (particularly with respect to changes in blood vessels). The patient cohorts were defined as pre-1990, 1990–2000 and post-2000. We defined 'severe vasculopathy' as a report of 'marked intimal thickening', 'onion skin appearance' or 'endothelialitis'. The transplant biopsy data returns were not sufficiently detailed to comment on interstitial or glomerular changes, for example, relating to BANFF classification or on potential donor-related factors that may have been evident on a pre-implantation biopsy. Renal transplant histology was not formally reviewed, and we made no specific attempts to distinguish vasculopathy as a result of rejection from other causes of vascular injury. It was not possible to obtain detailed information regarding immunosuppressive therapy.

The variables studied were selected so that data could be obtained from a standard electronic patient record, without requiring a review of the full set of clinical records.

*Statistical analysis*

Normally distributed data were expressed as mean [± 95% confidence interval (C.I.)] and non-parametric data as median (± interquartile range). The probability of an event over time was analysed using Kaplan–Meier life table analysis, with comparison between factors using the log-rank test. Patient and graft survival data were calculated by considering the date of transplantation as time zero. Continuous variables were divided into tertiles for this purpose. Hazard ratios were generated using Cox regression. Those factors associated with death or graft failure on univariate analysis at a significance level of $P < 0.2$ (in addition to age and gender) were analysed using a multivariate Cox regression proportional hazards model. The assumption of proportionality was tested for each variable; the 'cohort' covariate was found to violate the assumption of proportionality and was excluded from consideration for multivariate analysis. We used SPSS 9.0 to perform the analyses. A $P$-value of $< 0.05$ was considered to indicate statistical significance and all tests were two-tailed.

## Results

### *Questionnaire of physicians' attitudes towards transplantation in patients with AASV: 'Do we agree on how to manage these patients?'*

Twenty-five transplant physicians from 12 (67%) of the transplant units surveyed across the UK and Ireland completed and returned the questionnaire. In addition, we obtained seven returns from European transplant centres outside the UK and Ireland. The responses are summarized in Table 1. Less than 1 in 10 reported having a specific policy, although all agreed that patients should be in remission from AASV prior to transplantation. There was no agreement on how long this period of remission should be, with 60% of units stating that they would proceed with transplant $<$12 months post-remission induction. Although all agreed that remission mandates the complete absence of symptoms of AASV, few thought that the ANCA status played a role in this and only one quarter used a BVAS score to define remission.

One quarter would accept an AASV immunosuppression level up to and including requirement for steroids and mycophenolate mofetil at the time of transplant and 17% altered their standard transplant immunosuppression in patients with AASV. Although few felt that one should wait until the ANCA become negative before transplanting, three quarters recommended measuring ANCA post-transplant. Less than one-sixth routinely followed their patients post-transplant in a dedicated vasculitis clinic.

### *Study population*

We then sought to identify most patients with AASV that had received a renal transplant within the previous 20 years to identify factors associated with a poor outcome. Based on returns to UK Transplant with the EDTA code '74', 102 patients with WG in the UK received a renal transplant during this time, of which we obtained data on 56 by targeting those units listed as transplanting $\geq$4 patients with WG. Through direct queries to these units to identify other cases of AASV, and to further units in Ireland, we identified a further 63 patients with AASV satisfying the entry criteria. Of these 119 patients, 12 were excluded because of insufficient data on the form, leaving a total of 107 patients, which

**Table 1.** Results of a survey of 12 of 18 transplant centres in the UK and Ireland (from which there were 25 responses) and from seven centres across Europe

| With respect to renal transplantation of patients with AASV | % answering yes |
|---|---|
| Do you have a specific written policy? | 6% |
| Should patients be in clinical remission? | 100% |
| For how long should they be in remission? | |
| 1–3 months | 10% |
| 3–6 months | 9% |
| 6–12 months | 41% |
| >12 months | 40% |
| How is AASV remission defined? | |
| No symptoms of AASV | 100% |
| BVAS score = 0 | 28% |
| ANCA negative | 13% |
| What is the maximum tolerable level of AASV therapy at the time of transplantation? | |
| Prednisolone + MMF[a] | 28% |
| Prednisolone + azathioprine | 50% |
| Azathioprine alone | 3% |
| Prednisolone alone | 13% |
| Should patients be ANCA negative before transplantation? | 16% |
| Do you consider AASV patients as live donor kidney recipients? | 93% |
| Do you alter transplant immunosuppression because of AASV? | 17%[b] |
| Should ANCA be monitored post-transplant? | 75% |
| If so, how frequently? | |
| 1–3 months | 14% |
| 3–6 months | 67% |
| 6–12 months | 5% |
| Where should patients with AASV be followed up post-transplantation? | |
| General transplant clinic | 53% |
| Transplant and general renal clinic | 19% |
| Specialist vasculitis clinic | 15% |

[a]Mycophenolate mofetil.
[b]Alteration of immunosuppression in AASV included greater use or continuation of steroids (in units normally using a steroid-free or steroid weaning regimen) and avoidance of alemtuzamab use.

form the basis of this report. The baseline characteristics of these are summarized in Table 2. Although we asked for returns on all transplants (including live donor), all renal grafts were cadaveric. This probably reflects the fact that many of the studied patients were transplanted in or prior to the 1990s.

### *Mortality post-transplantation*

Overall median survival post-transplantation was 13.4 years (95% C.I. 9.4–17.4, Figure 1). Although we did not specifically look in detail for the cause of death, this was included on the returns in 21 (81%) of the 26 patients who died: malignancy in 6 (26% of those with data), infection in 4 (18%), cardiovascular in 4 (18%) and other causes in 7 (27%).

The only factor significantly associated with death on both univariate and multivariate analysis was receipt of the renal transplant <12 months post-induction of AASV remission (Table 3, Figure 1). This occurred in 15 cases, 9 (60%) of whom died during follow-up. Five of the 7 patients (71%) transplanted <6 months post-remission died.

**Table 2.** Clinical characteristics of the cohort of patients with AASV receiving a renal transplant ($N = 107$)

| Variable | Value |
|---|---|
| Gender (male/%) | 61 (57) |
| Median age at the time of transplant (range) | 49.4 (13.9–72.0) |
| Vasculitis type (% WG/MPA/RLV[a]/unknown) | 57/35/7/4 |
| Median time to transplant post-remission (interquartile range) | 3.0 y (1.5 to 5.6) |
| Transplanted <12 months post-remission induction (yes/%) | 15 (14) |
| Evidence of severe vasculopathy on transplant biopsy (yes/%) | 18 (16.8) |
| Died during follow-up (yes/%) | 26 (24.3) |
| Duration of follow-up (median/total patient years) | 5.5 (693) |
| Cohort of transplantation (*N*/%) | |
| Before 1990 | 11 (10.3) |
| 1990–2000 | 48 (44.9) |
| After 2000 | 48 (44.9) |
| ANCA status at transplantation (*N*, positive/negative/unknown)[b] | 25/49/33 |
| Positive ELISA (*N*: anti-PR3/anti-MPO) | 7/9 |
| ANCA positive at or in first year post-transplantation (*N*/%)[b] | 30 (28) |
| Graft failed before death (*N*/%) | 19 (18) |
| Graft outcome (*N*/%) | |
| Still functioning at last follow-up | *72 (68.6)* |
| Graft lost due to | |
| Death with a functioning graft | 16 (15.2) |
| Chronic allograft nephropathy | 5 (4.8) |
| Vascular catastrophe | 5 (4.8) |
| Recurrent vasculitis | 3 (2.9) |
| Acute rejection | 2 (1.9) |
| Other | 4 |

WG, Wegener's granulomatosis; MPA, microscopic polyangiitis.
[a]Renal-limited vasculitis.
[b]As defined by indirect immunofluorescence and/or ELISA.

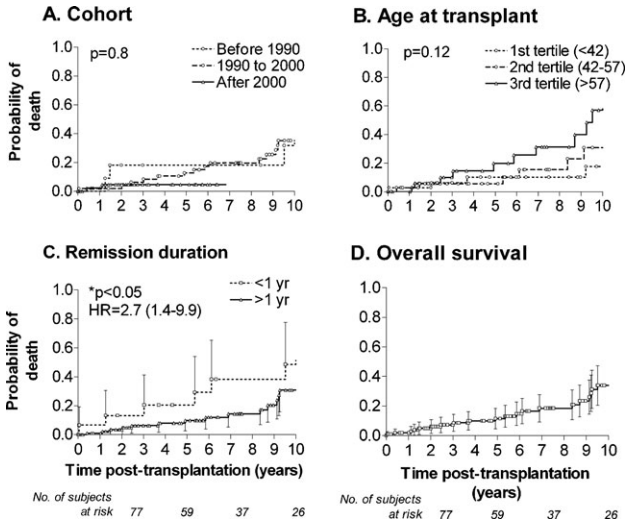


**Fig. 1.** Unadjusted survival probability in patients with AASV undergoing renal transplantation. Overall survival probability post-transplant was 65% (95% C.I. 50–80%) at 10 years and 90% (95% C.I. 83–97%) at 5 years. In graphs depicting tertiles, 95% confidence intervals have been omitted for clarity.

**Table 3.** Factors associated with mortality in patients with AASV receiving a renal transplant

| Factor | *P*-value | Hazard ratio (95% C.I.) |
|---|---|---|
| Factors associated with mortality in patients with AASV undergoing transplantation: univariate analysis | | |
| Transplant <12 months post-remission | 0.03 | 2.7 (1.4–9.9) |
| Gender | 0.97 | 1.34 (0.6–3.0)[a] |
| Age at transplant | 0.12 | 1.02 (0.9–1.05)[b] |
| AASV type | 0.69 | 1.54 (0.3–6.9)[c] |
| Cohort | 0.80 | 1.48 (0.31–7.1)[d] |
| ANCA positive at transplant | 0.97 | 0.98 (0.32–2.9) |
| Factors associated with mortality in patients with AASV undergoing transplantation: multivariate Cox regression analysis | | |
| Transplant <12 months post-remission | 0.04 | 2.3 (1.1–5.3) |
| Gender | 0.82 | 1.1 (0.47–2.7) |
| Age at transplant | 0.16 | 1.01 (0.98–1.05)[b] |

WG, Wegener's granulomatosis; MPA, microscopic polyangiitis.
[a]Male versus female.
[b]For each year.
[c]MPA versus WG.
[d]Before 1990 versus after 2000.

**Table 4.** Factors associated with graft failure (censored for patient death) in patients with AASV receiving a kidney transplant

| Factor | *P*-value | Hazard ratio (95% C.I.) |
|---|---|---|
| Factors associated with graft failure in patients with AASV undergoing transplantation: univariate analysis | | |
| Transplant <12 months post-remission | 0.4 | 1.57 (0.47–6.1) |
| Gender | 0.8 | 1.1 (0.51–2.4)[a] |
| Age at transplant | 0.5 | 0.99 (0.96–1.02)[b] |
| Cohort | 0.6 | 0.45 (0.11–1.82)[c] |
| Vasculitis type | 0.5 | 3.0 (0.41–22.8)[d] |
| Vasculopathy on transplant biopsy | 0.03 | 1.42 (0.56–3.57) |
| Factors associated with graft failure in patients with AASV undergoing transplantation: multivariate analysis | | |
| Vasculopathy on transplant biopsy | 0.01 | 3.8 (1.3–10.7) |
| Gender | 1.7 | 1.3 (0.6–4.7)[a] |
| Age at transplant | 0.98 | 0.9 (0.96–1.02)[b] |

[a]Male versus female.
[b]For each year.
[c]Before 1990 versus after 2000.
[d]WG versus MPA.

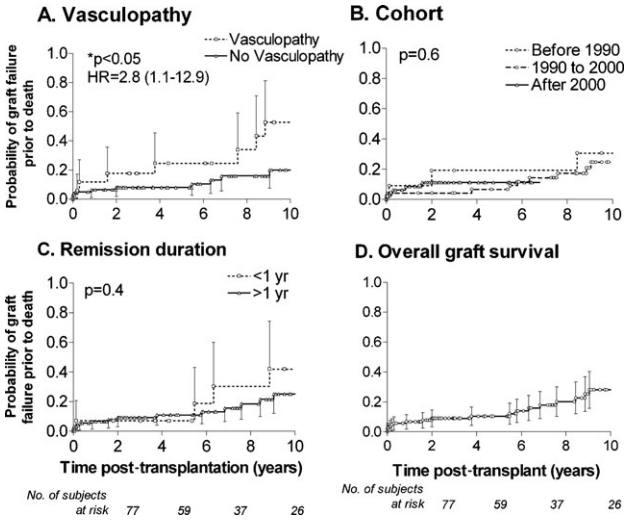


**Fig. 2.** Unadjusted graft survival probability in patients with AASV undergoing renal transplantation. Data are censored in the event of patient death. Overall graft survival was 70% (95% C.I. 58–82%) at 10 years and 90% (95% C.I. 82–98%) at 5 years.

### *Recurrent disease*

Only 5 patients (4.7%; 0.01 episodes of relapse per patient-year of follow-up) displayed evidence of recurrent vasculitis relapse during the follow-up, 1 of whom died from lung haemorrhage and 3 of whom (60%) lost the graft to recurrent renal vasculitis. One of these five was known to be ANCA positive (by indirect immunofluorescence or ELISA) at the time of transplant (although the ANCA status at transplant was unknown in three).

### *Graft outcome*

Overall 5-year graft survival (censored for patient death) was 90% (Figure 2, Table 4). The only factor significantly associated with graft loss prior to death was the presence of severe vasculopathy on transplant biopsy (on both univariate and multivariate analysis, Table 4). Eighteen (16.8%) patients had this outcome during the follow-up; in these patients, 10-year graft survival was reduced to 47% (95% C.I. 19–76) from 80% [95% C.I. 68–93, $P < 0.05$ (Figure 2A)]. The development of severe vasculopathy during the follow-up was associated with being ANCA positive (by immunofluorescence or ELISA) at transplant (odds ratio 4.4, 95% C.I. 1.1–16.8, $P < 0.05$, Figure 3A). However, ANCA positivity was not significantly associated with graft survival. In addition, the type of vasculitis, whether the remission time was <12 months pre-transplantation or which cohort the patient belonged to had no bearing on death-censored graft survival.

## Discussion

The outcome of renal transplantation in the setting of AASV is known to be good, with favourable graft survival and a low incidence of vasculitis relapse. In this study, the largest published series of vasculitic patients receiving a renal transplant, we sought to assess the following: firstly, whether there was consensus among European physicians as to how to manage the peri-transplant period in these patients; secondly, whether graft and patient survival was associated with factors evident at the time of transplant (such as ANCA status, duration of AASV remission and type of vasculitis) and thirdly, whether ANCA positivity (as defined by immunofluorescence and/or ELISA) was associated with transplant outcome. All respondents agreed that remission was defined by an absence of clinical symptoms. A few (13%) also felt that ANCA should be negative. This is interesting as ANCA monitoring prior to transplantation does not have sufficient positive predictive value on its own to merit alteration of treatment. In addition, ANCA status does not form part of recent EUVAS definitions of remission [15]. We found that, although all transplant physicians surveyed agreed that vasculitis should be in complete remission at the time of transplant, 60% felt that it was not

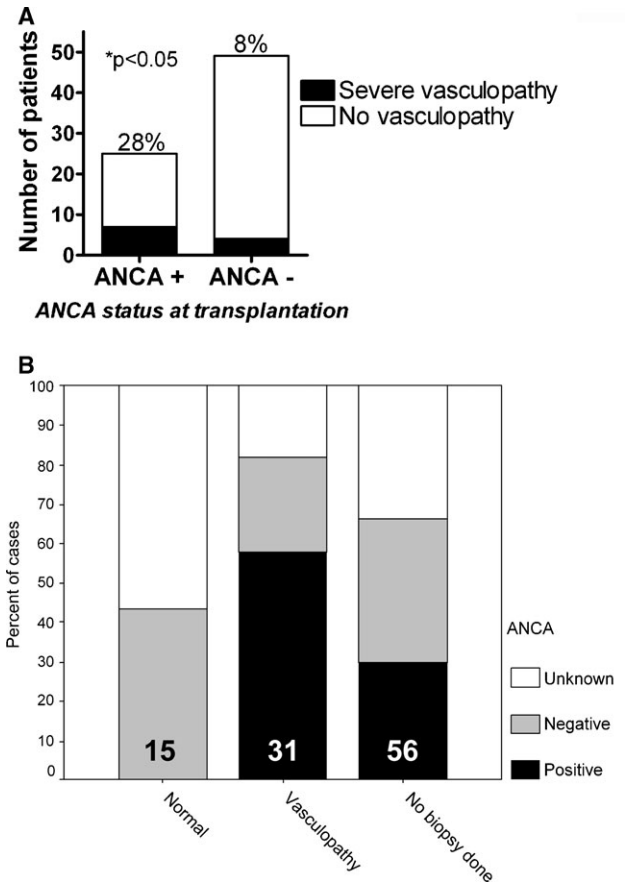


**Fig. 3.** (**A**) Association between ANCA status at transplant and the subsequent development of severe transplant vascular lesions. Proportions were compared using the chi-square test. The % figures above each bar represent the fraction of patients that developed severe vasculopathy in each group. (**B**) ANCA status at transplant in those patients that underwent a transplant renal biopsy, characterized according to the presence or absence of any vasculopathy. These data pertain to the first transplant biopsy only (a small number of patients had more than one biopsy). The numbers at the bottom of each bar reflect the total number of patients in each group.

necessary for this period of remission to extend beyond 12 months (as is generally practiced in anti-GBM disease). Critically, however, we found that the strongest predictor of mortality in these patients was transplantation shortly after induction of remission. We also found that ANCA positivity at the time of transplant was associated with an odds ratio of 4.4 of developing vasculopathy in the graft (although further conclusions regarding causation of this vasculopathy cannot be drawn) and that such vasculopathy was associated with an adverse graft outcome (hazard ratio 3.8). However, as found in previous reports [10,16,17], ANCA positivity *per se* at the time of transplant was not associated with adverse graft survival.

Ten years post-transplant, the patient survival was 65%, which compares favourably with patients transplanted for other causes of ESRF. The overall 10-year patient survival in UK renal transplant recipients receiving their grafts from 1993–95 was 67% (95% C.I. 66–69%) (www.uktransplant.org.uk). However, the figures pertaining to vasculitic recipients reported in this paper hide a sub-group of patients that experienced a high mortality rate: those in whom the transplant was performed a short period after induction of remission of AASV. This association of poor survival when transplantation occurs shortly after achieving remission is novel and should inform practice pertaining to timing of transplantation. Previous studies have suggested that delaying transplantation has no effect on disease relapse [10], although these studies failed to address whether there was a survival benefit in delaying transplantation following induction of remission of disease.

Because of a high risk of recurrent disease in the face of positive anti-GBM antibodies, it is generally recommended to wait for 1 year before transplantation in anti-GBM disease [18] (or 6 months after the antibodies have become undetectable [19]). We believe that the same principle should apply to AASV, although the rationale in this case is that these patients have usually been treated with high-dose steroids and cyclophosphamide in an attempt to induce and maintain remission, the adverse effects of which may persist for some time. Although we report an association that cannot be proved in this retrospective study, it is likely that this excess mortality (in 60% of those transplanted less than a year post-remission) was due to the fact that these patients had received intense immunosuppression shortly before their transplant, may have been relatively malnourished and were almost certainly more prone to infection. It is perhaps not surprising that adding renal transplantation to this scenario, with its attendant additive immunosuppression, would put these patients at risk of life-threatening infection or cancer.

As found in previous studies, graft outcome when transplanting for AASV was good, with 90% of transplants surviving 5 years (after censoring for patient death). This compares to an overall 5-year death-censored graft survival probability of grafts transplanted in 2000 in the United States of 80% (USRDS 2007). As in other studies, disease relapse was uncommon with a rate of 0.01 relapses/patient/year and only three patients lost their grafts due to recurrent disease. We were unable to detect any vasculitis-specific factors that were associated with an adverse graft outcome, specifically, the presence of ANCA when transplanting was not associated with increased graft loss. The finding of a severe vascular lesion on transplant biopsy was the only factor significantly associated with graft failure, a finding that is well known to pertain in renal transplantation for other primary renal diseases [20].

The association of ANCA with vasculopathy is noteworthy, although we wish to emphasize that (in view of the lack of formal histological review and paucity of donor factor information) firm conclusions regarding the impact of ANCA on the development of transplant vascular lesions cannot be drawn from this study. Transplant vasculopathy may be induced by a combination of factors, including humoral rejection, hypertension, CNI toxicity and/or donor vascular disease, and strongly predicts subsequent graft loss. Groups working in this field have not used a unified definition nor a common methodology to ascertain the presence of allograft vasculopathy, thereby making comparison of different studies difficult. Its pathogenesis is complex and frequently involves both allo-immune and non-immune factors. In addition, there is evidence that autoimmunity may contribute to the process. For example, associations between

vasculopathy and antibodies capable of binding (and activating) endothelial cells have been found, including anti-MHC antibodies (both class I and II) [21,22] anti-MICA (a polymorphic MHC class I-related antigen) and anti-endothelial cell antibodies (AECA) [23]. Complement-activating endothelial reactive antibodies can now be detected easily by immunostaining for C4d, detection of which has increased awareness of antibody-mediated vascular damage in allografts [24]. Some AECA are reactive to antigens expressed on activated or injured endothelial cells (EC), including autoantigens such as vimentin, and have been correlated with vasculopathy in cardiac transplant patients [22]. While ANCA do not directly bind endothelium, circulating AECA are found in a proportion of patients with AASV [25]. The target antigen remains obscure, but AECA are capable of activating EC and inducing their apoptosis [26]. Additionally, it is known that ANCA may induce EC damage indirectly, through activation and release of neutrophil serine proteases [27]. Moreover, in AASV, as well as in other autoimmune diseases such as systemic lupus erythematosus, accelerated arteriosclerosis has been described, although the exact mechanisms remain poorly defined. Taken together, these data support the concept that ANCA may contribute to endothelial damage, thereby promoting vasculopathy directly or indirectly, or may serve as a surrogate marker for other AECA promoting the increased vasculopathy incidence. We did not distinguish between vasculopathy due to rejection and due to other causes, so we cannot exclude the possibility that some of the observed effect on vascular injury may have been due to a modulation effect by ANCA of the rejection process. In addition, we have not routinely screened for AECA, nor did we routinely examine C4d staining on the biopsies, but in the context of AASV patients awaiting transplantation they should perhaps be considered as an additional risk factor for chronic allograft vasculopathy, and monitored prospectively.

This study was limited by being retrospective and by use of questionnaire-based clinical and outcome data that was necessarily lacking in fine detail. In particular, we were unable to obtain tissue to allow for blinded histological review, thereby limiting our ability to draw conclusions regarding the potential aetiology/pathogenesis of the vascular lesions observed. However, we felt that to answer the important questions posed in the arena of transplantation in AASV, it was more important to capture data on as many patients as possible. Given the rarity of this disease, a detailed single-centre review (as performed in previous studies) would not have answered these questions; the only approach with any likelihood of success was a multi-centre international approach. Therefore, we were unable to obtain precise data on, for example, trends of anti-PR3/MPO antibody levels over time or accurate assessment of transplant function. The major risk in this approach was one of recall bias in each of the transplant centres surveyed and a consequent failure to identify those patients with AASV who had an adverse outcome shortly after transplantation. We sought to minimize this by employing a central renal transplant registry (operated by UK Transplant) to identify all patients with WG receiving a transplant. We obtained data on 56 of the 102 individuals identified by UK Transplant, thereby raising the possibility of an ascertainment bias. All biopsies were performed in response to a clinical problem; protocol biopsies were not employed. Therefore, the returned histology reports are not necessarily representative of the totality of allograft pathology, although this limitation does not detract from the observation that the presence of ANCA was associated with worse vascular injury. In addition, we could not obtain reliable information on donor factors (such as donor age and histological factors) that are known to have a potentially important impact on graft outcome. We therefore cannot exclude the possibility that observed vascular lesions were present at the time of implantation, although it is unlikely that this factor would have differentially affected ANCA-positive and ANCA-negative patients.

In summary, it is prudent to wait for a year after induction of remission for AASV before proceeding with renal transplantation as there appears to be an excess mortality in those transplanted sooner than this. Although the presence of circulating ANCA at the time of transplant is associated with the development of vasculopathy, it was not associated with subsequent graft loss and, therefore, should not be considered a definite contraindication to transplantation. Further research is required to investigate the mechanisms underlying this observed vascular injury in the allograft.

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# The pattern of excess cancer in dialysis and transplantation

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## Abstract

**Background.** After transplantation, cancer risk varies from no increase for several common cancers to a many-fold increase for a number of, chiefly virus-associated, cancers. The smaller excess of cancer in dialysis has been less well described, but two studies suggested that impaired immunity might be responsible.

**Methods.** In a population-based cohort study of 28 855 patients who received renal replacement therapy (RRT), we categorized incident cancers as end-stage kidney disease (ESKD) related, immune deficiency related, not related to immune deficiency, or of uncertain status, according to whether they were, or were not, increased in published reports of cancer in ESKD prior to starting RRT, organ