Outcome of Renal Replacement Therapy in Antineutrophil Cytoplasmic Antibody-Associated Systemic Vasculitis

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Abstract. Antineutrophil cytoplasmic antibody-associated systemic vasculitis (AASV) frequently leads to end-stage renal disease (ESRD). Potentially fatal disease activity can continue after the onset of ESRD in both dialysis and transplant patients, despite the immunosuppressive effects of uremia and rejection prophylaxis, leading to concerns that such patients have greater morbidity and mortality. To assess the outcome of AASV patients receiving renal replacement therapy, a retrospective analysis of 59 patients from our unit who received chronic dialysis, renal transplantation, or both, was performed. The survival of AASV patients with ESRD was comparable to national registry controls, as were both graft and patient survival after renal transplantation. There is no evidence that standard immunosuppressive protocols should be altered for AASV patients receiving renal transplants. The rate of relapse of vasculitis for patients on chronic dialysis and after transplantation was 0.09 and 0.02 per patient per year, respectively. These rates are lower than those of other series and support the contention that continued immunosuppression after ESRD, as practiced in our unit, is warranted. Relapses usually responded to cyclophosphamide and high-dose prednisolone treatment. Significantly, vasculitic flare-ups in dialysis patients were sometimes initially misdiagnosed as dialysis complications, leading to fatal delays in effective treatment. Follow-up by physicians experienced in the diagnosis and treatment of vasculitis activity should continue in these patients.

Systemic vasculitis is the most common cause of rapidly progressive glomerulonephritis and frequently leads to end-stage renal disease (ESRD). The vasculitis syndromes responsible, Wegener's granulomatosis (WG), microscopic polyangiitis (MP), and, rarely, Churg–Strauss syndrome (CSS), affect small blood vessels and are usually associated with antineutrophil cytoplasmic antibodies (ANCA). They are now commonly grouped as ANCA-associated systemic vasculitis (AASV). Isolated pauci-immune necrotizing glomerulonephritis, previously known as "idiopathic RPGN," is also associated with ANCA and is widely considered to be a renal-limited form of vasculitis; thus, it is commonly classified within the MP category and we adopt this approach. It should be noted that the association between pauci-immune RPGN and ANCA is not absolute.

Until the 1960s, AASV had a dismal prognosis, but the use of corticosteroids and cyclophosphamide has transformed AASV into a treatable condition, provided therapy is instituted promptly. When diagnosis is delayed, perhaps due to the varied presentations of AASV, irreversible renal damage may occur, causing permanent dialysis dependence or progressive nephrosis, which leads relentlessly toward a need for renal replacement therapy (RRT).

Surprisingly little has been published about the outcome of patients with AASV beginning RRT. The results of dialysis and transplantation in this important group of patients thus remain unclear and, in particular, the frequency of vasculitic relapses is uncertain. Consequently, there is little information to guide the use of immunosuppressive therapy in vasculitis patients on RRT, and little information on the suitability of vasculitis patients as transplant recipients.

We have analyzed data on 308 patients referred to our unit for treatment of AASV and present data on 59 patients accepted into an RRT program, either at our unit (n = 33) or at their local hospital (n = 26), for whom follow-up is available.

Materials and Methods

Patients

We performed a retrospective analysis of a large cohort of patients with ESRD due to AASV. Of 308 patients treated for AASV at our unit between 1974 and 1997, 61 patients developed ESRD and were accepted into an RRT program; follow-up data were available on 59. The age distribution of this group is shown in Figure 1. Patients who required acute hemodialysis but subsequently recovered independent renal function were excluded from the analysis. Patients who died within 2 mo of presentation were also excluded because such deaths reflect acute AASV activity and hazards of intensive immunosuppressive treatment, rather than the impact of RRT.

Using the 1994 Chapel Hill International Consensus nomenclature for systemic vasculitis (1), the diagnosis was WG in 23, MP in 33 (10 with renal-limited disease), and CSS in three. Thirty-two were male and 27 were female. The median age at presentation was 52 yr (range, 13 to 77), and median age at commencement of RRT was 54 yr (range, 13 to 79).
Results

Overall Survival

Median survival for all patients from initiation of RRT was 107 mo (range, 2 to 182). Actuarial survival at 1 and 5 yr was 82 and 59%, respectively (Figure 2). Median age at death was 67 yr (range, 28 to 79). There was no significant difference between survival for patients with WG and those with MP when Kaplan–Meier survival curves were compared (Figure 3, two-tailed log-rank test, P = 0.13). There were no deaths among the CSS patients, although they comprised only 5% of the patients analyzed.

Renal Transplantation

Of the 59 patients studied, 22 received 24 kidney transplants. As expected, this group was younger than the nontransplanted cohort (Figure 1) and had a median age at onset of ESRD of 38 yr (range, 13 to 65). All patients receiving renal allografts were treated with the transplanting unit’s standard immunosuppressive regimen, typically comprising triple therapy with prednisolone, azathioprine, and cyclosporine from the early 1980s onward and prednisolone and azathioprine before that time. Survival of this group from commencement of RRT was 100% at 1 yr and 84% at 5 yr. Transplantation occurred a median of 14 mo (range, 0 to 33) after start of dialysis. Patient survival from the time of first transplantation was 100% and 85% at 1 and 5 yr, respectively (Figure 4). Graft survival at 1 and 5 yr was 86 and 69%, respectively. Three patients died with functioning grafts, from cardiac failure, stroke, and aspiration pneumonia, respectively. Six grafts failed: one from immediate renal artery thrombosis (no rejection), two from acute rejection (at 2 wk and 3 mo), two from chronic rejection (at 19 and 108 mo), and one from biopsy-proven recurrence of vasculitis in a poorly functioning graft (transplant immunosuppression with prednisolone and azathioprine), associated with detectable proteinase 3 (Pr3)-specific c-ANCA. The outcome of transplantation in this cohort is compared with national data in Table 1.

In total, vasculitis recurred in 2 of 22 transplant recipients. The second patient relapsed on triple transplant immunosuppression with biopsy-proven ethmoiditis and recurrence of Pr3-specific cANCA at 89 mo posttransplant. This flare-up responded to substitution of cyclophosphamide for cyclosporine, but the transplant failed at 108 mo from histologically proven chronic rejection. She experienced another flare-up of intestinal vasculitis 5 mo after restarting continuous ambulatory peritoneal dialysis (CAPD). The overall rate of recurrence for AASV patients with a functioning renal transplant was 0.02 relapses per patient per year.

Chronic Dialysis

Thirty-seven of the 59 patients received dialysis alone with a median age at onset of ESRD of 61 yr (range, 26 to 79). The majority of these patients were considered too old or unfit for transplantation; four remain on the transplant waiting list. First modality of dialysis was peritoneal dialysis in 20 patients and hemodialysis in 13 (and unknown in four patients dialyzing at local units). Four patients converted from peritoneal to hemodialysis during follow-up, two after severe bacterial peritonitis.
Survival of this cohort from commencement of RRT was 74% at 1 yr and 40% at 5 yr. This was significantly worse than survival in the group of patients who received renal transplants (Figure 5, two-tailed log-rank test, \( P = 0.0007 \)). Eighteen patients died: three from active vasculitis, five from bronchopneumonia, four from cardiac failure, three from withdrawal of dialysis, and one each from disseminated adenocarcinoma, sudden cardiac death, and respiratory failure. These data are compared with survival rates on dialysis reported to national and international registries in Table 2.

Ten vasculitic relapses occurred in 7 of 37 patients after ESRD. Relapses occurred in both WG and MP patients, but not in the small number with CSS, and involved the upper and lower respiratory tract, skin, joints, and intestinal tract. Most flare-ups responded to reinstitution of corticosteroids and cyclophosphamide, but some required the addition of plasma exchange (for pulmonary hemorrhage). The three fatal relapses were initially treated in local units as complications of dialysis—gut vasculitis resembling CAPD peritonitis and pulmonary hemorrhage mimicking pulmonary edema. The overall rate of recurrence for AASV patients on dialysis was 0.09 relapses per patient per year (Table 3).

**Table 1. Actuarial patient and graft survival after renal transplantation**

<table>
<thead>
<tr>
<th>Data Source</th>
<th>Patient Survival</th>
<th>Graft Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hammersmith series [1974 to 1997] (AASV transplants only)</td>
<td>100 (1 yr) 85 (5 yr)</td>
<td>86 (1 yr) 69 (5 yr)</td>
</tr>
<tr>
<td>UKTSSA [1984 to 1993] (30) (all CAD UK transplants)</td>
<td>92 (1 yr) 80 (5 yr)</td>
<td>84 (1 yr) 70 (5 yr)</td>
</tr>
<tr>
<td>USRDS [1990] (31)</td>
<td>93 (CAD) 79 (CAD)</td>
<td>80 (CAD) 59 (CAD)</td>
</tr>
<tr>
<td></td>
<td>96 (LRD) 89 (LRD)</td>
<td>90 (LRD) 74 (LRD)</td>
</tr>
</tbody>
</table>

* AASV, antineutrophil cytoplasmic antibody-associated systemic vasculitis; UKTSSA, United Kingdom Transplant Support Service Authority; CAD, cadaveric transplant; USRDS, United States Renal Data System; LRD, living related donor transplant.

**Discussion**

The outcome of patients with AASV requiring RRT is an important issue in view of the frequency with which such patients progress to ESRD (20% in our series, in which the majority of patients had significant renal involvement at presentation). However, the literature on AASV patient survival after ESRD is scant, and focuses mostly on WG. Other forms of vasculitis with less distinctive features were variously classified until recently, causing difficulties in data comparison between series. For example, Nissenson and Port (2) reported outcomes in patients with a diagnosis of polyarteritis nodosa (PAN), and included both classical PAN, with aneurysmal inflammation of medium-sized and small arteries, and MP, which is a pauci-immune necrotizing vasculitis of small vessels. The distinction is more than semantic in view of differences in long-term outcome between them (3). The Chapel Hill Consensus on nomenclature of systemic vasculitides (1) (published in 1994) offers a current standard for international clinical trials in systemic vasculitis, and has been adopted in our unit.

In 1981 Kurosz et al. (4) described nine patients with ESRD due to WG. Hemodialysis was commenced at age 25 to 43 and proceeded without complication until transplantation 2 to 24 mo later. Only four patients received immunosuppressive therapy while on dialysis, but none of the nine relapsed. A more systematic survey was reported by Nissenson and Port (2), who analyzed data from 28 of the 32 U.S. ESRD Networks, encompassing 89% of all new ESRD patients covered by Medicare from 1983 to 1985. Half of the patients were over the age of 60 at onset of ESRD, but survival was equal to that of a control nondiabetic population with 33-mo survival of 58 and 62% for WG and PAN, respectively. A total of 12 WG and five PAN patients received transplants. Of note, up to 10% of the analyzed patients recovered independent renal function, which may skew the data toward a better outcome.

In our analysis, median age of initiation of RRT was 54 yr, and actuarial survival at 1 and 5 yr was 82 and 59%, respectively, which compares favorably with data from other dialysis registries, regardless of renal diagnosis (Table 2). We also examined survival according to disease subgroup; no significant difference was noted between WG and MP patients. The absence of extrarenal involvement in 10 patients of the MP group might have been expected to improve overall outcome, but may have been offset by delay in diagnosis through the absence of extrarenal symptoms. CSS is a rare cause of ESRD and, indeed, was the underlying diagnosis in only three (5%) of our patients. There were no deaths over the follow-up periods of 51, 96, and 149 mo.

Andrews et al. (5) have suggested that CAPD is associated with increased peritonitis morbidity in immunosuppressed patients. It is reassuring that our AASV patients treated with either hemodialysis or CAPD according to the usual criteria, with no automatic hemodialysis preference, have an overall

![Figure 5. Kaplan–Meier plot of AASV patient survival after onset of ESRD according to RRT modality: dialysis only or dialysis plus renal transplantation. There is a significant difference between the two survival curves (\( P = 0.0007 \) by 2-tailed log-rank test).](chart)
Table 2. Actuarial survival of dialysis patients

<table>
<thead>
<tr>
<th>Data Source</th>
<th>Age at Onset ESRD</th>
<th>1-yr Actuarial Survival (%)</th>
<th>5-yr Actuarial Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ESRD patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hammersmith series [1974 to 1997] (all AASV ESRD patients)</td>
<td>54 (median, n = 59)</td>
<td>82</td>
<td>59</td>
</tr>
<tr>
<td>Nissenson and Port [1983 to 1985] (U.S. database–all WG ESRD patients) (2)</td>
<td>49% ≥60 (n = 131)</td>
<td>80</td>
<td>Not available</td>
</tr>
<tr>
<td>USRDS (all ESRD patients) (31)</td>
<td>Unadjusted registry data (all ages)</td>
<td>78 [1984]</td>
<td>40 [1984]</td>
</tr>
<tr>
<td>EDTA-ERA [1986 to 1991] (all ESRD patients)</td>
<td>Unadjusted registry data (all ages)</td>
<td>78 [1990]</td>
<td>37 [1990]</td>
</tr>
</tbody>
</table>

* Dialysis only

<table>
<thead>
<tr>
<th>Data Source</th>
<th>Age at Onset ESRD</th>
<th>1-yr Actuarial Survival (%)</th>
<th>5-yr Actuarial Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hammersmith series [1974 to 1997] (AASV ESRD patients who received dialysis alone)</td>
<td>61 (median)</td>
<td>74</td>
<td>40</td>
</tr>
<tr>
<td>USRDS [1990] (all ESRD patients, censored at transplant) (31)</td>
<td>55 to 59</td>
<td>80</td>
<td>32</td>
</tr>
<tr>
<td>EDTA-ERA [1986 to 1991] (ESRD patients who received dialysis alone)</td>
<td>60 to 64</td>
<td>76</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>55 to 64</td>
<td>85</td>
<td>47</td>
</tr>
</tbody>
</table>

* ESRD, end-stage renal disease; ERA, European Renal Association. Other abbreviations as in Table 1.

b European Renal Association—European Dialysis and Transplant Association (personal communication, Dr. Elizabeth Jones, ERA-EDTA).

Table 3. Relapse rate during renal replacement therapy in AASV patients

<table>
<thead>
<tr>
<th>Data Source</th>
<th>No. of Patients</th>
<th>Relapse Rate on Dialysis (relapses/patient per yr)</th>
<th>Relapse Rate after Transplantation (relapses/patient per yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hammersmith series [1974 to 1997]</td>
<td>59</td>
<td>0.09</td>
<td>0.02 (n=22)</td>
</tr>
<tr>
<td>Haubitz et al. [1980 to 1995] (11)</td>
<td>18</td>
<td>0.24</td>
<td>0.06</td>
</tr>
<tr>
<td>Schmitt et al. [1982 to 1993] (21)</td>
<td>18</td>
<td>0.3</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Follow-up of 39 mo. Our data confirm that dialysis patients may relapse; 11 relapses occurred in eight of the 59 patients, corresponding to a relapse rate of 0.09 per patient per year. However, the relapse rate that we report is lower than that in other published series (see Table 3). This difference may reflect our policy of prolonged maintenance immunosuppression in selected dialysis patients. Our general policy is to induce remission with oral prednisolone and cyclophosphamide (with additional plasma exchange in severe disease), to substitute azathioprine for cyclophosphamide at 3 mo, and to slowly reduce the doses during the first year (8). Therapy is rarely discontinued before the third year, unless the presenting illness is confined to the kidney and renal recovery is not achieved. We favor continuing low-dose steroids and azathioprine in patients with persisting ANCA who are at increased risk of relapse (9). In this series, the cumulative immunosuppression before end-stage renal failure was reached varied widely between patients, because the time to ESRD varied from 0 to 207 mo from presentation.

Renal transplantation was first described in AASV in 1972 by Lyons and Lindsay (10), who reported the successful allografting of a 29-yr-old man with WG. Several case reports and small series followed, which clearly demonstrated that allotransplantation was an effective approach to ESRD in WG with good short- and medium-term graft and patient survival. The outcome of renal transplantation in MP is less well described than in WG. Nissenson and Port's U.S. ESRD Network analysis (2) simply reported five cadaveric allografts in the PAN group of patients, some of whom probably had MP, with 62% patient survival at 36 mo (graft survival was not given). In
a recent series of 18 patients with AASV receiving renal transplants, 1- and 3-yr graft survival was 94 and 87%, respectively (11). Nyberg’s group reported that transplant outcome in a heterogeneous group of vasculitis patients was similar to that of controls, after a median of 82 mo follow-up (12).

Our data represent the largest single-center series of renal transplantation in AASV. As expected, the patients were relatively young (Figure 1), and graft and patient survival was comparable to national data collated by the UK Transplant Support Service Authority, in patients of similar age (90% under age 60 at the time of transplantation) (Table 1).

The initial hope that standard rejection prophylaxis might be sufficient to prevent vasculitic relapse after transplantation (13) evaporated when Steinman et al. reported a 26-yr-old man who developed sinusitis, epistaxis, myalgia, and microscopic hematuria 4 yr after transplantation, despite prednisolone and azathioprine therapy (14). All features of the flare-up subsided when the patient was switched from azathioprine to cyclophosphamide. In 1983, Curtis et al. described the first biopsy-proven recurrence of focal necrotizing glomerulonephritis (GN) in the graft (15). Recurrent arthritis in the graft is also possible: Reaich et al. reported a case in which extensive renal vasculitis led to graft infarction 5 d after transplantation (16). Extranodal vasculitis activity may occur in isolation (17), even when not a feature of the original illness (18). Emeron et al. described a cadaveric allograft donor who had focal necrotizing GN on time zero biopsy and, retrospectively, a positive ANCA (19). The recipient of one kidney had focal necrotizing GN on an early biopsy and was successfully treated with methylprednisolone; the other recipient’s course was complicated by delayed primary function and severe rejection, without evidence of glomerulonephritis on serial biopsies.

Relapse of WG after renal transplantation was first comprehensively reviewed by Clarke et al. (20), who suggested that cyclosporine-based posttransplant immunosuppression was associated with a higher rate of vasculitic relapse (71%, n = 7) than azathioprine-based therapy (18%, n = 22), although this has not been confirmed by recent reports. We find no evidence to support the contention that cyclosporine-based immunosuppression results in poorer control of vasculitis activity in the posttransplant population, and indeed our relapse rate is lower than that in other series. In Clarke’s series, the majority of relapses, whether renal or pulmonary, responded to substitution of cyclophosphamide for cyclosporine or azathioprine, although two resulted in graft loss. A similar approach was described in the brief report by Schmitt et al. (21). More recently, Haubitz and coworkers reported on 15 WG transplant recipients receiving prednisolone and cyclosporine, followed for a mean of 56 mo (11); graft survival was comparable to a control group. Three extrarenal relapses occurred: one fatal and two responding to higher dose corticosteroids and cyclophosphamide. No renal relapses were seen. As in WG, relapse after transplantation in MP may affect the kidney, either in isolation (22) or as part of a generalized relapse (11), and is typically treated by conversion to cyclophosphamide (12,23). Thirteen MP transplant recipients were recently described by Nyberg et al. (12), of whom three experienced proven recurrence in the graft, with the loss of one graft despite both cyclophosphamide and plasma exchange. Few data were given with respect to extrarenal vasculitis activity.

In our series, the vasculitis relapse rate after transplantation was very low, at 0.02 per patient per yr, which is lower than other estimates and was approximately 20% of our chronic dialysis relapse rate (see Table 3). This reduction is consistent with the experience of others, who report that the frequency of relapse after renal transplantation falls to approximately 25 to 35% of the chronic dialysis relapse rate. As suggested previously, our lower absolute relapse rates probably reflect our use of maintenance immunosuppression in dialysis patients.

The utility of ANCA as a predictor of relapse after transplantation has generated much debate. Reports of successful renal transplantation in the face of a positive myeloperoxidase (MPO)-specific ANCA were presented by Noel et al. in 1993 (24), by Grotz et al. in 1995 (25), and Frasca et al. in 1996 (26). Rostaing and colleagues recently reported transplantation of eight AASV patients, of whom seven were ANCA-positive at transplantation (23). Only one relapsed; she had a very high MPO-specific ANCA titer and had not received pretransplant immunosuppression. Four patients remained ANCA-positive (one Pr3-ANCA; three MPO-ANCA) during follow-up but did not relapse. In both Haubitz’s (11) and Nyberg’s (12) series of AASV transplant recipients, relapses were described both in patients who were ANCA-positive at transplantation and some who were negative.

These data suggest that the presence of ANCA should not preclude transplantation in patients who are clinically well. However, the risk of relapse should not be overlooked in any AASV patient, and serial monitoring of ANCA may give useful information about imminent relapse, although some authors have questioned this (27). Our practice, in vasculitis patients as a whole, is to consider patients with persisting or rising ANCA to be at increased risk of relapse (28,29). We monitor them closely and avoid reduction of maintenance therapy, but do not advocate escalation of therapy in the absence of clinical features of relapse. Rises in ANCA titer may precede relapse in some (11,25), but not all (12), patients. In our series, both patients relapsing after transplantation had detectable Pr3-specific ANCA at the time, but retrospective sera were not available.

As knowledge grows in the management of AASV patients on RRT, it is apparent that their survival is comparable to that in nondiabetic ESRD patients. However, the nephrologist must be alerted to the possibility of relapse, which may masquerade as a complication of dialysis and delay effective treatment. There remain a place for follow-up by physicians experienced in the recognition and treatment of vasculitis.

Acknowledgments
Dr. Allen is supported by an Action Research Training Fellowship. We gratefully acknowledge all referring physicians.

References


