

Renal transplantation

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GUIDELINES

No recommendations possible based on Level I or II evidence

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- Anti-neutrophil cytoplasmic antibody (ANCA)-associated systemic vasculitis (AASV) is not a contraindication to renal transplantation. Despite the risk of disease recurrence post-transplantation, patient and graft outcomes in AASV are similar to those of renal transplant recipients with other causes of renal failure.
- The optimal timing for renal transplantation in patients with AASV has not been determined, but it is recommended that clinical remission is achieved prior to undertaking transplantation.
- The decision to undertake renal transplantation and the timing of transplantation in patients with AASV should not be guided by levels of ANCA alone.
- Standard transplantation immunosuppression regimens for patients with AASV are appropriate.
- The diagnosis of disease relapse after renal transplantation should not be based on ANCA monitoring alone, as is the case for AASV in the non-transplant population.
- Cyclophosphamide and high-dose corticosteroids can be used to treat relapses that occur in AASV patients post-renal transplantation.

BACKGROUND

Anti-neutrophil cytoplasmic antibody-associated systemic vasculitis (AASV) may result in permanent organ failure despite the improvements in therapeutic options. End stage kidney disease (ESKD) develops in 20%–25% of cases and renal transplantation has become a beneficial management goal.

Retrospective studies have shown that graft and patient survival in AASV patients after renal transplantation are comparable to those in non-diabetic patients, but several issues such as the timing of transplantation, the impact of serum ANCA levels pre- and post-transplant and recurrence of AASV following transplantation, are yet to be fully determined.

The objectives of this guideline are to identify the indications and contraindications for renal transplantation in patients with AASV, the impact of post-transplantation immunosuppression and the rates and treatment for relapses following transplantation.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for vasculitis were combined using 'and' with MeSH terms and text words for renal transplantation. The search was carried out in Medline (1966 – November Week 3, 2006). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

Date of searches: November 2006, April 2007.

WHAT IS THE EVIDENCE?

There are no randomised controlled trials (RCTs) on this topic. Only case reports, small case series and cohort studies have been published addressing this issue. The first reported case of a patient with AASV receiving a renal transplant was in 1972 with the successful transplantation of a patient with Wegener's granulomatosis (WG).¹ Multiple case reports have subsequently followed.

The first case series published involved 9 patients with WG who had undergone renal transplantation.² Prednisolone and azathioprine were used as immunosuppression and only one relapse was detected in this cohort after a mean follow-up of 47 months. The authors concluded that standard post-transplant immunosuppression was successful in controlling AASV and that cyclophosphamide should be reserved for recurrence.

A comprehensive, pooled analysis of all reported case series up to 1999 involving AASV patients and recurrence of disease following transplantation was published by Nachman *et al.*³ Single case reports were excluded to avoid positive reporting bias. This study included nine reported series and the author's own series (an additional 25 patients) and outlined a 17% relapse rate among 127 patients with follow-up of between 4 and 89 months. The mean time to

relapse in this analysis was 31 months. Clinical parameters were not useful in predicting relapses, including duration of dialysis, disease subtype, type of transplant or ANCA levels (26% relapse if ANCA-positive at time of transplant, with no significant difference if ANCA-negative).

The most recently reported study of AASV and renal transplantation is a large single-centre cohort study which involved 35 patients (20 with WG and 15 with microscopic polyarteritis [MPA]) who underwent transplantation between 1996 and 2005.⁴ Patients received prednisolone, mycophenolate mofetil (MMF) and tacrolimus as standard immunosuppression, with most having antibody induction (63% having anti-thymocyte globulin [ATG]), 14% basiliximab). Overall and death-censored graft survivals were 94% and 100%, respectively, at 5 years post-transplantation. With a mean follow-up of 4.4 years, the relapse rate was low at 9% (relapses usually occurring beyond the first year post-transplant, with no effect on allograft function) and no specific risk factors for relapse were determined. Studies involving newer and more effective immunosuppression in AASV however, are limited.

Another recently reported case series of AASV patients with renal transplants is a retrospective study of 9 patients transplanted between 1987 and 2000.⁵ All patients received cyclosporin, azathioprine and prednisolone. Two of the 9 patients relapsed (22%, a relapse rate of 0.04 per patient per year), both with upper respiratory tract involvement, but transplantation in the AASV population compared favourably with a control non-diabetic group (18 patients) which received transplants over a similar time period (renal function, $P = 0.05$ at 6 months). Cyclophosphamide was used to treat relapses with good effect.

The largest cohort of renal transplant patients with AASV as the primary cause of ESKD was retrospectively analysed as part of the Collaborative Transplant Study (multi-centre), which involved 378 patients with WG and a first cadaveric transplant.⁶ The transplants were undertaken between 1985 and 2000 and WG patients were compared with renal transplant outcomes in 3912 patients with IgA, 1220 with membranoproliferative glomerulonephritis (MPGN), 14,482 with polycystic kidney disease (PCKD) and 15,584 with diabetes mellitus. In the WG group, there was an 80% 10-year patient survival which, when compared with other causes of ESKD, was similar to MPGN and better than diabetes and PCKD. Wegener's granulomatosis patients had a mean age of 47 years with a 65% graft survival at 10 years, similar to patients with IgA and PCKD. The overall outcome for IgA patients was better than in WG patients (IgA group, 84.5% 10-year patient survival) although the mean age was older in WG patients compared with IgA. This study also showed that the use of haplotype-related transplants may improve graft survival (but not overall patient survival) in the WG population and that triple immunosuppression with the addition of either azathioprine or MMF in comparison to prednisolone and cyclosporin alone was not superior with similar 3-year and 5-year graft survivals on initial analysis.⁶ The authors concluded from this study that the overall survival in AASV patients was no different compared to those with non-

systemic disorders, and that different immunosuppressive regimens are not associated with different outcomes. Subsequent analysis of this data has shown that immunosuppression with MMF after renal transplantation is actually associated with a higher relapse rate than treatment with azathioprine ($P < 0.05$).⁷

Which patients with ANCA-associated vasculitis should be transplanted?

Quality of life has been shown to improve significantly after renal transplantation, compared to dialysis, for other causes of ESKD. Although this has not formally been proven for patients with AASV, graft and patient survival of patients with AASV are comparable to those with other causes of renal failure. Despite the potential for relapse, transplantation of patients with WG or MPA is an advisable mode of therapy, providing general contraindications to transplantation, such as infection or malignancy, are not present.

Comparison of long-term outcomes of AASV patients with ESKD who are transplanted with those remaining on dialysis, involve many disparities. In general, patients having transplants are younger than those on dialysis, and may also have fewer comorbidities, making differences difficult to determine. A large retrospective study of 59 patients showed that AASV patients who are transplanted have a better patient survival than those who remain on dialysis, however, those transplanted were younger, making results difficult to interpret.⁸

A retrospective Australian study of 1505 patients with biopsy-proven glomerulonephritis (GN) who had received a primary renal transplant assessed the incidence and outcome of recurrent GN post-transplantation.⁹ The 10-year allograft loss due to recurrent disease in all patients was 8.4%, and of patients diagnosed with pauci-immune crescentic GN ($N = 102$), it was 7.7%. This was similar to other causes of GN such as IgA nephropathy (9.7%), membranous nephropathy (12.5%), focal segmental glomerulosclerosis (12.7%) and MPGN (14.4%). Allograft loss after 10 years from all causes was 45.4%, predominantly due to chronic rejection, with no significant difference between the types of GN (pauci-immune crescentic GN, 53.7%). This was also comparable to allograft loss in patients with other types of ESKD (45.8%). There were no modifiable risk factors for recurrence of GN in this study, and so the authors concluded that no alteration to the general approach to renal transplantation for this population, including those with AASV, was warranted.

There is always concern about the development of malignancy post-transplantation and this was addressed for AASV in one Dutch cohort study of 43 patients (10 with anti-glomerular basement membrane disease and 33 with AASV).¹⁰ With a mean follow-up of 62 months, there was an increase in malignancies compared with a matched control group of renal transplant recipients with other underlying diseases ($P = 0.02$), although these were predominantly skin cancers and there was no impact on patient survival. Patient and graft survival at 5 years post-

transplantation were 77% and 60%, respectively, which were not significantly different to the control group (79% and 56%, respectively).

ANCA levels and transplantation

Anti-neutrophil cytoplasmic antibody levels are a useful marker of disease activity in the non-transplant AASV population. Prospective and retrospective studies have shown reduction in titres with remission and increases in circulating levels with disease relapses, although there are conflicting reports. Given that some studies show recurrences may occur more frequently in ANCA-positive patients, should renal transplantation be performed in patients with positive ANCA?

One early case report described a patient with MPA who received a cadaveric renal transplant despite persisting positive ANCA levels, and who had no evidence of disease activity 2 years later.¹¹ A subsequent case series by Frascà *et al.* then reported three patients with MPA and persisting positive myeloperoxidase (MPO) ANCA titres in remission who successfully underwent renal transplantation.¹² Cyclosporin, azathioprine and prednisolone were used as immunosuppression and with 21 and 38 months' follow-up, two of the three patients had well-functioning grafts with no evidence of clinical disease. The other patient required a transplant nephrectomy at 3 months because of surgical complications.

Multiple case series have since supported that pre-transplantation ANCA titres have no predictive value with regards to outcomes. A retrospective, case-control study of 17 AASV patients with renal transplants compared to age- and sex-matched controls revealed inconsistencies between ANCA levels at the time of transplantation and relapses.¹³ All AASV patients were only transplanted after remission was achieved and overall outcomes of AASV patients were comparable to those with ESKD from other types of GN.

The Collaborative Transplant Study revealed that 81% of AASV patients with renal transplants were ANCA positive at any time point, with 65% PR3-ANCA positive and 22% MPO-ANCA positive.⁷ Of note, ANCA levels did not influence relapse rates or outcomes, including graft and patient survival. The pooled analysis by Nachman *et al.* also supports that positive ANCA levels are not associated with an increased risk of relapse post-transplantation.³ Retrospective studies in AASV patients have consistently shown that positive ANCA levels should not preclude renal transplantation and there is also little evidence to support serological monitoring of ANCA titres to predict or detect relapses post-transplantation.

When should ANCA-associated vasculitis patients with renal failure be transplanted?

Most studies involve AASV patients being transplanted after remission of disease has been achieved and therefore it is difficult to determine potential graft and patient outcomes in patients who still have clinical disease activity at the

time of transplant. Given there is no controlled data, this question is difficult to answer, and therefore it is recommended that stable clinical remission be achieved prior to transplantation.

A minority of AASV patients (3% to 5%) do not achieve remission and case reports have described successful renal transplants in WG patients with remaining upper respiratory tract disease activity,¹⁴ however, transplantation generally should be delayed until complete remission.

For AASV patients with ESKD on dialysis, the issue of clinical disease activity may be difficult to determine given there may still be persisting positive ANCA levels despite the irreversible renal failure. The timing of transplantation should not be guided by ANCA levels alone and extra-renal manifestations or constitutional symptoms in patients with AASV should be considered in the assessment of clinical remission. If there are concerns about persisting vasculitis activity, waiting 6 months after the commencement of dialysis before undertaking transplantation may be a conservative approach. However, there is no evidence to support this, and most studies have shown no association with the duration of dialysis pre-transplantation and graft or patient outcomes.

What immunosuppression should be used in ANCA-associated vasculitis patients following transplantation?

The question of the most appropriate immunosuppression in the transplantation of AASV patients was initially raised by a retrospective review of published case reports showing that relapses post-transplantation in AASV patients were higher in those on cyclosporin compared with azathioprine (71% vs 18%, $P = 0.02$).¹⁵ Another early study addressing this issue reported on a small sample of 4 AASV patients with renal transplants, two of whom developed relapses at 18 and 25 months, and concluded that cyclosporin did not control AASV completely but was a good first line therapy in transplantation with minor side effects.¹⁶ The authors argued that using cyclosporin first line would therefore save cyclophosphamide treatment in the event of disease relapse. This study also proposed the preliminary suggestion that ANCA titres were not prognostic in transplantation.

The finding of a lack of beneficial effect of cyclosporin in AASV patients after transplantation however, has not been consistently demonstrated, with several subsequent studies with larger patient numbers revealing similar outcomes with varying regimens. The addition of cyclosporin to azathioprine- and prednisolone-based regimens was not shown to influence the relapse rate in a large, retrospective, pooled analysis of 127 patients involving reported case series.³ Of those on cyclosporin, there was a 20% relapse rate but not significantly different to those not on cyclosporin.

The impact of various immunosuppressive agents in AASV patients having renal transplants has been addressed recently in the Collaborative Transplant Study, as described earlier.⁶ This retrospective study had initially shown no

difference in outcomes or relapses between the administration of combination therapy cyclosporin and prednisolone, azathioprine and prednisolone, cyclosporin, azathioprine and prednisolone or cyclosporin, MMF and prednisolone. However, subsequent review of the continuing Collaborative Transplant Study revealed an association between MMF and a higher relapse rate when compared with treatment with azathioprine ($P < 0.05$).⁷ MMF as a substitution for azathioprine is increasingly being used for the treatment (induction and maintenance) of AASV at initial diagnosis but more studies are required to determine its effect on prevention of relapses post-transplantation.

The most recently reported study of transplanted patients with AASV showed very few relapses (and no renal relapses) with the use of induction therapy (predominantly ATG, but also basiliximab).⁴ The maintenance immunosuppression regimen in this study involved prednisolone, MMF and tacrolimus, and the authors suggested that with newer protocols there may be lower risks of disease recurrence (9% in this study). However, no RCTs have been performed to assess the optimal transplant immunosuppression for AASV patients.

Relapses – rates and treatment

Recurrence of disease post-renal transplantation is relatively low in AASV patients (0.02 to 0.1 relapses per patient per year). Although variable rates are reported, they are generally lower than relapse rates of the non-transplanted AASV population, perhaps because of the maintenance immunosuppressive therapy following transplantation. This difference may also relate to the fact that relapses in transplant patients are reported from the time of transplantation rather than the initial diagnosis of AASV as for the non-transplant population.

One early retrospective study of 8 patients reported a relapse frequency of 12%, with only one patient having disease recurrence at 10 months.¹⁷ All except 1 patient had positive ANCA at the time of transplantation, although all patients were in clinical remission with a mean time from the last vasculitis activity of 46 months. Although the patient who relapsed had persisting positive ANCA levels, there was a lack of any relationship among the others between ANCA and disease outcome.

A retrospective case-control study performed by Haubitz *et al.* involved 18 patients with AASV who underwent renal transplantation.¹⁸ This revealed similar graft survival in patients with autoimmune diseases compared with other causes of ESKD. There was also a lower incidence of disease relapse in those transplanted compared with patients continuing haemodialysis, and autoantibodies at the time of transplantation did not influence outcomes. There were no renal relapses in WG patients ($N = 15$), although three had extra-renal manifestations after transplantation. One of the three MPA patients had a relapse at 24 months after transplant.

Duration of dialysis pre-transplantation has been observed to be a risk factor in one study, with an association

found between patients with relapses and a shorter duration of dialysis pre-transplant (mean 10 months for patients with relapses versus 54 months for those with no relapses) but this study had small numbers ($N = 9$) making significant conclusions hard to draw.⁵

Follow-up data from the Collaborative Transplant Study has suggested that relapses may be more likely to occur in AASV patients post-transplantation if patients have had a relapse prior to the transplant ($P < 0.001$).⁷ In this retrospective study, 33% of the 378 WG patients had experienced at least one relapse before renal transplantation was performed. There was only an overall relapse rate of 9.5% of cases after transplantation, with renal transplant involvement in 40%. Renal relapses following transplantation did significantly reduce graft survival ($P < 0.05$), although not patient survival, and again, time on dialysis pre-transplant had no influence on relapse rate or outcome.

There has also been a suggestion that there is a lower rate of disease recurrence post-transplantation in patients with WG compared with MPA,¹⁴ however, this has not been supported by other studies including Nachman *et al.*'s pooled analysis where there was no difference between WG and MPA patients.³

The prevention and management of relapses after transplant have not been prospectively examined. Generally, in the literature patients are managed with cyclophosphamide-based therapy with success in inducing remission in 69% of cases.^{3,19} One case report described successful treatment of recurrent GN in a patient with AASV following transplantation with a combination of cyclophosphamide, plasma exchange and intravenous immunoglobulin²⁰ however, therapy with cyclophosphamide and high-dose glucocorticoid has been most often reported to be effective. Rituximab may be useful in patients with AASV, however, only one case of its use post-transplantation has been reported.⁴

SUMMARY OF THE EVIDENCE

Although treatment of AASV has improved considerably, about 20% of patients develop ESKD and require renal replacement therapy. Successful renal transplantation in patients with AASV has been reported since 1972, and case reports and case series have included patients predominantly in disease remission, with both negative and positive serum ANCA antibodies, as well as a few patients with active vasculitis at the time of transplantation.

Despite the substantial relapse rate, renal transplantation is a good option for patients with AASV, with post-transplantation prognosis reported to be as good as for patients with ESKD from other forms of GN. There are, however, no prospective studies addressing the issue of transplantation in the AASV population and most reports are of patients receiving renal transplants after clinical remission of vasculitis has been achieved. It is therefore recommended to wait for stable clinical remission of AASV before proceeding to transplantation.

Relapses are reported to occur in around 10%–20% of patients following renal transplantation, with renal involve-

ment in 60% and extra-renal manifestations in 40%. Relapses can occur at any stage, early or late, but on average, arise between 2 and 3 years following transplantation. There are no consistent clinical parameters to predict relapse, with neither pre-transplant course, duration of dialysis, the type of AASV, levels of circulating ANCA nor the type of renal transplant influencing outcomes. The only recently reported significant association is between pre-transplant relapses and a greater risk of relapse following transplantation.

Relapse rates of AASV following renal transplantation are approximately half of the rates seen in the non-transplant AASV population, although disparities in the determination of this comparison are present. No consistent differences in relapse rates and outcomes post-transplantation have been shown with various immunosuppression agents and regimens compared to standard protocols. Newer immunosuppressive regimens report reduced relapse rates (<10%) and may be more beneficial but no prospective studies are available.

Retrospective studies have also shown that serological monitoring of ANCA post-transplantation revealed conflicting data and therefore a recommendation that diagnosis of disease relapse after transplantation should not be based on ANCA monitoring alone is suggested. Reports of relapses post-transplantation most commonly involve treatment with cyclophosphamide with success in about 70% of cases, however, there are also no available prospective studies to determine the optimal management of this population. Rituximab may be a potential alternative agent to manage relapses.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.

UK Renal Association: No recommendation.

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines: Guideline 1.5.3. *Recurrence of systemic disease.* ANCA vasculitis is not a contraindication to transplantation: there is a low but substantial risk of recurrence, which is independent of the presence of circulating ANCA or type of vasculitis. Graft survival is similar in patients with ANCA-associated vasculitis and those with other causes of renal failure. (Evidence Level B).

Guideline IV. Long-term management of transplant recipient. IV.2.6. *Late recurrence of other diseases.* C. In the case of recurrent ANCA-associated renal or systemic vasculitis, it is recommended to reinforce the immunosuppression with appropriate agents. (It is further suggested that with renal relapses cyclophosphamide be used and/or an increase in steroid therapy, with remission in 70% of cases).²¹

International Guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

Prospectively collect information regarding graft and patient outcomes for AASV patients with renal transplants, including ANCA levels and immunosuppression.

SUGGESTIONS FOR FUTURE RESEARCH

Many fundamental questions concerning renal transplantation in AASV patients have not been answered, such as the optimal immunosuppression and the treatment of relapses, and may be amenable to study in randomised controlled trials but would be very difficult, given the small numbers involved.

CONFLICT OF INTEREST

Nigel Toussaint has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

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APPENDICES

Table 1 All reported case series of patients with ANCA-associated systemic vasculitis post-renal transplantation

Study ID	N	Mean age (years)	Time of transplant post-disease (months)	ANCA +ve at transplantation (%)	Immuno-suppression regimen	Relapse (N)	Relapse (%)	Time to relapse (months)	ANCA +ve at relapse (%)	Follow-up (months)	Follow-up graft survival (%)	Follow-up patient survival (%)
Kuross <i>et al.</i> , 1981 ²	9	36.1	31.2	—	PNL, Aza	1	11.1	48	—	47.1	66.7	66.7
Schmitt <i>et al.</i> , 1993 ¹⁴	11	—	—	—	PNL, Aza	3	27.3	—	—	—	—	—
Stegeman <i>et al.</i> , 1994 ²²	8	—	—	62.5	CyA, PNL, Aza	2	25	38.5	100	(6–21)	75	100
Grotz <i>et al.</i> , 1995 ¹⁶	4	—	—	75	CyA, PNL, Aza	2	50	21.5	100	(18–60)	50	100
Frasca <i>et al.</i> , 1996 ¹²	3	34.3	28	100	CyA, PNL, Aza	0	0	—	—	20.7	66.7	100
Haubitz <i>et al.</i> , 1997 ¹⁸	18	36	—	38.9	CyA, PNL, Aza	4	22.2	—	75	56	87	94.4
Rostaing <i>et al.</i> , 1997 ¹⁷	8	51	46	87.5	CyA, PNL, Aza +ATG	1	12.5	10	100	38	75	87.5
Nyberg <i>et al.</i> , 1997 ¹³	17	46	—	47.1	CyA, PNL, Aza	5	26.3	35	80	82	82.4	100
Allen <i>et al.</i> , 1998 ⁸	22	—	14	—	CyA, PNL, Aza	2	9.1	89	100	—	72.7	86.4
Nachman <i>et al.</i> , 1999 ³	14	42	—	92.9	CyA, PNL	0	0	—	—	44	64.2	100
Nachman <i>et al.</i> , 1999 ³	11	52.4	—	100	CyA, PNL	2	18.2	31	100	71	54.5	77.8
Elmedhem <i>et al.</i> , 2003 ⁵	9	49.2	44	44.4	CyA, PNL, Aza	2	22.2	45	100	62	100	100
Gera <i>et al.</i> , 2007 ⁴	35	44	25	43	Tac, PNL, MMF+ATG	3	8.6	37	100	52.8	94	100
Total	169	—	—	—	—	27	15.98	—	—	—	—	—

PNL = prednisolone; Aza = azathioprine; CyA = cyclosporin; ATG = anti-thymocyte globulin; Tac = tacrolimus; MMF = mycophenolate mofetil.

Table 2 The Collaborative Transplant Study involving patients with Wegener's granulomatosis post-renal transplantation

Study ID	N	Mean age (years)	Mean time of transplant post-disease (months)	ANCA +ve at transplantation (%)	Immuno-suppression regimen	Relapse (N)	Relapse (%)	Mean time to relapse (months)	ANCA +ve at relapse (%)	Follow-up (months)	Follow-up graft survival (%)	Follow-up patient survival (%)
Schmitt <i>et al.</i> , 2006 ⁷	378	—	—	—	CyA, PNL, Aza	—	—	—	—	120	65	80

CyA = cyclosporin; PNL = prednisolone; Aza = azathioprine.