



Kidney transplantation and ANCA-associated vasculitis

F. J. VAN DER WOUDE, MD, PHD

Although the outcome of treatment has improved considerably, about 20% of patients with ANCA-associated vasculitis (AASV) will develop renal insufficiency and will have to be treated with renal replacement therapy.¹ One of the options for these patients is renal transplantation. Renal transplantation has become a standard renal replacement therapy worldwide, and allograft survival rates have steadily improved over the last decades. The average cadaveric graft is now projected to function more than 13 years and the average live-donor graft for more than 21 years.² This means that we will not only be confronted more often with the question of whether kidney transplantation is the right option to choose for the patient with AASV and renal insufficiency, but that we also can expect to see a greater number of patients with recurrent glomerulonephritis after kidney transplantation. The relevance of the problem was recently emphasized by data from Australia.² In this country, from 1979 to 1988, the incidence of all-cause graft loss fell by 45.5 per 1,000 transplants (95% CI, 40.9 to 50.2), largely because of a fall in the incidence of graft loss caused by acute rejection. In contrast, the incidence of recurrent disease rose by 1.3 per 1,000 (95% CI, 0.6 to 2.1). In line with these findings, it has also been shown that recipients of human leukocyte antigen (HLA)-identical living related donor grafts rarely experience rejection, however at the expense of a high rate of recurrent glomerulonephritis.³ In a study from the Netherlands, recurrence of glomerulonephritis was present in 36 to 42% of those biopsied, resulting in 24% of graft losses.³

It is clear that information on the long-term course of AASV patients after transplantation is crucial for practicing physicians, to guide their patients in making the choice for or against renal transplantation. In addition, the ongoing development by pharmaceutical companies of new immunosuppressive drugs for application after kidney transplantation may inspire us to try new immunosuppressive protocols for induction or maintenance treatment of AASV before the disease has caused renal insufficiency. For

example, studies with mycophenolate mofetil have been reported⁴ and are ongoing.

In this short review I will discuss indications and contraindications for renal transplantation in AASV patients, recurrence of vasculitis after transplantation, and the impact of post-transplant immunosuppression on immunoregulation in AASV.

■ INDICATIONS AND CONTRAINDICATIONS FOR RENAL TRANSPLANTATION

It is well established that quality of life improves significantly after kidney transplantation as compared to hemodialysis or peritoneal dialysis treatment. Only rather recently could it be shown that transplantation also results in a significant prolongation of patient survival.⁵ It is very difficult to demonstrate that this is also true for AASV patients. In a recently published single-center retrospective study,¹ transplanted AASV patients were younger than those remaining on hemodialysis. This makes the better patient survival observed in the transplanted patients difficult to interpret. It would require a multicenter case-control study with transplanted AASV patients as cases and AASV patients on the waiting list as controls to document a beneficial effect of transplantation on patient survival or relapse rate. To the best of my knowledge, such a study has not been reported. It has to be doubted that such a study is feasible.

Are AASV patients especially at risk for opportunistic infections or other transplantation-related complications? Although this subject has never formally been studied, patients with severe atrophy of the nasal mucosa and local infections or with a limited bone marrow reserve after repeated courses of cyclophosphamide therapy are prone to develop infections after transplantation that are difficult to treat. One should therefore be reluctant to put such patients on the waiting list for kidney transplantation. In addition, it has been reported that, in such patients, reactivation of CMV infection after transplantation may lead to thromboembolic complications such as venous thrombosis of the extremities and pulmonary embolism.⁶

How relevant are ANCA-titers in the pretransplant work-up? The utility of ANCA as a predictor of relapse has generated some controversy. We found that ANCA titers, even of IgG subclasses, or detected with the newest catching ELISAs, failed to predict relapses.⁷ Reports of successful renal transplantation in the face of a positive myeloperoxi-

From the Vth Medical University Clinic, Klinikum Mannheim, Heidelberg University, Mannheim, Germany. Address correspondence to F.J.V.D.W., Vth Medical University Clinic, Klinikum Mannheim, Heidelberg University, Theodor-Kutzer-Ufer 1-3, 68135 Mannheim, Germany. E-mail: Fokko.van-der-Woude@med5.ma.uni-heidelberg.de

dase (MPO)-specific ANCA were presented by Noel et al in 1993,⁸ by Grotz et al in 1995,⁹ and Frasca et al in 1996.¹⁰ In a pooled analysis of recurrence after transplantation in 39 AASV patients,¹¹ there was no statistically significant difference in the relapse rate between those with and without circulating ANCA at the time of transplantation. So, unlike the situation in anti-GBM disease, where persisting anti-GBM antibodies are associated with a much higher recurrence rate, positive ANCA titers in patients who are clinically well are not a contraindication for transplantation.

ANCA-associated disease is known to occur in families,¹² and the occurrence of AASV after nephrectomy in a kidney donor has been described.¹³ Are AASV patients good candidates for living, related transplantation? Since there is no registry of living donors related to AASV patients, this question is difficult to answer. One could specifically screen for AASV-related signs and symptoms and measure ANCAs and other autoantibodies in potential donors related to AASV patients. In case of positivity, another donor should be sought.

■ RECURRENCE

A comprehensive, pooled analysis of all reported series of AASV using the terms *transplantation*, *vasculitis*, *Wegener's granulomatosis*, and *microscopic polyangiitis*, was published in 1999¹¹; nine reported series and patients from Lund and the author's own series from the Chapel Hill region were included, covering a total of 127 patients. In order to avoid reporting bias, only case series (including more than one patient) were included. Doing a PubMed search on January 12, 2002, I was unable to find additional later case-series.

The major findings of this important study¹¹ are as follows:

Recurrent AASV occurred in 22 of 127 patients, corresponding to a relapse rate of 17.3%. The average time to relapse was 30.9 months, ranging from 4 to 89 months. (There are single case reports of relapses later after transplantation.¹⁴) Of the 21 patients with recurrent disease for whom clinical information was available, renal involvement occurred in 12 patients, whereas 10 patients had relapsing disease affecting extrarenal organs only. Recurrent vasculitis affecting the upper respiratory tract occurred in eight patients, the lungs in six patients, the gut in two, the skin in four, the joints in four, and the eyes in two.

The length of renal replacement therapy prior to transplantation was available on 7 patients who suffered a relapse and 41 patients who did not relapse. There was no statistically significant difference in the distribution of time on dialysis prior to transplantation between relapsers and non-relapsers. Of the 16 patients with relapse for whom treatment information was available, 12 received cyclophosphamide, 3 received azathioprine (in addition to cyclosporin A and prednisone), and 1 received high-dose methylprednisolone alone. In 11 patients remission could be induced. There was no statistically significant difference in the relapse rate between patients treated with cyclosporin A and those not receiving cyclosporin A. Relapses occurred in 20.4% of patients with Wegener's granulomatosis compared with 15.7% of patients with microscopic polyangiitis or necrotising crescentic glomerulonephritis (NS). Similarly, patients with C-ANCA were

no more likely to suffer a relapse than patients with P-ANCA (20 vs 17.2%).

The relapse rate in this analysis (17%) is somewhat lower than the expected rate reported in nontransplant patients, which ranges from 30 to 45%.^{15,16} In the series from the Hammersmith Hospital, London, UK, the vasculitis relapse rate after transplantation was only 0.02 per patient per year as compared to approximately 20% on dialysis.¹ These data suggest that maintenance immunosuppression after kidney transplantation lowers relapse rates of AASV. How could standard post-transplant immunosuppressive therapy have such a favorable influence?

■ IMPACT OF POST-TRANSPLANT IMMUNOSUPPRESSION ON IMMUNOREGULATION IN AASV

It is well known that current immunosuppressive drugs, applied after kidney transplantation, mainly affect cellular immunity compared with humoral immunity. Relevant preexisting alloreactive antibodies, such as anti ABO-blood-group antibodies, must therefore be removed by invasive procedures such as plasmapheresis, combined with splenectomy, to make successful transplantation possible. Interestingly, azathioprine maintenance immunosuppression gives much better long-term results in these patients compared with cyclosporin A.¹⁷ It is therefore not very likely that the favorable effect of immunosuppressive drugs, such as corticosteroids or calcineurin-inhibitors, on the vasculitis relapse rate is mediated by an effect on the humoral immune response or inhibition of the production of preexisting ANCA. Theoretically, this could be different for azathioprine or mycophenolate mofetil.

Is there evidence that dysregulated cellular immunity is present in AASV?

Although cellular immunity against ANCA-antigens as a pathogenetic mechanism was postulated early after the discovery of ANCA,¹⁸ it has been difficult to demonstrate that specifically in patients with AASV there is increased reactivity of lymphocytes with proteinase 3- or myeloperoxidase-antigen or antibody-derived peptides.^{19,22}

The first convincing evidence of a dysregulation of cellular immunity in AASV was described in 1992 by Schmitt et al.²⁰ They measured soluble interleukin-2 receptor (sIL-2R) levels in 102 patients with Wegener's granulomatosis. Levels of sIL-2R were elevated in all patients, even in the absence of disease activity. However, levels of sIL-2R were significantly higher in patients who had relapses than in those who did not. These findings were later confirmed and extended.²¹⁻²³ All patients with AASV show signs of disturbed cellular immunity, such as reduced CD28 expression on CD3-positive cells and increased expression of the early T-cell activation marker CD 69 on CD3-positive cells, as well as of CD 38 on CD8-positive cells. These abnormalities persist during immunosuppressive therapy.

In a recent survey of our patients with AASV, we found a significantly increased expression of CD25 on CD4-positive cells also in patients without signs of disease activity; the pattern of the phenotypic lymphocyte subpopulation distribution appeared to be highly specific for AASV (Neumann I et al, Abstract, this meeting). It is unlikely that this T-cell abnormality is secondary to increased antigen-presenting activity by myeloid cells, since the latter

phenomenon can only be demonstrated during active disease.²⁴ The persistence of dysregulated cellular immunity during remission in AASV might explain the relapsing course observed in most patients. Furthermore, the successful treatment of AASV with agents that directly affect T-cells such as monoclonal antibodies to CD4 and CD52²⁵ or rabbit anti-thymocyte globulin (ATG)²⁶ supports the hypothesis that dysregulated cell-mediated immunity is a proximal event in the pathogenesis of AASV. It will therefore be interesting to see what effects newer immunosuppressive agents applied after kidney transplantation with effects on cellular immunity—such as anti-ILR-2 monoclonal antibodies, deoxy-spergualin, or rapamycin—will have on lymphocyte phenotype and recurrence rates of AASV in transplanted patients.

■ CONCLUSIONS

Kidney transplantation is a realistic therapeutic option for patients with renal insufficiency and AASV. Ongoing disease activity, persisting infections, or irreversible damage caused by previous immunosuppressive therapy are contraindications for transplantation. There is no reason to be-

lieve that the duration of dialysis therapy or the nature of the AASV and/or ANCA will have a profound impact on the relapse rate after transplantation. Since AASV may occur in relatives, care must be taken to rule out AASV in potential living related organ donors. Prognosis for patient and graft survival after transplantation in AASV is good, and relapse rates are lower compared to hemodialysis.

The favorable effect of kidney transplantation on relapse rate could possibly be mediated through post-transplant maintenance immunosuppression. Since dysregulated T-cell immunity is likely to be key to the pathogenesis of AASV, kidney transplantation could therefore be considered a model for learning which new immunosuppressive drugs (often used in large industry-sponsored trials) have the strongest favorable effect on the course of the disease. Immunosuppressive drugs used to treat or prevent transplant rejection could be tried as induction or maintenance treatment in new AASV patients. A prospective randomized trial for maintenance therapy in patients in remission (IMPROVE-PROTOCOL) with mycophenolate mofetil has recently been started in Europe.

■ REFERENCES

- Allen A, Pusey C, Gaskin G. Outcome of renal replacement therapy in antineutrophil cytoplasmic antibody-associated vasculitis. *J Am Soc Nephrol* 1998; 9:1258-1263.
- Chabdan SJ. Glomerulonephritis in the renal graft. *J Am Soc Nephrol* 2001; 12:394-402.
- Andresdottir MB, Hoitsma AJ, Assmann KJ, Koene RA, Wetzels JF. The impact of recurrent glomerulonephritis on graft survival in recipients of human histocompatibility leucocyte antigen-identical living related donor grafts. *Transplantation* 1999; 68:623-627.
- Nowack R, Gobel U, Klooker P, Hergesell O, Andrassy K, van der Woude FJ. Mycophenolate mofetil for maintenance therapy for Wegener's granulomatosis and microscopic polyangiitis: a pilot study in 11 patients with renal involvement. *J Am Soc Nephrol* 1999; 10:1965-1971.
- Schnuelle P, Lorenz D, Trede M, van der Woude FJ. Impact of renal cadaveric transplantation on survival in end-stage renal failure: evidence for reduced mortality risk compared with hemodialysis during long-term follow-up. *J Am Soc Nephrol* 1998; 9:2135-2141.
- Wolf G, Porth J, Stahl RAK. Thrombosis associated with cytomegalovirus infection in patients with ANCA-positive vasculitis. *Am J Kidney Dis* 2001; 38:1-5.
- Nowack R, Grab I, Flores-Suarez LF, Schnuelle P, Yard B, van der Woude FJ. ANCA titres, even of IgG subclasses, and soluble CD 14 fail to predict relapses in patients with ANCA-associated vasculitis. *Nephrol Dial Transplant* 2001; 16:1631-1637.
- Noel L, Morin M, Thervet E, Legendre C, Vandapel O, Kreis H, Lesavre P. Successful kidney transplantation in a patient with microscopic polyarteritis and positive ANCA [abstract]. *Clin Exp Immunol* 1993; 93 [suppl 1]:43.
- Grotz W, Wanner C, Rother E, Schollmeyer P. Clinical course of patients with antineutrophil cytoplasm antibodies after kidney transplantation. *Nephron* 1995; 69:234-236.
- Frasca G, Neri L, Martello M, Sestigiani E, Borgnino L, Bonomini V. Renal transplantation in patients with microscopic polyarteritis and antineutrophil cytoplasmic antibodies: report of three cases. *Nephron* 1996; 27:82-85.
- Nachman PH, Segelmark M, Westman K, Hogan SL, Satterly KK, Charles Jennette J, Falk R. Recurrent ANCA-associated small vessel vasculitis after transplantation: a pooled analysis. *Kidney Int* 1999; 56:1544-1550.
- Nowack R, Lehmann H, Flores-Suarez LF, Nanhau A, van der Woude FJ. Familial occurrence of systemic vasculitis and rapidly progressive glomerulonephritis. *Am J Kidney Dis* 1999; 34:364-373.
- Gulati MS, Miller F, Nord EP. Pauci-immune rapidly progressive glomerulonephritis after nephrectomy in a renal donor. *Am J Kidney Dis* 1999; 33:1-3.
- Masterson R, Sheerin N, Abbs I, Goldsmith D. Late allograft loss due to recurrence of P-ANCA-associated systemic vasculitis in a patient with relapsing polychondritis. *Nephrol Dial Transplant* 2001; 16:1705-1707.
- Nachman PH, Hogan SL, Jennette JC, Falk JR. Treatment response and relapse in ANCA-associated microscopic polyangiitis and glomerulonephritis. *J Am Soc Nephrol* 1996; 7:33-39.
- Westman KWA, Bygren PG, Olsson H, Ranstam J, Wieslander J. Relapse rate, renal survival and cancer morbidity in patients with Wegener's granulomatosis or microscopic polyangiitis with renal involvement. *J Am Soc Nephrol* 1998; 9:842-852.
- Schnuelle P, van der Woude FJ. Should A2 kidneys be transplanted into B or O recipients? *Lancet* 1998; 35:1675-1676.
- van der Woude FJ, van Es LA, Daha MR. The role of the C-ANCA antigen in the pathogenesis of Wegener's granulomatosis. A hypothesis based on both humoral and cellular mechanisms. *Neth J Med* 1990; 36:169-171.
- Peen E, Malone C, Myers C, Williams RC, Peck AB, Csernok E, Gross WL, Staud R. Amphipathic variable region heavy chain peptides derived from monoclonal human Wegener's anti-PR3 antibodies stimulate lymphocytes from patients with Wegener's granulomatosis and microscopic polyangiitis. *Clin Exp Immunol* 2001; 125:323-331.
- Schmitt WE, Heesen C, Csernok E, Rautmann A, Gross WL. Elevated serum levels of soluble interleukin-2 receptor in patients with Wegener's granulomatosis. Association with disease activity. *Arthritis Rheum* 1992; 35:1088-1092.
- Stegeman CA, Cohen Tervaert JW, Huitema MG, Kallenberg CG. Serum markers of T cell activation in relapses of Wegener's granulomatosis. *Clin Exp Immunol* 1993; 91:415-420.
- Ballieux BE, van der Burg SH, Hagen EC, van der Woude FJ, Melief CJ, Daha MR. Cell-mediated autoimmunity in patients with Wegener's granulomatosis. *Clin Exp Immunol* 1995; 100:186-193.
- Christensson M, Pettersson E, Sundqvist KG, Christensson B. T cell activation in patients with ANCA-associated vasculitis: inefficient immune suppression by therapy. *Clin Nephrol* 2000; 54:435-442.
- Iking-Konert C, Vogt S, Radsak M, Wagner C, Hansch GM, Andrassy K. Polymorphonuclear neutrophils in Wegener's granulomatosis acquire characteristics of antigen presenting cells. *Kidney Int* 2001; 60:2247-2262.
- Lockwood CM. Refractory Wegener's granulomatosis: a model for shorter immunotherapy of autoimmune diseases. *J R Coll Physicians Lond* 1998; 32:473-478.
- Hagen EC, de Keizer RJ, Andrassy K, van Boven WP, Bruijn JA, van Es LA, van der Woude FJ. Compassionate treatment of Wegener's granulomatosis with rabbit anti-thymocyte globulin. *Clin Nephrol* 1995; 43:351-359.