ABSTRACT

Despite major advances in the management of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) achieved in the last decades, a large proportion of AAV patients still develop end-stage renal disease. The survival of AAV patients dependent on dialysis is significantly worse compared with dialysis-independent AAV patients, but is comparable to other non-diabetic patients requiring dialysis. Renal transplantation (RTx) is the method of choice among renal replacement therapies and there has been increasing evidence that it is a suitable method with favorable patient- and graft-survival also in AAV patients. It is recommended to perform RTx after ≥12 months of remission, and ANCA positivity at the time of RTx is generally not considered a contraindication. Even though the risk of relapse after RTx is relatively low with current post-transplant immunosuppressive regimens, disease recurrence may occur. Besides cyclophosphamide, rituximab might become a therapeutic alternative for post-transplant AAV recurrence in the near future but its efficacy and safety in this setting needs to be confirmed in larger studies.

Keywords: ANCA, outcome, relapse, renal transplantation, vasculitis

INTRODUCTION: END-STAGE RENAL DISEASE IN ANTI-NEUTROPHIL CYTOPLASMIC ANTIBODY-ASSOCIATED VASCUITIS

Anti-neutrophil cytoplasmic antibody (ANCA)-associated systemic vasculitides (AAV), particularly granulomatosis with polyangiitis (GPA, formerly Wegener’s) and microscopic polyangiitis (MPA), have been recognized as the leading cause of rapidly progressive glomerulonephritis (RPGN), followed by anti-glomerular basement membrane (anti-GBM) disease and immune-complex glomerulonephritis. Despite advances in the diagnosis and treatment of AAV, about 20–30% of AAV patients develop end-stage renal disease (ESRD) within 5 years, either as a direct consequence of RPGN, chronic smouldering renal disease or hemodynamically mediated progression not related to the activity of the disease [1].

A number of clinical and histopathologic factors have been identified as possible predictors of renal survival in AAV in various studies, including renal function at baseline or at 6 months; initial treatment response; occurrence of renal relapses; percentage of normal glomeruli, chronicity index score on renal biopsy and International Working Group of Renal Pathologists (IWGRP) classification of glomerular lesions developed by European Vasculitis Society (EUVAS) [1–4]. Taken together, the available data point to the importance of early diagnosis and timely initiation of appropriate treatment. It should be noted that even in the most severe necrotizing and crescentic presentations immunosuppressive therapy is indicated as there has never been reported that characteristics of patient presentation or on kidney biopsy could demonstrate a ‘point of no return’ where immunosuppression is considered futile. There has been a good consensus that the potential benefit of initial treatment outweighs the risk of treatment-related death even in patients with low baseline glomerular filtration rate and severe scarring [2, 5], although the optimal length of immunosuppressive treatment in patients who remain dialysis dependent and do not have any signs of extra-renal activity remains less clear [6].
As the overall survival of AAV patients has been improving, our ability to address the consequences of renal failure in AAV patients becomes paramount. AAV-related ESRD has been estimated to account for up to 3–5% of all dialysis patients but a number of the AAV patients requiring dialysis may remain undiagnosed, particularly those with renal-limited disease [7]. Interestingly, the number of AAV patients among all incident ESRD patients in two recent reports from large registries from different parts of the world was relatively consistent and made only 1% [8, 9]. Nevertheless, the number of AAV patients with ESRD in registries may be underestimated due to the use of not always clearly defined codes for AAV, and a somewhat higher percentage seems to be more probable. In addition, there might be differences among disease prevalence among different geographical regions. Despite some limitations of data from dialysis and transplant registries with regard to the absence of data on ANCA positivity, extra-renal involvement or prior immunosuppressive treatment, the registries provide important information on a large number of patients with ESRD. At present, with ANCA testing being routinely available, AAV should be considered as a potential cause of ESRD in all patients with unknown origin of renal failure, especially when rapid decline of renal function is noted. The establishment of right diagnosis may not only help some patients to recover independent renal function but also helps to guide further steps in those who remain dialysis-dependent.

**SURVIVAL OF AAV PATIENTS ON RENAL REPLACEMENT THERAPY**

Renal involvement in AAV, particularly with chronic kidney disease (CKD) stage 5 leading to ESRD, is undoubtedly associated with a worse patient survival compared with AAV patients with dialysis-independent renal function [3, 10]. On the other hand, overall mortality of AAV patients requiring dialysis has been reported to be similar to non-diabetic general dialysis population in a number of retrospective as well as registry-based studies [6, 8, 9, 11–14], with a potentially higher risk of death from infection observed in some [9, 11] but not all [8] studies, which may simply reflect different approaches to maintenance of immunosuppressive treatment on dialysis.

Renal transplantation (RTx) has been shown to improve quality of life in patients with ESRD and several studies have shown that RTx offers a survival benefit compared with maintenance dialysis [15, 16]. The survival benefit of RTx has been demonstrated in AAV patients with ESRD, but the transplanted patients are usually younger than those remaining on dialysis, with presumably lower number of comorbidities, and thus, direct comparison is difficult [12]. Transplanted AAV patients have lower vasculitis relapse rates compared with those on maintenance dialysis [12] and patients with CKD who are not on dialysis [17]. Although the first successful RTx in GPA was performed more than 40 years ago [18], RTx has become the renal replacement therapy (RRT) of choice only in the past two decades due to concerns of disease recurrence with older immunosuppressive regimens.

The results of the studies published in extenso that have systematically dealt with long-term outcomes after RTx in AAV patients in detail and included ≥20 patients [8, 12, 19–25] are summarized in Table 1. In general, both patient- and graft-survival rates were at least as good as those of the control populations of non-diabetic patients and comparable with the data on survival available in large dialysis and transplant registries. Frequent infections have not seemed to be a major concern any more according to recent reports. As shown in Table 1, the 5-year patient survival ranged between 77 and 96%, and the 5-year graft survival between 60 and 100%, with an increasing trend in the most recent reports. A single brief report studied the outcomes of RTx in a specific subgroup of vasculitis patients who were double positive for ANCA and anti-GBM and found no graft loss in six double positive patients after a median time of follow-up of 66.5 months [26]. In a study describing a large cohort of GPA patients after RTx [27], the patient survival was even significantly better in GPA than in polycystic kidney disease, and only slightly worse compared with transplanted patients with IgA nephropathy, who were, however, also significantly younger (47.2 versus 41.8 years). Shen et al. demonstrated better adjusted graft survival in GPA patients than in the non-diabetic population [28].

<table>
<thead>
<tr>
<th>Study</th>
<th>Transplant era</th>
<th>Number of patients</th>
<th>Mean follow-up post-RTx (months)</th>
<th>Vasculitis relapse rate/patient/year</th>
<th>Graft survival</th>
<th>Patient survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allen et al. [12]</td>
<td>1974–97</td>
<td>22</td>
<td>NA</td>
<td>0.02</td>
<td>69% at 5 years</td>
<td>85% at 5 years</td>
</tr>
<tr>
<td>Schmitt et al. [19]</td>
<td>1982–93</td>
<td>20</td>
<td>48</td>
<td>0.1</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Nachman et al. [20]</td>
<td>1970–97</td>
<td>127</td>
<td>44</td>
<td>0.07 (estimated)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Deegens et al. [21]</td>
<td>1968–2000</td>
<td>33</td>
<td>62</td>
<td>0.01</td>
<td>60% at 5 years</td>
<td>77% at 5 years</td>
</tr>
<tr>
<td>Gera et al. [22]</td>
<td>1996–2005</td>
<td>35</td>
<td>53</td>
<td>0.02</td>
<td>100% at 5 years</td>
<td>94% at 5 years</td>
</tr>
<tr>
<td>Little et al. [23]</td>
<td>1977–2007</td>
<td>107</td>
<td>66</td>
<td>0.01</td>
<td>90% at 5 years and 70% at 10 years</td>
<td>90% at 5 years and 65% at 10 years</td>
</tr>
<tr>
<td>Geetha et al. [24]</td>
<td>1996–2010</td>
<td>85</td>
<td>64</td>
<td>0.02</td>
<td>98% at 5 years and 79% at 10 years</td>
<td>93% at 5 years and 67% at 10 years</td>
</tr>
<tr>
<td>Marco et al. [25]</td>
<td>1984–2007</td>
<td>49</td>
<td>62</td>
<td>0.01</td>
<td>64% at 10 years</td>
<td>67% at 10 years</td>
</tr>
<tr>
<td>Tang et al. [8]</td>
<td>1996–2010</td>
<td>93</td>
<td>NA</td>
<td>NA</td>
<td>82% at 5 years and 50% at 10 years for MPA and 96% at 5 years and 62% at 10 years for GPA</td>
<td>82% at 5 years and 68% at 10 years for MPA and 96% at 5 years and 85% at 10 years for GPA</td>
</tr>
</tbody>
</table>
In contrast to the results of most other studies including a systematic review [29], Tang et al. [8] reported on a worse patient- and graft survival in MPA patients compared with non-AAV patients in a study from the Australian and New Zealand Dialysis and Transplant (ANZDATA) Registry. The reasons for the worse outcome data for MPA patients in this study are not clear and call for further studies. Based on the results of genetic analysis [30] as well as clinical observations [31], it has been stressed that GPA and MPA, or proteinase 3-ANCA (PR3-ANCA) and myeloperoxidase-ANCA (MPO-ANCA) associated diseases, respectively, are different entities that should be perhaps studied separately in the future, which would, however, make studies in MPA, at least in Europe, hardly feasible due to relatively low number of patients with this disease in general, not to mention those after RTx.

WHEN (NOT) TO PERFORM RTx IN AAV

Two important issues have been discussed in almost all papers on the topic of RTx in AAV [32, 33], namely the optimal timing of RTx after a previous active phase of AAV and the significance of ANCA positivity for the outcome of RTx. Although, there are reports of successful RTx in patients with active disease [33], most authors agree that the disease should be quiescent for some time before RTx is performed but no strict recommendations about the precise duration of remission were available until recently. Little et al. demonstrated that patients transplanted <1 year post-remission had the highest risk of death with a hazard ratio of 2.3 [23]. Both the Kidney Disease: Improving Global Outcomes (KDIGO) Guidelines for Glomerulonephritis [34] and the Canadian Society of Transplantation [35] recommend that AAV patients should be in remission for 1 year prior to proceeding to RTx. The definition of remission in AAV is not uniformly defined, but it generally requires no clinical symptoms of active ongoing AAV. The use of a standardized scoring system, Birmingham Vasculitis Activity Score (BVAS) [36], may help to compare results among studies but was routinely used only in a quarter of physicians in the study by Little et al. [23].

The question of ANCA positivity at the time of RTx remains more controversial. There have been numerous reports suggesting that ANCA positivity per se is not associated with disease activity and a recent study concluded that reduction of immunosuppression may lead to increase in ANCA levels in patients without relapse, providing an explanation for the lack of predictive value of serial ANCA measurements [37]. On the other hand, persistent ANCA positivity is a known risk factor for relapse in AAV patients in general. While some authors did not detect any relationship between ANCA status and relapse after RTx [20], in other studies association of ANCA positivity at the time of RTx with an increased risk of relapse reached borderline significance (P = 0.05) [24]. Another study did not find any relationship between ANCA positivity and overall graft survival, but revealed that ANCA-positive recipients were more likely to develop severe vasculopathy in the graft [23]. In a recent pooled analysis of previous reports and their own cases [25], Marco et al. found a significant difference (P = 0.008) in relapse rates between patients with and without ANCA positivity at the time of RTx. Interestingly, the risk of relapse did not differ between PR3-ANCA and MPO-ANCA positive patients but was higher in GPA patients compared with MPA (P = 0.038) [25]. An individual approach to each patient is probably needed but the KDIGO Guideline does not recommend to delay RTx because of ANCA positivity provided that the patient is in clinical remission [34]. In any case, routine monitoring of ANCA levels should be a standard of post-transplantation care in AAV patients and follow-up not only by transplant physicians but also vasculitis specialists is of benefit. Patients with positive/increasing ANCA may merit more close monitoring for disease relapse.

RELAPSES AFTER TRANSPLANTATION

AAV relapses after RTx consist of extra-renal disease flares and disease recurrence in the graft. The risk of relapse in AAV patients on dialysis has been shown to be lower compared with pre-dialysis patients [6], even though the relapse rates varied in different studies, and the risk seems to further diminish in transplant patients [12]. Relapse rates ranging from as low as 0.006 to 0.1 per patient per year reported in selected studies are shown in Table 1 and are similar to those observed in several smaller studies [38, 39]. Although not directly compared, there seems to be a decrease in relapse rates in the most recent studies, possibly due to better efficacy of modern anti-rejection post-transplant therapy [32]. In retrospective studies, the time to relapse after RTx varies widely, with a range of only 5 days to more than 13 years [25], and a mean time of 31 months [20]. The severity and location of relapses may also be very different [32]. In the already mentioned pooled analysis [25], 38% of relapsing patient had renal involvement, 48% had extra-renal involvement and the remaining patients displayed signs of both renal and extra-renal involvement. Not surprisingly, the extra-renal involvement (particularly of upper and/or lower respiratory tract) seems to be more common in PR3-ANCA than in MPO-ANCA-associated disease [25]. It has to be noted that diagnosis of AAV flare on RRT may be very difficult as the relapses may mimic infections and other complications of immunosuppressive therapy used after RTx, and continuous vigilance in all AAV transplant recipients is therefore required.

IMMUNOSUPPRESSIVE TREATMENT AFTER TRANSPLANTATION

The basic choice of immunosuppressive regimen after RTx has been in the hands of a transplant center and did not differ between AAV patients and control groups in most studies but rather reflected the era of transplantation. Until about the early 1980s, the therapy had typically consisted of azathioprine (AZA) + corticosteroids, and cyclosporine was routinely used since then. In the most recent reports, the post-transplant protocol usually included induction immunosuppression (most commonly with antithymocyte globulin) and oral combined immunosuppression consisting usually of tacrolimus + mycophenolate-mofetil.
+ corticosteroids [22, 24]. This creates a chronological bias and makes it hardly possible to compare the influence of specific regimens used in different periods. In 1999, Nachman et al. concluded that cyclosporine-based immunosuppression did not provide a protective effect compared with regimens based on corticosteroids and AZA [20]. In an analysis of 378 GPA patients, no difference in 5-year graft survival was observed among various immunosuppressive protocols but the use of mycophenolate-mofetil (MMF) seemed to be associated with a higher risk of relapse than AZA [27]. In line with this finding, a large international randomized study IMPROVE, performed in non-transplanted patients with AAV and comparing MMF and AZA for remission maintenance, also showed that the use of MMF led to a higher risk of relapse compared with AZA (hazard ratio 1.69, P = 0.03) [40]. Nevertheless, the more recent studies on RTx in AAV, most commonly using MMF + tacrolimus + corticosteroids, reported very favorable patient outcomes, including low relapse rates (see Table 1).

### TREATMENT FOR DISEASE RELAPSES AFTER TRANSPLANTATION

Once a post-RTx relapse of AAV occurs, the choice of immunosuppression is basically similar to that of non-transplanted AAV patients, ranging from the sole increase of corticosteroids to use of cyclophosphamide and plasma exchange therapy in selected patients based on severity of the disease relapse. Cyclophosphamide (CYC) is still the golden standard in the induction treatment of generalized AAV and ANCA-related glomerulonephritis and has been successfully used also in post-transplant relapses in many studies [20, 32].

In non-transplanted AAV patients, an anti-CD20 monoclonal antibody, rituximab, has attracted a lot of attention recently. Its efficacy at least comparable to CYC, and potentially even better than that of CYC in the subgroup of relapsing patients, was demonstrated in randomized trials on the induction treatment of AAV [41, 42], and preliminary results of a randomized study confirm good efficacy of rituximab also in the maintenance phase [43].

In transplantation, rituximab belongs to a standard post-transplant therapy e.g. in the treatment of antibody-mediated rejection or in the case of ABO blood groups or human leukocyte antigen incompatible transplantations [44]. In the treatment of recurrent post-transplant AAV, the experience with the use of rituximab is limited to case reports. Even though there have been an increasing number of reports supporting its good efficacy and safety also in the post-transplant settings [45–47], this field clearly requires further studies to confirm the potential benefit of rituximab.

### CONCLUSION

In conclusion, available data confirm that RTx is a safe and effective method for the treatment of ESRD in AAV patients. With modern immunosuppressive strategies, the outcomes of AAV transplant recipients are similar to other non-diabetic diagnoses and the risk of post-transplant relapses is generally low. With the progress in the treatment of AAV and the emergence of novel therapies with biologic agents, the efficacy of these biologics in the treatment of recurrent vasculitis merits further study. Information on the non-vasculitic comorbidities that affect AAV patients such as infections, malignancy and cardiovascular disease, the frequency of relapses and the influence of disease type, ANCA type and ANCA status at the time of transplant and post-transplant immunosuppression on these outcomes will require collaboration among the transplant and vasculitis centers and establishment of (inter)national registry for prospective data collection.

### ACKNOWLEDGEMENTS

This study was supported by the Ministry of Education of the Czech Republic (grant no. PRVOUK P25/LF1/2) and by the Ministry of Health of the Czech Republic (grant no. RVO-VFN 64165).

### CONFLICT OF INTEREST STATEMENT

D.G. served as consultant to Genentech. Z.H. and V.T. declare no conflict of interests.

### REFERENCES

11. Hruskova Z, Berden A, de Groot K et al. Characteristics and outcome of patients with granulomatosis with polyangitis (Wegener’s) and microscopic polyangiitis on renal replacement therapy—data from the ERA-EDTA registry. La Presse Medicale 2013; 42: 675

Received for publication: 22.7.2014; Accepted in revised form: 18.9.2014

Renal transplantation in AAV