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Linköping University Post Print

N.B.: When citing this work, cite the original article.

Original Publication:

Mårten Segelmark, Renal transplantation in ANCA-associated vasculitis, 2013, La Médicale, (42), 4, 568-571.

<http://dx.doi.org/10.1016/j.lpm.2013.01.023>

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Postprint available at: Linköping University Electronic Press

<http://urn.kb.se/resolve?urn=urn:nbn:se:liu:diva-105257>

Renal transplantation in ANCA associated vasculitis

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Renal transplantation is the treatment of choice for end-stage renal disease. It provides better results with respect to patient survival and morbidity as well as it offers superior possibilities for rehabilitation as compared to various dialysis modalities(1). Since renal engagement, often healing with scarring, is common in anti-neutrophil cytoplasm antibody (ANCA) associated vasculitis (AAV) (2), renal transplantation is a therapeutic option that frequently needs to be considered in AAV patients.

There are several publications clearly indicating that AAV patients do fairly well after renal transplantation and that AAV should definitely not be considered as a contra-indication for transplantation(3-12). However, there are several issues regarding the treatment of AAV before and after transplantation that remain unresolved which will be addressed in this brief review. These issues include the epidemiology of AAV and transplantation, timing of transplantation, risk of relapse, role of ANCA measurements and treatment of relapses after transplantation.

Scope of the problem

There are limited data on the number AAV patients having received a renal transplant and as well as numbers on waiting lists. Understanding of the epidemiology of AAV in end-stage renal disease is hampered by unresolved matters regarding nomenclature and classification of vasculitis(13). Before the age of prevalent ANCA testing many patients with AAV went into renal failure without a distinct diagnosis. Weidemann et al reported in 1993 on ANCA among 1277 dialysis patients, about 7 % were positive and a distinct AAV diagnosis could retrospectively be made in a substantial portion of them(14). Many European renal registries use the EDTA codes where patients with renal limited AAV

(RLV) could be classified as either “crescentic glomerulonephritis” (EDTA code 17) or “glomerulonephritis not described above” (code 19) depending on the severity of the glomerular lesions, and if no biopsy is performed as “unknown” (code 00). AAV patients with extra-renal symptoms could be listed as either “Wegener’s Granulomatosis” (code 74), “renal vascular disease due to polyarthritis” (code 73) or “other multisystem disease” (code 89). No meaningful epidemiological data on AAV and end-stage renal disease can be extracted from registries using EDTA codes, but codes as 17 and 74 can be used to identify cohorts to study outcome of AAV after transplantation(7) .

Epidemiological studies in AAV have found incidence rates between 15 and 23 cases per million per year in recent publications(15-17). Data from the US suggest the rates being substantially lower among Afro-Americans(18). Apart from that there are no convincing data that the incidence of AAV varies among different countries except what can be explained by age differences. However, antigen specificity and disease phenotype do vary between populations(19). Figures from England, Japan and Sweden indicate the incidence of ANCA associated nephritis (AAN) to be 15 per million(16, 19). The long term risk of end-stage renal disease (ESRD) among AAN patients seems to be around 30 % (or 20% among all AAV patients)(2, 9, 20), figures which infer an incidence of ESRD caused by AAV of 5 per million. The mean age of patients with AAN in both Sweden and Japan is close to 70 years and there is lag time from diagnosis to dialysis dependency. As transplantation is less common above the age of 70 and rare over 75 a substantial portion of AAV patients with ESRD will not be eligible for renal transplantation. In a study by Allen et al only 37 % (22/59) of AAV patients with ESRD actually received a transplant even though the median age in that study was relatively low (about 52 a start of renal replacement)(9). A reasonable estimate would be that incidence renal transplantation in the industrialized world is in the range of 1-2 per million; and that 1-3 % of all transplant recipients have AAV, in countries like Sweden where the rate of transplantation is around 50 per million.

Graft function and patient survival after transplantation

There are several publications reporting on graft and patient survival in AAV(3, 5-12). A general theme in these reports is that AAV patients exhibit survival rates similar to other non-diabetic transplant patients(7). Patient survival rates are as high as 86-93 % five years after transplantation, tending to be better in more recent reports(6). Another consistent finding is that disease phenotype and serotype does not seem to influence survival after transplantation. In a similar manner graft outcomes seem to match the results from transplantation in other renal diseases, without obvious differences between granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). In a large registry study 10-year graft survival for GPA patients was 80 %(7), and more recently graft survival censored for death was reported to be as high as 97.9 % after five years in a large multicenter study(6).

Timing of transplantation

An exacerbation of vasculitis, the induction therapy given to curb it, the transplantation operation as well as the anti-rejection therapy all inflict stress on the immune system increasing the risk for opportunistic infections. It seems logical to postpone transplantation until the patient is in remission and the immune system has recovered from the induction therapy. This also seems to be the common practice in Europe, according to a survey presented by Little et al(10). In the study evidence was also found that patients transplanted <12 months after diagnosis of AAV had increased mortality and tended to exhibit vasculopathy on transplant biopsies. Other studies have failed to see any relationship between time since last flare or after onset of dialysis therapy and adverse outcome. Actually even some patients transplanted with ongoing disease activity have been reported to do well(11).

Relapse after transplantation

AAV is a relapsing disease. About 50% of patients experience a relapse within 5 years of diagnosis, and the risk is a major concern with respect to transplantation(21). A renal relapse can rapidly

destroy a graft and confront the patient with substantial risks for additional morbidity(22). These hazards, however, should not be exaggerated and must be balanced with the situation if no transplantation is performed. It is important to keep in mind that extra-renal relapses occur also during dialysis and that most renal relapses respond to therapy. Schmitt et al. compared the risk for relapse before and after transplantation in a cohort of 20 GPA patients and found the overall relapse rate to be higher during dialysis (0.3 per year versus 0.1 per year) as compared to after transplantation(11). A more recent study, focusing on MPA patients, also found more relapses during dialysis than after transplantation(23). Several attempts have been made to quantify the risk of relapse of AAV after transplantation. In a pooled analysis published in 1999 we found that 17 % of the patients experienced a relapse, the mean follow-up in these cases was 31 months, which roughly can be transformed to a rate of 0.07 per year(4). Two recent large multicenter reports found substantially lower relapse rate, 0.02 and 0.01 respectively(6, 10). Geetha et al suggest this to be due to a better effect of modern anti-rejection therapy to prevent relapses(6). Another possibility would be that patients today tend to receive better induction therapy for their AAV before transplantation. In earlier published cohorts some relapsing patients had not received any induction therapy(12) and as mentioned above there are also reports of patients having received a transplant during ongoing granulomatous inflammation(11).

The role of ANCA testing

Despite its limitations ANCA is a commonly used biomarker for disease activity in AAV(24). It has been shown that persistent ANCA-positivity during remission is a risk factor for relapse(25). Consequently it would not be surprising if ANCA-positivity at the time of transplantation would be a risk factor for later relapses. This is, however, not a uniform finding in published reports. In a pooled analysis we did not find any statistically significant relationship between ANCA-positivity at transplantation and subsequent relapses(4). Elmedhem et al reported on eight patients, 4 being positive and 4 negative at transplantation, two relapses were recorded both in patients being ANCA-

negative at transplantation(3). On the other hand Geetha et al. found ANCA at time of transplantation to be a risk factor for relapse(6). In many patients with flares, a rise in ANCA is a late event, so if ANCA is less helpful for prediction it can still help to distinguish relapses from other causes of renal impairment. Patients who are ANCA-positive at time of diagnosis will in most cases also be positive at time of relapse and ANCA levels will be increased compared to remission, at least when analyzed with sensitive assays such as capture PR3-ANCA ELISA(26). The ability of ANCA-tests to confirm a flare does not seem to be blunted after transplantation, positive tests at time of relapse was noted in 3/3(8), 5/5(23), 2/2(9) and 7/7(6) cases. Such a use of ANCA testing naturally requires ANCA to be tested on a regular basis during remission, in order to facilitate interpretation of test results at time of a suspected flare.

Treatment of relapses

The total number of AAV exacerbations after transplantation described in the literature is still low, and no prospective trials have been reported. Treatments recorded in case series include most therapies used for AAV patients who have not been transplanted, such as corticosteroids alone, increased basal immunosuppression, cyclophosphamide, rituximab and various combinations of these agents(3, 4, 6, 9, 12, 22, 23, 27). Recurrent disease in the grafts seems to respond well to cyclophosphamide in most reported cases. However, in the RAVE trial(28), rituximab exhibited superior ability to induce complete remission in relapsing patients as compared to cyclophosphamide. As disease activity after transplantation always is relapse, rituximab is from a theoretical standpoint an attractive alternative. Furthermore renal transplant recipients already have a substantially increased risk of malignancies making avoidance of cyclophosphamide prudent(29).

Concluding remarks

Renal transplantation is and should be the treatment of choice for end-stage renal disease also for patients with AAV. Transplanted AAV patients exhibit a survival equal or superior to patients with

other renal diseases, and very few grafts are lost due to recurrence of vasculitis. There is, however, a constant threat of relapse and today there are no reliable clinical or biochemical predictors, but the rate of relapse seems to be lower after transplantation as compared to dialysis treatment. Changes in ANCA levels can most probably help to distinguish relapses from other causes of graft dysfunction. Relapses should be treated with increases in immunosuppressive therapy, but the best way to tailor therapy remains unknown.

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