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Renal replacement therapy in lupus nephritis

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Keywords: haemodialysis; lupus nephritis; peritoneal dialysis; renal transplantation

Introduction

Recently, the therapeutic options for the treatment of lupus nephritis (LN) have increased by the promising results of treatment with mycophenolate mofetil (MMF), anti-CD20 and other biological medications. However, whether these treatments will reduce the ultimate development of end-stage renal failure (ESRF) is not known yet. Although compared to prednisone monotherapy, treatment with prednisone and cyclophosphamide or azathioprine reduces the cumulative incidence of ESRF in LN; still 20% of the patients develop ESRF [1]. In this editorial, we will review the results of the various forms of renal replacement therapy [i.e. haemodialysis, peritoneal dialysis and (pre-emptive) renal transplantation] in patients with ESRF due to LN.

Haemodialysis

Initially, there was reluctance to dialyse lupus patients with ESRF because of the systemic nature of the disease and the (previous) use of immunosuppressives. In 1973, Coplon and colleagues documented that haemodialysis and renal transplantation in lupus patients had a favourable short-term prognosis, which was confirmed in an extended report after 12 years of experience [2].

Thereafter, numerous reports of single-centre experience confirmed that in general, survival of lupus patients on haemodialysis was comparable or even better than that in non-lupus patients. In an extensive review of the literature, Mojic and Klippel [3] found that survival of lupus patients on dialysis of 80–90% at 5 years was comparable to that in non-SLE dialysis patients and better than that in other systemic autoimmune diseases. However, lupus patients on dialysis were younger and predominantly females, both factors which have a favourable impact on survival. In general, clinical and serological disease activity decreased during dialysis, notwithstanding the fact that the degree of immunosuppression could be lessened. An analysis that we performed in 55 lupus patients undergoing dialysis treatment illustrates this [4]. In only 8% of patients, disease activity increased, and in >50% disease activity decreased or disappeared \( (P < 0.001) \). The percentage of patients using high dose of prednisone decreased from 69% to 15% and the use of cytotoxic drugs from 72% to 7%. Although disease activity in general tends to quench, there are some reports on ongoing extrarenal disease activity in the first year after the initiation of haemodialysis [5,6], especially in black patients [7]. Patients who developed ESRF within a short time period due to a rapidly progressive LN behave differently. In 10–20% of these patients, renal function may (partly) recover within a 4-month period [2], which allows cessation of haemodialysis. These patients very often also show persistence of considerable disease activity during initial dialysis treatment, necessitating the continuation of immunosuppressive treatment. Early mortality of lupus patients on haemodialysis is frequently the result of infection rather than of active lupus [3].

A potential problem in lupus patients on haemodialysis is the presence of anti-phospholipid antibodies (aPL) or even of the anti-phospholipid syndrome (APS). There are no prospective studies available on whether vascular access thrombosis/stenosis occurs more frequently in lupus patients on haemodialysis. Some reports suggest that SLE patients have an increased risk [8,9]. This was recently confirmed in a retrospective case-control study in 36 lupus and control patients on haemodialysis [10]. After 1 year, 66.6% of the lupus patients had developed vascular access thrombosis compared to 38.9% in the control group [odds ratio: 3.1 (95% CI: 1.2–8.2)]. Unfortunately, the presence of aPL was not assessed. Other symptoms of APS like myocardial infarction or cerebral stroke were not more frequent in lupus patients on dialysis; however, again the association with aPL or APS was not evaluated [11].

Peritoneal dialysis

Data on CAPD treatment in lupus patients are more scarce. Early experience suggested that lupus disease activity was more prominent during CAPD than during HD, while data...
on survival were lacking [12]. We conducted a retrospective analysis on dialysis treatment in 55 patients with ESRF secondary to LN [4]. In this study, 23 patients on CAPD and 32 patients on HD were included with a median duration of dialysis of 36 months. Survival at 5 years on CAPD and HD was not significantly different (80% and 92%, respectively). Data on disease activity, as measured with the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), time-adjusted event rates and use of immunosuppressive drugs, were not different between CAPD and HD treatment. In both treatment groups, disease activity diminished similarly. The number of patients with high non-renal SLEDAI (> 10 points) decreased from 31% to 14%, the number of complete remissions (non-renal SLEDAI 0) increased from 4% to 35% and intermittent disease activity (SLEDAI 1–10) was present in 51% during dialysis. The event rates for the different disease manifestations were not different between CAPD- and HD-treated patients, except for thrombocytopenia and elevated anti-dsDNA antibodies, which occurred significantly more frequently during CAPD. As stated before, this decrease in disease activity occurred, while immunosuppressive treatment was tapered off considerably. A more recent retrospective chart review does show a significant difference in disease activity between HD and CAPD. The follow-up maximal SLEDAI score increased during peritoneal dialysis, but the long-term prognosis was not significantly different between these two treatment modalities [13]. Two recent publications addressed the incidence of peritonitis, other infections and outcome in lupus patients on CAPD in comparison with matched non-lupus controls [14,15]. The results are summarized in Table 1. In both studies, controls were matched for age and gender and recruited in the same period, and diabetes patients were excluded from the control group. In the study of Siu et al. [15], the control patients had biopsy-proven non-lupus glomerulonephritis. Risk factors for infectious complications were a significant lower albumin level at start of PD and the high proportion of patients still on immunosuppressives. In both studies, significant higher incidences of peritonitis and other infections were observed in lupus patients. Exit site infections were higher in the study of Huang et al. [14]. Also, overall mortality was higher in the SLE group (32%) than in the control group (9%). Finally, in one study [14], one-third of the lupus patients had to discontinue CAPD. The impact of immunosuppression on the high incidence of peritonitis and other infections in CAPD patients is further documented by a study from Guy's Hospital [16]. They analysed peritonitis incidence in a cohort of patients treated with CAPD within a 1-year time period, using (n = 39) or not using (n = 146) immunosuppressives. Immunosuppressives were prescribed for various conditions; the most prevalent reasons were glomerulonephritis, SLE and vasculitis. The peritonitis frequency in the immunosuppressed patients was 1.8 episodes/patient-year and in those without immunosuppression 0.68 (P < 0.001). This was associated with a higher hospital admission rate (64% versus 22%; P < 0.001) and a greater necessity of PD-catheter removal (28.2% versus 9.6%; P < 0.01). Although statistically not significant, there was a trend that severity of immunosuppression was associated with the number of CAPD peritonitis episodes. This study reveals that immunosuppression is an important risk factor for CAPD peritonitis, irrespective of the disease for which immunosuppression is given. Apart from the short-term effects, CAPD peritonitis may have additional serious side effects in lupus patients. It can induce exacerbations of the disease and it may contribute, especially in lupus patients, to the development of encapsulating peritoneal sclerosis [17]. So these data suggest that CAPD may not be the first choice of renal replacement therapy in lupus patients, who are still on immunosuppressive therapy. However, one should realize that also on haemodialysis infection is a leading cause of mortality [3]. Prospective data are clearly needed comparing infection rates in lupus patients on PD or HD.

### Renal transplantation

**Pre-transplant screening**

Since lupus patients have an increased incidence of cardiovascular disease and mortality [18], they must be screened...
for the presence of coronary artery disease with either dipyridamol thallium scintigraphy or dobutamin stress echocardiography. If abnormal, a coronary angiography should be performed and if necessary a coronary revascularization. In addition, a careful clinical and serological assessment needs to be done to determine lupus disease activity. If the disease is active, the transplantation should be postponed until disease quiescence is obtained. Especially patients who develop ESRF within a short time period (<12 months) are at high risk for post-transplant complications. The presence of aPL or the APS should be evaluated, as the risk for the development of thrombotic micro-angiopathy in the renal allograft and for transplant vessel thrombosis is increased. Stone et al. followed a group of 85 transplanted SLE patients. Fifteen of the 25 patients with aPL suffered from a clinical event associated with APS, while only 5 of the patients without aPL had such an event ($P < 0.0001$) [19]. Whether aPL positive patients should be treated periand postoperatively with anti-coagulants is not known yet. Moreover, anticoagulation perioperatively can lead to serious bleeding complications. In our unit, we treat all renal transplant recipients with prophylactic doses of low-molecular-weight heparin during the first week after transplantation. Lupus patients have a high prevalence (30–90%) of anti-lymphocyte antibodies [20]. This may cause positive cross-matches. Therefore, during the pre-transplant work-up cross-matches should be performed with autologous lymphocytes. These results can be taken into account when cross-matching with donor lymphocytes is performed. Most lupus patients are extensively treated with corticosteroids for their disease. Therefore, bone mineral density should be assessed before transplantation to guide post-transplant prophylaxis for osteoporosis with additional calcium, vitamin D and eventually bisphosphonates. Obviously, also standard assessments should be carried out according to the US or EDTA guidelines for pre-transplant screening. As in every transplant candidate, the possibility of a pre-emptive transplantation should thoroughly be investigated, because of its superior results, which will be detailed below.

**Cadaveric renal transplantation**

The report of Coplon et al. in 1983 [2] indicated that the results of renal transplantation in lupus patients were comparable to results in other patient groups. An analysis performed by Nossent et al. on behalf of the Dutch Working Party on SLE showed that patient survival after renal transplantation at 1 year and another for 5 years was 86.5% and graft survival was 67.6% and 54.1%, respectively [21]. However, in this study no comparison was made with results in other patient groups. These data were confirmed by the analysis of Mojcik and Klippel of 24 studies reported until then in the literature [3]. They calculated an overall patient survival of 86% and a graft survival after cadaveric renal transplantation of 56%. Data from the Eurotransplant Registry [1] for first cadaveric renal transplants in the period 1984–1992 in 165 lupus patients compared to 21 726 non-lupus patients showed similar graft survival at 1 year (80% versus 82%) and 3 years (66% and 70%). Also, patient survival was similar at 1 year (95% versus 93%) and at 3 years (92% versus 90%). However, the analysed studies differed considerably with regard to number of patients, duration of follow-up, ethnic composition, type of immunosuppression and period of transplantation. The single-centre study of Stone et al. [22] corrected for these confounding factors by using a control group of patients that was transplanted in the same period, treated with either cyclosporine A or tacrolimus and matched for age, sex, race, type of allograft, number of previous transplants and year of transplantation. In this analysis the outcome for lupus patients was less favourable. The allograft survival for lupus patients versus controls was at 1 year: 81.7% versus 88.2%; at 2 years 74.7% versus 84.4%; at 5 years 45.9% versus 75% and at 10 years 18.5% versus 34.8%. The relative hazard ratio of allograft loss in lupus patients was 2.1 (95% CI: 1.06–4.06; $P < 0.04$). The reasons for this increased allograft loss in lupus patients was recurrence of LN leading to graft loss (3.8%) and thrombosis or thrombotic microangiopathy attributed to aPL (15.4%) [23]. These less favourable results were not confirmed in an analysis using data from the United States Renal Data System (USRDS). Ward [11] reported that the hazard ratio adjusted for confounding factors for graft loss in 772 lupus patients undergoing first cadaveric renal transplantation was 1.08 (95% CI: 0.94–1.23; $P = 0.28$) compared to 32 644 control patients. Also, mortality did not differ between the groups. An analysis of the United Network of Organ Sharing (UNOS) database [24] also did not show a difference in patient and graft survival between SLE patients and non-lupus patients after transplantation with kidneys from either living (SLE: 789; non-lupus: 21 228) or cadaveric donors (SLE 1170; non-lupus: 42 651). However, a recent large follow-up study using data from both the USRDS and UNOS registry compared 2886 SLE recipients with 89 958 non-SLE recipients [25]. Lupus patients showed a worse transplant (HR 1.09, 95% CI: 1.02–1.15, $P < 0.05$) and patient survival (HR 1.18, $P < 0.05$) compared to diabetes patients if corrected for many confounding factors. There were no significant differences when kidneys from living donors were transplanted. These aggregated data, mainly from the USRDS [11] and UNOS [24], indicate that graft survival and patient survival in lupus patients are more or less comparable to other patient groups although this is not confirmed in all reports [25]. Less discrepancy is seen with regard to the results of transplantation with kidneys from living donors showing no differences between SLE and control patients [24,25].

**Living donor transplantation**

Initial single centre reports indicated, as for transplantation in other diseases, that results in lupus patients for living donor transplantation (LDTx) were superior to cadaveric donor transplantation (CADTx). Experience at the University of Wisconsin showed 5-year graft survival of LDTx of 89% versus 41% in CADTx ($P = 0.003$) [26]. These favourable results were confirmed in the USRDS analysis [11]. In 390 lupus patients undergoing LDTx, 5-year graft and patient survival were 77 and 94.4%, respectively, compared to 58.1% and 83.3% in 772 lupus patients receiving
Recurrence of LN after renal transplantation

The general observation is that recurrence of LN in the renal allograft is low with frequencies ranging from <1% to 3.8% [3]. However, some studies report a higher incidence [30,31]. In some of these studies, rather aspecific findings like mesangial proliferation were scored as recurrence. A careful review of 106 transplant biopsies in 97 lupus patients revealed histological recurrence in nine cases (8.4%) [32]. This recurrence contributed to graft loss in four of the nine cases (3.8%). So even with a meticulous analysis of transplant biopsies, the recurrence rate is rather low compared to other glomerular diseases. Since it has been reported that recurrent lupus nephritis responded well to MMF, further studies are needed to see whether maintenance treatment with MMF will decrease the recurrence rate further.

Lupus disease activity after renal transplantation

In most studies, lupus disease activity declines further after renal transplantation. The overall incidence of extrarenal flares after transplantation in a number of studies was 5.7% as calculated by Mojcik and Klippel [3]. The study by Nossent et al. [21] revealed that the maximal non-renal SLEDAI decreased after transplantation compared to during dialysis and before dialysis. None of the patients after transplantation had SLEDAI values >10%, and 71% had SLEDAI values of 0. So it appears that either due to the natural course of the disease and/or because of the continuous use of immunosuppressives, lupus disease becomes quiescent after renal transplantation.

Summary

Treatment of lupus patients with haemodialysis has comparable results as in non-lupus patients. In contrast, during CAPD treatment peritonitis, other infectious complications and technique failure are more frequent in lupus patients, with an increased overall mortality. Therefore, haemodialysis is preferred over CAPD, especially if the patient is still using immunosuppressives. During both dialysis modalities in general, disease activity decreases, which enables tapering off immunosuppression. During pre-transplant screening, special attention should be given to cardiovascular disease manifestations, lupus disease activity, the presence of anti-phospholipid antibodies and anti-lymphocyte antibodies and bone mineral density. Lupus patients are good candidates for renal transplantation. If possible, lupus patients should be transplanted pre-emptively with a kidney from a living donor since this approach leads to the best results. We prefer maintenance immunosuppression after 6–12 months without calcineurin blockers because they bear a higher risk of graft loss. Therefore, immunosuppressive treatment in the induction phase of ~6–12 months, aimed at prevention of acute rejection episodes, should comprise calcineurin blockers. However, the goals during the maintenance phase are different and aim at preservation of renal function, avoidance of nephrotoxicity, reduction of risk factors for atherosclerosis and suppression of lupus disease activity. Since lupus patients have accelerated atherosclerosis [18], special attention should be given to the impact of immunosuppressives on cardiovascular risk factors. These are semi-quantitatively listed in Table 2. From this table it becomes clear that during maintenance immunosuppression other drugs (i.e. MMF or azathioprine) should be used preferentially. Especially MMF is a good candidate because it could have anti-atherogenic properties [29] and shows a lower risk of graft loss (5-year graft loss 29.6% for lupus recipients of a cadaveric donor graft who were on MMF versus 40.2% for patients not on MMF) [24]. Recent studies have also indicated that MMF could have good efficacy in treating LN although long-term studies are needed to draw definite conclusions. If MMF usage leads to side effects, azathioprine forms a reasonable alternative. A drawback of both drugs is that they have to be combined with low doses of prednisone with its inherent side effects, especially in lupus patients who already received corticosteroids in their pre-transplant period. Therefore, Ponticelli has advocated a prednisone-free regimen by using cyclosporine monotherapy [28]. The ultimate choice of the maintenance immunosuppressive regimen in the individual lupus patient after renal transplantation should be guided by the individual characteristics of the patient, but the preference of the authors is a combination of MMF and a low dose of prednisone.

Immunosuppressive therapy after renal transplantation

There are no prospective studies in lupus patients comparing the effects of the various immunosuppressive drugs. In general, it can be stated that the results of using calcineurin blockers are superior. This is also observed in lupus patients because 1-year graft survival in the cyclosporine era was 89% compared to 68% in the pre-cyclosporine era [26]. Therefore, immunosuppressive treatment in the induction phase of ~6–12 months, aimed at prevention of acute rejection episodes, should comprise calcineurin blockers. However, the goals during the maintenance phase are different and aim at preservation of renal function, avoidance of nephrotoxicity, reduction of risk factors for atherosclerosis and suppression of lupus disease activity. Since lupus patients have accelerated atherosclerosis [18], special attention should be given to the impact of immunosuppressives on cardiovascular risk factors. These are semi-quantitatively listed in Table 2. From this table it becomes clear that during maintenance immunosuppression other drugs (i.e. MMF or azathioprine) should be used preferentially. Especially MMF is a good candidate because it could have anti-atherogenic properties [29] and shows a lower risk of graft loss (5-year graft loss 29.6% for lupus recipients of a cadaveric donor graft who were on MMF versus 40.2% for patients not on MMF) [24]. Recent studies have also indicated that MMF could have good efficacy in treating LN although long-term studies are needed to draw definite conclusions. If MMF usage leads to side effects, azathioprine forms a reasonable alternative. A drawback of both drugs is that they have to be combined with low doses of prednisone with its inherent side effects, especially in lupus patients who already received corticosteroids in their pre-transplant period. Therefore, Ponticelli has advocated a prednisone-free regimen by using cyclosporine monotherapy [28]. The ultimate choice of the maintenance immunosuppressive regimen in the individual lupus patient after renal transplantation should be guided by the individual characteristics of the patient, but the preference of the authors is a combination of MMF and a low dose of prednisone.

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### Table 2. Cardiovascular risk factors of immunosuppressive drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Hypertension</th>
<th>Hyperlipidaemia</th>
<th>Hyperglycaemia</th>
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<tbody>
<tr>
<td>Tacrolimus</td>
<td>+</td>
<td>±</td>
<td>+++</td>
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<tr>
<td>Cyclosporine</td>
<td>++</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Mycophenolic acid</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Azathioprine</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>mTOR antagonists</td>
<td>–</td>
<td>+++</td>
<td>/±</td>
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<tr>
<td>Prednisone</td>
<td>/++</td>
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</tr>
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CADTx. Similar results were obtained in additional analyses [24,25]. Therefore, LDTx is the preferred treatment for SLE patients with ESRF. If a living donor is available, the possibility of a pre-emptive transplantation should be considered, since the results of such an approach are superior in terms of graft and patient survival, irrespective of the cause of the original kidney disease [27]. This will prevent dialysis-associated morbidity, mortality, costs and loss of quality of life. Pre-emptive transplantation should not be pursued in those patients with ongoing disease activity or severe iatrogenic morbidity. A waiting period before transplantation to obtain decreased disease activity and to improve clinical condition might then be a better solution [28].
cardiovascular risk than for instance MMF. After renal transplantation lupus disease activity further declines. The rate of recurrence of lupus nephritis in the renal allograft is low (<4%).

Conflict of interest statement. None declared.

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