OUTCOME OF KIDNEY TRANSPLANTATION IN PATIENTS WITH LUPUS NEPHRITIS – A SINGLE CENTER EXPERIENCE AND REVIEW OF THE LITERATURE

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Aims: Kidney transplantation (KT) is the treatment of choice for end-stage kidney disease in patients with systemic lupus erythematosus (SLE). Still, these patients tend to fare worse than other patient groups with chronic kidney failure. The main aim of this retrospective observational study was to evaluate the outcomes of KT in patients with SLE. Methods: Data were obtained from medical records and charts. Results: From February 2007, a total of 12 SLE patients, average age 37 (18-56) years, underwent deceased donor KT at our Center. Comorbidities were primarily cardiovascular. At the time of KT, 91.7% of patients showed no signs of SLE activity. Immunological matching was favorable and all allografts showed satisfactory initial function. Median graft survival for the whole patient population was 41 (0-93) months. In 66.7% of patients with stable graft function, median survival was 61 (22-93) months, in three patients longer than five years. One patient died 4 months after the transplantation from neurologic complications, whereas 25% of allografts were lost in the early post-transplant period, in 0-5 months after KT. Our patient outcomes showed no clear correlation between age, previous KT or number of comorbidities. Episodes of acute rejection or recurrent lupus nephritis brought a higher risk of poor outcome. Conclusion: While there still are many unanswered questions relating to the management of this immunologically very sensitive group of patients, forming a multidisciplinary transplantation team would enable pre-transplant evaluation of SLE patients with possible risk assessment and adjustment of follow up strategy to achieve an optimal survival outcome.

Key words: lupus nephritis, renal replacement therapy, kidney transplantation, outcome

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic inflammatory disorder of connective tissue characterized by the presence of autoreactive B- and T-lymphocytes responsible for the production of a heterogeneous spectrum of autoantibodies (1). Lupus nephritis (LN) is a serious complication, which affects up to 60% of adults with SLE, contributing as a significant cause of morbidity and mortality (2). Despite better understanding of the pathophysiological process and new, more aggressive treatment protocols, the incidence of end-stage kidney disease (ESKD) has increased significantly between 1982 and 2004 from 1.16 cases per million person-years in 1982 to 3.08 and 4.9 cases per million person-years in 1995 and 2004 (3). Thus, choosing the optimal modality of renal replacement therapy (RRT) is of great importance (4,5). Although the 5- and 10-year survival rates were similar in patients treated with hemodialysis (HD) and peritoneal dialysis (PD), kidney transplantation (KT) was shown to be highly superior (6). When compared to dialysis,
KT achieves better survival rate and better quality of life, at the same time reducing the SLE activity (7-9). Over the course of time, since transplantation started in the 1950s until the 1990s, the 5-year survival rate in LN patients after transplant increased from less than 50% to more than 93% (10). Although clinical outcome after KT in patients with LN has lately been shown to be comparable to other causes of ESKD (for example, diabetes mellitus and arterial hypertension), a controversy still exists. Infection, recurrent disease, acute and chronic rejection and thrombosis are some of the risks factors leading to graft failure in SLE patients (11). Furthermore, SLE patients have a higher rate of cardiovascular disease, which is a common cause of death after transplant (2,12). The aim of this study was to evaluate the outcomes of KT in patients with SLE and discuss future management options for improved survival in this patient category.

PATIENTS AND METHODS

A total of 12 patients having undergone KT during the period from February 2007 until October 2013 were included in this retrospective observational study. We investigated disease duration, type of RRT and dialysis vintage, comorbidities, induction and maintenance therapies, and blood values for signs of SLE activity or decreased graft function.

RESULTS

Patient characteristics

There were eight female (66.7%) and four male (33.3%) patients, median age 37 (18-56) years. The average duration of RRT before transplant was 7 (1-18) years. One patient had been previously transplanted. His first graft was lost due to LN recurrence in 1991, two years after transplantation. Comorbidities were primarily cardiovascular.

All patients received kidney from deceased donors. Eleven (91.7%) patients showed no clinical or serologic signs of SLE activity at the time of transplantation; total complement activity (CH50), as well as the levels of complement proteins C3 and C4 were normal, anti-dsDNA and antinuclear antibodies (ANA) were not detected by indirect immunofluorescence technique prior to transplantation. Antiphospholipid (APS) antibodies were also negative. Immunological matching was favorable. Maintenance immunosuppressive therapy included calcineurin inhibitor, mycophenolic acid and steroids. Patient data are summarized in Table 1.

Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, range), years</td>
<td>37 (range, 18-56)</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>33.3</td>
</tr>
<tr>
<td>Dialysis modality (n)</td>
<td>10</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>2</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td></td>
</tr>
<tr>
<td>Dialysis vintage (median, range), years</td>
<td>7 (range, 1-18)</td>
</tr>
<tr>
<td>Comorbidities (n)</td>
<td></td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>10</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>2</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1</td>
</tr>
<tr>
<td>Valvular insufficiency</td>
<td>1</td>
</tr>
<tr>
<td>HCV infection</td>
<td>2</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>1</td>
</tr>
<tr>
<td>Avascular necrosis of the femoral head</td>
<td>1</td>
</tr>
<tr>
<td>Number of HLA mismatches</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Immunosuppression protocol (n)</td>
<td></td>
</tr>
<tr>
<td>CSA + MPA + steroid</td>
<td>4</td>
</tr>
<tr>
<td>TAC + MPA + steroid</td>
<td>8</td>
</tr>
</tbody>
</table>

HCV – hepatitis C virus; CSA – cyclosporine A; TAC – tacrolimus; MPA – mycophenolic acid

Patient survival

One patient died 4 months after the transplantation from neurological complications. She had no clinical signs of SLE at the time of transplantation, however, elevated anti-dsDNA antibodies, ANA, PRA (80%) and low platelet count were recorded before transplantation. After consulting the immunologist who followed-up the patient, she underwent transplantation. Induction therapy included Thymoglobulin. Graft function was immediate, but the patient developed severe acute humoral rejection on day 13 post-transplant. After intensifying immunosuppressive therapy with 5 boluses of corticosteroids combined with 4 plasma-exchanges (one plasma volume, albumins as replacement fluid) on alternate days, her laboratory values stabilized and she was discharged from the hospital. Four months later, she went into a coma after a short period of febrility and died shortly thereafter. Her family refused autopsy.

Graft survival

Out of 12 patients, 11 (91.7%) are still alive, eight (66.7%) with stable graft function. Median graft survival for the whole patient population was 41 (0-93) months. In those with stable graft function, median survival was 61 (22-93) months, in three patients longer than five years. The causes of graft loss included death with a functioning graft, pseudoaneurysm of the
renal graft artery, thrombosis of the renal graft vein, and severe biopsy confirmed acute allograft rejection accompanied with sepsis. All patients with allograft loss had 2 or more comorbidities, one being hypertension. The others were atherosclerotic necrosis of the femoral head and triple (aortic, mitral and tricuspid) valve insufficiency in the patient with acute rejection, epilepsy in the patient with venous thrombosis, and atrial fibrillation in the patient with the graft artery pseudoaneurysm. Disease duration, defined as the time from diagnosis until the year of transplant, was shorter in the group who lost their allograft, i.e. mean 11.7 years compared with 12.7 years in those with stable graft function (n=8) (not significant). Two (16.7%) patients experienced thrombotic events, one of the graft artery, which led to explantation, and the other of the deep veins of the leg and this patient has a functioning graft today. Serological screening for APS antibodies prior to transplantation was negative in both patients. There was no correlation between immunological matching and transplant outcome.

Post-transplant complications

Early post-transplant period was complicated with secondary wound healing in two patients, lymphorrhea in one patient, and development of lymphocele followed by obstructive uropathy and hydronephrosis of the graft in one patient. Major complications that arose after transplantation were cardiovascular and included atrial fibrillation in one patient, valvular insufficiency, graft artery pseudoaneurysm, graft vein thrombosis and deep vein thrombosis. Also, one patient developed new-onset diabetes after transplantation (NODAT). One patient developed urinary bladder carcinoma and was switched from cyclosporine to sirolimus. One year later, the graft function deteriorated requiring graft biopsy. Biopsy was complicated with perirenal hematoma measuring 15x8 cm. The histopathologic finding indicated LN recurrence in the allograft although she had been serologically negative for 15 years.

One patient developed cytomegalovirus infection, which was successfully treated with valgancyclovir. Hematologic complications included two cases of leukopenia that demanded use of filgrastim, and erythrocytosis in one patient. Acute rejection was recorded in two patients. One had already described acute humoral rejection, and the other patient experienced two episodes of acute cellular allograft rejection successfully treated with steroid boluses. Two patients had problems with tendons. One developed rupture of the Achilles tendon, and the other had severe tendinitis after the use of ciprofloxacin, which was immediately stopped. It is interesting to mention our female patient who underwent a dual kidney transplant from a pediatric donor in 2002, although she was not included in the study. She was diagnosed with SLE in 1997 after a biopsy taken during an episode of preeclampsia. After transplantation, the graft function was immediate although ultrasound showed mild dilatation of the ureter and pyelon on one side. That kidney was explanted in 2009 due to recurrent urinary tract infections. Histopathologic evaluation showed signs of necrosis of ureter epithelium, urinary leak and hydronephrosis. The other kidney is functioning well and her lab values are satisfactory. She has had no other manifestation of SLE since the biopsy in 1997.

DISCUSSION

Systemic lupus erythematosus is a chronic multisystem disorder affecting many organs, with renal involvement being the most important predictor of mortality (2). As this specific population of patients tends to develop ESKD at a much younger age, choosing the individual RRT protocol is a priority, with KT being the ultimate goal (4,5,13). The majority of studies that compared different renal replacement modalities demonstrated that KT offered better outcomes and lower complication rates in comparison with other treatment modalities (6,14-16). Although living related KT (LRKT) was shown to give better results than grafts from deceased donors, other studies revealed that grafts from deceased donors had similar outcomes to LRKT (17-19). Preemptive KT has also been pointed out as a treatment option with superior survival outcomes. It offered lower risk of death and rejection with a significantly greater chance of getting an allograft from a living donor (20). However, when discussing preemptive KT we should clearly state that not all SLE patients are eligible for this kind of approach. Current recommendations state that patients who progress to ESKD as a result of LN worsening or newly diagnosed SLE patients with rapidly progressive renal disease should start HD treatment for 3 to 6 months prior to proceeding to KT. The rationale behind this is to achieve overall remission of SLE activity before KT, as HD is believed to have a ‘burn-out' effect on the disease. Furthermore, it seems that some patients with aggressive forms of rapid progressive glomerulonephritis recover their renal function after starting HD (3,21). Even though all our recipients received kidneys from deceased donors, 66.7% have completely satisfying graft function with median graft survival of 41 (0-93) months for the whole patient population. It has been shown that greater Charlson comorbidity index and immunizing events prior to KT (higher panel reactive antibody (PRA) levels, previous transplantations, multiple blood transfusions and pre-transplant pregnancy) have been associated with worse outcomes (19).
High PRA levels were associated with increased loss of allograft, but had no effect on mortality (14). According to some studies, the level of anti-dsDNA antibodies are not a reliable serological parameter for disease activity in transplanted patients or a good predictor of outcome. However, low complement levels has been shown to correlate with a higher risk of allograft loss (15,16,22,23). In a study dividing SLE patients into low complement and normal complement groups, the graft survival was 78.6% in the normal complement group and 30% in the low complement group after 96 months of follow up. The authors found a connection between low complement, proteinuria and poorer allograft survival. The majority of these patients had chronic allograft nephropathy with a glomerular component on biopsy compared to the normal complement group who had normal biopsy findings. They also found that low complement was more common in the group with SLE who had WHO class IV diagnosed before transplant. Complement levels before transplantation had no impact on allograft or patient survival (24). Our patient with lethal outcome had high anti-dsDNA and PRA before transplantation. Even though a high PRA is not considered a prognostic factor for lethal outcome, we can speculate whether high level of antibodies induced immune response while she received intensive immunosuppressive protocol with Thymoglobulin induction, plasma exchange before transplantation, and maintenance treatment with tacrolimus, mycophenolate mofetil and steroids. The presence of antiphospholipid antibodies has been associated with an increased incidence of graft vessel thrombosis and other thrombotic events in recipients. A study comparing SLE patients with a control group demonstrated thrombotic events in 17.4% and 5%, respectively. However, it seems that not all antibodies have the same predictive prognostic value. One study showed that β2 GPI antibodies, antiphosphatidyl serine/prothrombin antibodies and lupus antigen strongly correlated with the increased risk of thrombosis, whereas anticardiolipin had a weaker association. In addition to thrombosis, bleeding was an increased problem, as well as antiphospholipid syndrome (APS) recurrence in the grafted kidney. Outcome was compared between 3 groups APS+, APS+/− and APS− with a fatal outcome in 33%, 16% and 3.4%, respectively; 75% of the fatal outcomes in the APS+ group occurred within three months of transplantation. In four patients where efficient anticoagulation was instituted early post-transplant, three still experienced a major thrombotic event (25). Recent studies have confirmed the negative impact of antiphospholipid antibodies on survival, but reveal that the pre-transplant history of antiphospholipid syndrome has an even greater impact (26). Our result of 16.7% (n=2) incidence of a thrombotic event could suggest that some patients had antiphospholipid antibodies, although the screening prior to transplantation showed no signs of serological positivity. Also, a case of post-biopsy extensive bleeding was recorded.

Recurrence of lupus nephritis (RLN) in the transplanted kidney has been investigated as a cause of the increased rate of graft failure in SLE patients. Results have shown that the incidence is 1%-3%, but in studies of protocol biopsies, LN was found in as many as 43% (27). Most of these were WHO class I or II, which is clinically nonsignificant and did not have an impact on graft outcome (28). The possible explanations for conflicting results in this question is that there is no consensus on the definition of disease recurrence, immunoflourescence or electron microscope are not routinely used in diagnosis, and lastly because of the small number of patients that undergo follow up biopsy (29-31). Two of our patients had RLN. One had lost his first graft due to RLN, and the other still has a functioning graft. Our patient outcomes showed no clear correlation between age, previous transplantation or number of comorbidities. Episodes of acute rejection or RLN brought a higher risk of poor outcome.

**CONCLUSION**

Despite advances in the treatment of SLE, the incidence of ESKD in this population is steadily increasing. Most of the studies established KT as a far superior treatment option compared with dialysis, with a higher survival rate and lower rate of complications. Preemptive KT and the use of living kidney donors seem to further improve the outcomes, but only in patients with quiescent SLE activity. Nevertheless, patients with SLE tend to have an increased risk of graft rejection and mortality than other ESKD patients. As this can be explained by their immune status, we propose thorough pre-transplant evaluation of every SLE patient in order to ensure safe approach to KT. We also recommend carefully formed post-transplant follow up strategy. Although the incidence rates of RLN seem to be higher than previously thought, we do not recommend protocol biopsies as RLN mainly is of silent nature and does not require any change in the immunosuppressive regimen. However, new-onset proteinuria, increased serum creatinine, glomerular hematuria and low serum complement levels should immediately raise suspicion of RLN and should be quickly recognized. In patients with APS, it is important to keep close immunological control since anticoagulant therapy is clearly not enough to prevent thrombotic events. While there are still many unanswered questions relating to the management of this immunologically very sensitive group of patients, forming a multidisciplinary transplantation team including rheumatologists and nephrologists would en-
able thorough evaluation of SLE patients with possible risk assessment and adjustment of follow up strategy to achieve an optimal survival outcome.

R E F E R E N C E S


Uvod i ciljevi: Transplantacija bubrega metoda je izbora u liječenju završnog stadija kronične bubrežne bolesti u bolesnika s lupusnim glomerulonefritisom (LN). Ipak, u usporedbi s drugim bolesnicima ova skupina unatoč napretku u liječenju i dalje pokazuje lošiji ishod. Glavni cilj ovog istraživanja bio je usporediti ishode našeg Centra s ishodima drugih studija te raspraviti nove mogućnosti u praćenju i liječenju ove skupine pacijenata.

Ispitnici i metode: Svi istraživani parametri prikupljeni su iz dostupne medicinske dokumentacije.


Ključne riječi: lupusni nefritis, transplantacija, ishod