Recent issues concerning renal transplantation in systemic lupus erythematosus patients

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Introduction

Renal transplantation among patients with end-stage renal disease (ESRD) caused by lupus nephritis has become an accepted alternative for long-term treatment. However, the outcome of renal transplantation in patients with systemic lupus erythematosus (SLE) is still controversial. Infection, recurrent disease, both acute and chronic rejection, and thrombosis may play a role in early graft loss. New findings for graft and patient outcome, immunological markers and immunosuppressive treatment have recently emerged. We discuss these different aspects here, with the exception of the clinical consequences of the presence of anti-endothelial cell antibodies.

Outcome analysis

An initial report that early graft survival in SLE patients was comparable to that of patients with other causes of ESRD has been confirmed by subsequent studies [1,2]. However, several of these studies were conducted in single centres with small numbers of patients. Furthermore, in these studies the control group was often historical. In larger multicentre studies and reports based on registry data, cadaveric graft survival often tended to be lower when ESRD was caused by lupus nephritis than when SLE was not involved. In these studies, the reported incidence of early graft loss in SLE patients varied between 25 and 40% during the first month after transplantation [3]. In a meta-analysis of several series of renal transplant recipients, including 770 patients with SLE, the authors of nine of 20 articles reported an increased risk of early graft loss [4]. In a large multicentre study including 142 patients, the 1-year allograft survival rate after cadaveric transplantation of patients with SLE was 67%, significantly worse than that of patients without SLE [5]. After one year, most studies showed that graft survival in lupus patients was similar to that in control population [2]. These conflicting data may be secondary to differences in donor source, type of immunosuppression, and composition of the control group. It is also important to analyse separately the results for patients who received cadaveric vs living-related transplants. A recent study conducted within the United States Renal Data system, in which comparisons were adjusted for possible confounding factors, showed that graft survival and patient survival after a first renal transplantation were similar for patients with ESRD caused by lupus nephritis and patients with ESRD from other causes [6]. Reported patient survival at 1, 3 and 5 years was 94.4, 89.6 and 83.8% respectively. Graft survival for same time periods was 79.1, 67.0 and 58.1% respectively. In this study, patients with ESRD due to lupus nephritis were younger, more likely to be women, and more likely to be Black or Asian, than patients with other causes of underlying renal disease. The SLE patients had also received more blood transfusions. It is important to take into account these confounding factors, because statistical analysis demonstrated a higher risk of graft loss in an unadjusted model, but no difference in an adjusted model. Thus in our opinion this study demonstrates that lupus nephritis per se is not a greater risk factor for poor outcome after renal transplantation than other causes of ESRD. Unfortunately, reliable data are not available for comparison of the outcome of ESRD patients with lupus nephritis treated by renal transplantation with the outcome of those treated by dialysis.
**Specific risk factors for patients with lupus nephritis**

**Immunological failure**

The increased incidence of immunological failure and its role in graft loss is also controversial. Thus, although Grimbert et al. [1] found no increased risk of such failure in lupus patients, others reported a higher incidence of acute rejection during the first year in SLE patients than in a control population (69 vs 56%; \(P = 0.01\)). The incidence of chronic rejection may also be higher in SLE patients [7]. Immunological failure may be associated with increased panel reactive antibodies in SLE patients, which may be partly due to the presence of non-HLA lymphocytotoxic antibodies. Blood transfusions are also more frequently needed in patients with ESRD caused by lupus nephritis.

**Disease activity and recurrent nephritis**

Usually, disease activity declines after renal transplantation. In a Dutch analysis, most patients (72%) had no disease activity after renal transplantation, as judged by systemic lupus erythematosus disease activity index scores, even though there have been individual reports of patients developing recurrent SLE activity after transplantation [8]. Serological parameters appear to be unreliable markers of both recurrence and outcome after transplantation. A brief period of dialysis treatment before transplantation (i.e. less than 6 months) had no adverse effect on transplantation outcome in most studies.

Recurrence of lupus nephritis in transplanted kidney is unusual, and its reported incidence is 1–3%. However, this incidence may have been underestimated, because of the absence of routine biopsies, and of the similarities between recurrent lesions and other lesions observed during the course of renal transplantation. Nyberg et al. [9] reported a recurrence rate of 43% among 16 SLE patients. The choice of the parameters used by them to define recurrence, namely mesangial proliferation and deposition of IgM and C3, may explain this high incidence because these parameters lack specificity. The clinical consequences of recurrent nephritis may be serious. In one study, it was the cause of graft loss in four of nine patients with recurrent nephritis. The recent report of the complete disappearance of histological lesions in two renal allografts with initial lesions of class IV/V lupus nephritis demonstrated partial effectiveness of the currently used immunosuppressive treatments. Finally, although the same results for both graft survival and lupus recurrence have been reported after cadaveric and living-donor transplantation, even from a monozygotic twin, screening for potential donors must concentrate on the search for sub-clinical or potential SLE cases. The use of new immunosuppressive drugs that may reduce lupus activity may decrease the risk of disease recurrence. We think that transplantation may be performed even if biological disease activity is present. Complete screening on the day of transplantation is important for prospective evaluation after transplantation.

**Thrombotic complications**

Thrombotic complications play an important role in early graft losses in lupus patients, especially when antiphospholipid antibodies (APAs) are present. APAs are directed against the β2-glycoprotein I (β2GPI) rather than the phospholipid itself. They prolong phospholipid-dependent coagulation in vitro, but are associated with thrombosis in vivo. APAs have been reported to be present in 30–44% of patients with SLE. After transplantation, renal-artery or -vein thrombosis has also been reported in lupus patients, and according to one report, renal-artery thrombosis was responsible for 6% of graft losses when APAs were present. The role of APAs was stressed by Radhakrishnan et al. [10]. In SLE patients, these authors reported four thrombotic events in five patients who were APA positive, vs none in five APA-negative patients. However, these events were not associated with graft loss or death. In the absence of a controlled prospective trial, patients with APA and a history of recurrent nephritis have been reported after cadaveric and living-donor transplantation. In a Dutch analysis, most patients (72%) also been reported in lupus patients, and according to one report, renal-artery thrombosis was responsible for 6% of graft losses when APAs were present. Therefore, the presence of antiphospholipid antibodies in SLE patients, which may be partly due to the presence of non-HLA lymphocytotoxic antibodies. Blood transfusions are also more frequently needed in patients with ESRD caused by lupus nephritis.

**Immunosuppressive treatment**

To date, no study has dealt either with the effects of new immunosuppressive drugs on short- and long-term survival, or with the incidence of recurrent nephritis. Among new treatments, mycophenolate mofetil (MMF) and co-stimulation inhibitors are promising. MMF is an inhibitor of purine synthesis. It was found effective in the prevention of progressive nephritis in a murine model of SLE [11]. In humans, both encouraging results and less successful uncontrolled experience have been reported. A controlled trial is urgently needed. The effects of antibodies against the co-stimulatory molecules CD154 and B7 have also been evaluated in animal models of renal transplantation and lupus nephritis, and these antibodies will probably be used in the future.

**Conclusion**

Renal transplantation is a good alternative for treatment of SLE patients with ESRD. However, data permitting comparison of the effects of renal transplantation and dialysis are lacking. Lupus patients carry a higher risk of immunological failure and thrombotic events. Treatment with new powerful immunosuppressive drugs may improve the outcome of these patients. Because many patients have received immunosuppressive drugs before transplantation, special attention must be paid to the choice of anti-infectious strategy. In the long term, neoplastic complications
may also be more frequent in ESRD patients with SLE. Assessment of the thrombotic risk before transplantation is also important. The presence of APAs indicates the need for active anticoagulation.

References


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