Case Report

Sirolimus-based immunosuppression for transplant-associated thrombotic microangiopathy

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Introduction

Thrombotic microangiopathy (TMA) is a well-recognized complication of solid organ transplantation. Both calcineurin inhibitors cyclosporine [1] and tacrolimus [2] have been associated with TMA. Treatment strategies for TMA have included plasmapheresis [1,2], calcineurin inhibitor dose reduction [1,2], calcineurin inhibitor withdrawal [1,2], and conversion from one calcineurin inhibitor to the other [3]. However, calcineurin inhibitor dose reduction or discontinuation increases the risk of acute allograft rejection and recurrent TMA has been described in patients that were converted from cyclosporine to tacrolimus [4,5]. We present two cases of biopsy-proven transplant-associated TMA that were successfully treated by discontinuation of tacrolimus followed by the use of sirolimus, mycophenolate mofetil (MMF) and prednisone for the prevention of allograft rejection.

Case 1

A 42-year-old white male with end-stage renal disease due to type I diabetes mellitus received a cadaveric renal transplant in June 2000. Both donor and recipient were sero-negative for cytomegalovirus. Initial immunosuppression consisted of thymoglobulin 100 mg/day and methylprednisolone. The allograft functioned immediately and on post-operative day 1 the serum creatinine had fallen from 597 to 247 μmol/l and the platelet count was 259 000 mm³. On post-operative day 6, the serum creatinine reached a nadir of 103 μmol/l and tacrolimus was started at a dose of 5 mg p.o. twice a day (BID). On post-operative day 8, the serum creatinine increased to 140 μmol/l, the platelet count was 182 000/mm³, and the tacrolimus level was 5.7 ng/ml. The following day, the serum creatinine increased to 282 μmol/l, the platelet count was 219 000/mm³, and a renal biopsy was performed. The biopsy revealed multiple thrombi in the glomerular capillaries without any interstitial lymphoid infiltrate, tubulitis, or endo-thelitis, confirming the diagnosis of TMA. The tacrolimus was discontinued and the patient continued to receive thymoglobulin and methylprednisolone. Plasmapheresis was initiated and continued for a total of seven treatments. On post-operative day 10, the serum creatinine peaked at 359 μmol/l and then began to decline. During this period, the platelet count fell to a nadir of 93 000/mm³ on post-operative day 13. The platelet count returned to within the reference range 4 days later, where it has remained to the present.

On post-operative day 19, the serum creatinine was 131 μmol/l. Sirolimus was started at a dose of 8 mg/day and the dose was adjusted to maintain levels between 5 and 15 ng/ml. MMF was also started at 2000 mg/day. The patient has had no complications with this immunosuppressive regimen and remains rejection-free. The TMA has not recurred. At the last follow-up (19 months post-transplant) the serum creatinine was 104 μmol/l, the platelet count was 301 000/mm³, and the sirolimus level was 6.7 ng/ml. Current immunosuppression consists of sirolimus 4 mg/day, MMF 1000 mg/day, and prednisone 7.5 mg/day.

Case 2

A 44-year-old white female with end-stage renal disease due to autosomal dominant polycystic kidney disease received a living-related renal transplant in November 2000. Both donor and recipient were sero-positive for cytomegalovirus. Initial immunosuppression consisted of tacrolimus 5 mg p.o. BID, MMF 1000 mg p.o. BID, and methylprednisolone. The allograft functioned immediately and the serum

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Suppressive action and common toxicities [6]. Both tacrolimus have similar mechanisms of immunophilin binding proteins, cyclosporine and as recurrent TMA has been reported after a change However, this treatment option is not without risk acute rejection others have recommended switching the early post-transplant period. To reduce the risk of risk of allograft rejection is increased, especially in manoeuvre often leads to resolution of the TMA, the tacrolimus was 8.9 ng/ml, and the platelet count was 124 000 mm$^3$. A renal biopsy was performed which revealed fibrin thrombi in the glomerular capillaries. There was a small focus of neutrophils in the interstitium but there was no lymphocytic infiltrate, tubulitis, or vasculitis. The biopsy confirmed the diagnosis of TMA and the tacrolimus was discontinued. Sirolimus was started at 5 mg/day and the MMF was decreased to 500 mg BID. Plasmapheresis was started and continued for 6 days. On post-operative day 11, the platelet count fell to 114 000 mm$^3$ and reached a nadir of 52 000 mm$^3$ 4 days later. Over the next few days the platelet count improved but the serum creatinine continued to rise reaching 581 µmol/l on post-operative day 20. A second renal biopsy was performed which revealed acute tubular necrosis; there was no evidence of rejection and the characteristic features of TMA had completely resolved. Over the next 2 weeks the renal function steadily improved and on post-operative day 48 the serum creatinine was 125 µmol/l and the platelet count was 158 000 /mm$^3$. The TMA has not recurred and the patient remains rejection-free with excellent allograft function. At the last follow-up (12 months post-transplant), the serum creatinine was 108 µmol/l, the platelet count was 245 000/mm$^3$, and the sirolimus level was 8.9 ng/ml. Current immuno-suppression consists of sirolimus 8 mg/day, MMF 1000 mg/day, and prednisone 7.5 mg/day.

Discussion

Most reports of transplant-associated TMA have recommended a dose reduction or complete withdrawal of calcineurin inhibitors [1,2]. Although this manoeuvre often leads to resolution of the TMA, the risk of allograft rejection is increased, especially in the early post-transplant period. To reduce the risk of acute rejection others have recommended switching from one calcineurin inhibitor to the other [3]. However, this treatment option is not without risk as recurrent TMA has been reported after a change from cyclosporine to tacrolimus, culminating in graft loss in one report [4,5]. Although they have different immunophilin binding proteins, cyclosporine and tacrolimus have similar mechanisms of immuno-suppressive action and common toxicities [6]. Both drugs have similar effects on the vasculature leading to vasoconstriction, increased endothelin levels, increased thromboxane A$_2$, and decreased nitric oxide production [7]. These vascular changes have been associated with the endothelial cell injury that is central to the pathogenesis of TMA [7]. As cyclosporine and tacrolimus both have the potential to damage endothelial cells the rationale for converting from one drug to the other during an episode of TMA is not well founded.

Sirolimus is a macrolcyclic lactone that has an immunosuppressive mechanism of action and side-effect profile that is distinct from cyclosporine and tacrolimus [6,8]. Sirolimus does not lead to vaso-constriction or nephrotoxicity, features common to the calcineurin inhibitors [8]. In an animal study, sirolimus had an opposite effect on the micro-vasculature compared with cyclosporine [9]. Sirolimus use resulted in high local nitric oxide levels with minimal intimal hyperplasia whereas cyclosporine led to significant intimal hyperplasia and no inducible nitric oxide expression [9]. The data may suggest that sirolimus has less potential for endothelial toxicity than calcineurin inhibitors.

The combination of sirolimus, MMF, and corticosteroids has been compared with a cyclosporine-based regimen with comparable results in terms of biopsy-proven acute rejection, patient survival, and renal allograft survival [10]. In addition, the glomerular filtration rate was significantly higher in the sirolimus-treated group compared with the patients receiving cyclosporine [10]. Thus, the combination of sirolimus, MMF, and corticosteroids appears to be an effective alternative to cyclosporine-based immunosuppression for the prevention of renal allograft rejection.

The cases presented herein are typical of transplant-associated TMA, in that thrombocytopenia and other clinical features of TMA were mild or absent at the time of diagnosis, despite a severe deterioration in allograft function [11]. In both instances the diagnosis of TMA was not suspected and required a renal biopsy. We have reported an alternative and rational approach to the management of transplant-associated TMA. Rather than reducing the dose of calcineurin inhibitor or switching from one calcineurin inhibitor to the other, we have demonstrated that sirolimus can replace the calcineurin inhibitor, allowing for complete resolution of the TMA. This did not occur at the expense of acute rejection, and to date both subjects enjoy excellent allograft function. A calcineurin inhibitor-free regimen of sirolimus, MMF and prednisone has the advantage of reducing the risk of recurrent TMA while providing adequate prophylaxis from acute rejection.

References


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