Long-Term Outcome of Living Related Renal Transplantation in a Patient with Short Bowel Syndrome

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Short-bowel syndrome (SBS) is defined as the malabsorptive state that occurs after extensive resection of the small intestine. In patients with SBS, oral administration of drugs usually becomes difficult because of the severity of intestinal failure. We describe a successful living related renal transplantation (LRRTx) in an 18-year-old male with SBS. Shortly after birth, the patient developed necrotizing enterocolitis requiring massive resection of the small intestine, which resulted in SBS. At seven years of age, the patient developed proteinuria and was diagnosed as focal segmental glomerulosclerosis (FSGS). His kidney function was gradually deteriorated toward the end-stage renal failure. The patient received LRRTx at age of 18 years. To evaluate the absorption capacity of the patient, we investigated pharmacokinetics of calcineurine inhibitors (tacrolimus and cyclosporine). The drug concentration, which is sufficient to provide effective immunosuppression, was achieved with cyclosporine, but not with tacrolimus. The patient therefore received a triple immunosuppressive therapy with oral cyclosporine, methyl-prednisolone and mycophenolate mofetil. To prevent both recurrent FSGS and rejection, we repeatedly analyzed the trough level and the pharmacokinetics of cyclosporine after LRRTx. The patient was successfully treated with oral immunosuppression for over 5 years, without hemodialysis. To our knowledge, this is the first report showing the long-term outcome of LRRTx treated with oral cyclosporine in a patient with SBS.

Keywords: short bowel syndrome; oral immunosuppressive therapy; living related renal transplantation; calcineurine inhibitor; pharmacokinetics

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Clinical Features

A 38-week-gestation male infant weighing 1628 g was delivered by cesarean section. The patient underwent extensive resection of the small intestine due to necrotizing enterocolitis on day 20 after birth. He developed SBS and total parenteral nutrition (TPN) was introduced. After three months of treatment, he was discharged without TPN.
However, he was repeatedly hospitalized due to enterocolitis requiring several months of TPN. At 7 years of age, he developed proteinuria and was diagnosed as FSGS, based on histopathological findings. Short-term treatment with prednisone improved his proteinuria. When he was 11 years old, he underwent another resection of the small intestine due to intussusception. The length of his residual small intestine was approximately 0.9 m. The nephropathy slowly progressed and the creatinine clearance was 28 ml/min at 16 years old. Two years later, he was diagnosed as ESRF with exacerbation of malnutrition attributed to appetite loss, and renal transplantation was the only choice left. After admission to our institution, he was received TPN and hemodialysis. Two months after starting hemodialysis, he was referred to our department to evaluate the possibility of LRRTx.

The patient weighed 45.3 kilograms and was 159 centimeters tall at the time of admission to our unit. There was no history of renal disease in his family. Laboratory studies showed the following values, sodium 145 mEq/L; potassium 2.8 mEq/L; chloride 106 mEq/L; blood urea nitrogen (BUN) 17 mg/dL; serum creatinine (s-Cre) 6.5 mg/dL; aspartate aminotransferase 14 IU/L; alanine aminotransferase 12 IU/L; gamma-glutamyl transferase 22 IU/L; total bilirubin 0.3 mg/dL; albumin 3.6 g/dL.

To assess his drug absorption capacity and to select the most appropriate regimen after renal transplantation, PK study was performed with a single dose of cyclosporine (Neoral®) and tacrolimus (Prograf®) during the pre-transplant evaluation. He was administered 200 mg of cyclosporine or 4 mg of tacrolimus orally on separate occasions. Serial blood samples were drawn at approximately 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, and 10 hours later. After the administration of cyclosporine, the area under the curve for 4 hours (AUC0-4) was almost half the value observed in healthy volunteers in past reports (Thielke et al. 1988). However, its maximum blood concentration (C-max) was 782.4 ng/mL 3 hours after the dosing, which was within the therapeutic range (Fig. 1). On the other hand, after the administration of tacrolimus, the C-max was 16.5 ng/mL, and the AUC0-4 was extremely low; namely, a sixth of the value observed in healthy volunteers (Thielke et al. 1988) (Fig. 1). These results showed that cyclosporine was available for this patient.

In March 2004, the patient underwent LRRTx from his mother. Initial immunosuppressive therapy was started with intravenous cyclosporine, methyl-prednisolone (m-PSL) and oral mycophenolate mofetil (MMF). Anti-CD25 antibody (basiliximab) was administered concurrently on the day of surgery and on postoperative day (POD) 4. The method of intravenous cyclosporine and m-PSL was exceptional used in our unit when a recipient selected regimen with cyclosporine especially in case of liver transplantation (Sato et al. 2009). His digestive symptoms were improved two weeks after the renal transplantation, and thus intravenous cyclosporine was switched to oral administration. AUC0-4 was analyzed again on POD 14 and 18 (Fig. 2). The level of cyclosporine achieved approximately the therapeutic value. His postoperative course was stable without hemodialysis. No complication such as acute rejection or recurrent FSGS was observed. The s-Cre level was 1.5 mg/dL 7 weeks after renal transplantation, and he was discharged without parenteral nutrition.

Fig. 3 shows his clinical course after renal transplantation. The patient was repeatedly hospitalized (28 times in total after renal transplantation; 13 times because of urinary tract infections (UTI), 8 times due to colitis, twice due to cytomegalovirus infections, once because of acute rejection and 4 times for other reasons. Biopsy was performed three times. The histopathological findings indicated acute rejection on one occasion. There was no evidence of recurrent FSGS.

The s-Cre level was 2 mg/dL at 11 months after the
Acute cellular rejection and drug-induced nephropathy were indicated by histopathological examination of a biopsy specimen. He received steroid pulse therapy and the dosage of cyclosporine was reduced. After these treatments, his renal function improved. However, 20 days after pulse therapy, the s-Cre increased again, and a second biopsy was performed. Contrary to our fears, there was no evidence of acute cellular rejection or recurrent FSGS on pathological findings. Since cyclosporine nephrotoxicity was not ruled out, the trough level was maintained within 100 ng/mL (Fig. 3). Recurring UTI or colitis led to dehydration and loss of appetite were considered as other harmful factors for his renal function. Oral prophylactic antibiotics were started 27 months after renal transplantation, and resulted in a decrease of hospitalization (Fig. 3). The PKs at 4 months and at 3 years after renal transplantation is shown in Fig. 2. His physical size remained at approximately the same level of the first hospit-
talization. The AUC<sub>0-4</sub> at 4 months after the operation was slightly low, but no clinical finding of rejection was observed. Interestingly, the maximum drug concentration time (T-max) shifted early phase as time passes (Figs.1 and 2).

At 51 months after renal transplantation, the s-Cre slightly elevated, with a concomitant decrease in the trough level of cyclosporine (Fig. 3). Since rejection or recurrent FSGS was suspected, the dose of cyclosporine was increased. The trough level of cyclosporine was restored, but the s-Cre still increased to 3.7 mg/dL. To assess the status of grafted kidney, biopsy was performed. Furthermore, steroid pulse therapy was added, because it was considered that increase of cyclosporine was inadequate to control rejection or recurrent FSGS. Although infiltration of lymphocytes and global sclerosis were detected, the histopathological findings did not suggest obvious rejection, recurrent FSGS and cyclosporine nephrotoxicity. The response to pulse therapy was favorable. However, about 1 month after this episode, he relapsed to the previous state; in fact he was repeatedly hospitalized within a short period due to colitis and UTI despite the prophylactic therapy. Inconveniently these events occurred with increase of s-Cre suggesting dehydration or rejection and also drug-induced nephropathy. Sixty-one months after renal transplantation, he showed dehydration and severe acidosis. Fluid replacement and compensation for lack of bicarbonic acid rapidly improved his condition. Thereafter, he has received fluid and bicarbonic acid replacement as an outpatient a couple of times a week.

The patient has overcome a lot of difficulties and has been under oral immunosuppressive therapy for over 5 years after renal transplantation without hemodialysis.

Discussion

The major problems following SBS are chronic diarrhea, dehydration, electrolyte abnormalities, and malnutrition, as a result of severe malabsorption and malabsorption (Keller et al. 2004; Duro et al. 2008). As regarding renal complication, it is well documented that hyperoxaluria related to malabsorption leads to urolithiasis, oxalate nephropathy, and ultimately development of ESRF (Chadwick et al. 1973; Earnest et al. 1974; Barilla et al. 1978; Das et al. 1979; Mole et al. 2001). In addition, the acute renal failure due to fluid/electrolyte imbalance, and sepsis, particularly central catheter-related have also been reported (Banerjee and Warwicker 2002). While FSGS is well documented as a prevalent disease (Hattori et al. 2002; Seikaly 2004), relationship between SBS and FSGS is uncertain because of the lack of literature. In our patient, renal disease might have developed irrespective of SBS and slowly progressed to ESRF without an episode of acute renal failure or hyperoxaluria.

Nowadays, renal transplantation is common treatment for ESRF; yet, there have been only a few reports about renal transplantation for patients with SBS complicated by ESRF (Kistler et al. 1995; Nunes et al. 2003; Patel et al. 2004). It was unclear whether the usual immunosuppressive agents, dosages, and regimen could actually be administered to this male with SBS. Several reports have described the absorption of calcineurine inhibitors in SBS. Oral administration of tacrolimus provided an effective level of immunosuppression after liver transplantation in some patients with SBS (Novelli et al. 1999; Olio et al. 2006). As for cyclosporine, successful immunosuppression was attained in two patients with SBS by intravenous but not oral administration (Roberts et al. 1988). Further information was available from a pharmacokinetic study (Thielke et al. 1988). While the absorption capacity was diminished, the pattern of concentration curve of calcineurine inhibitors in a SBS patient was similar to others without SBS. The data suggested that either tacrolimus or cyclosporine administered orally might be suitable for the treatment.

However, interindividual variability of absorption ability may be accentuated in patients with SBS. In fact, in our patient the drug concentration that provided an effective level of immunosuppression was attained with cyclosporine but not with tacrolimus, although the results were obtained with a single dose analysis due to poor recipient’s condition. Since the concentration curve of cyclosporine was similar to the report described above (Thielke et al. 1988), trough level (C0) and AUC<sub>0-4</sub> of cyclosporine was considered to be an indicator of dosage adjustment.

Various intestinal conditions may affect the absorption capacity of calcineurine inhibitors. Elevated C-max and prolongation of T-max were reported in patients with diarrhea after renal transplantation treated with tacrolimus (Sato et al. 2004). Principal symptoms of repeated colitis afflicting this patient were pyrexia and abdominal distension. Although severe diarrhea was less frequently found in the present patient, the possibility remained that colitis might influence the PKs, consequently leading to drug-induced nephropathy or infection such as cytomegalovirus and UTI.

Another important issue in our patient was the high recurrence rate of FSGS after renal transplantation. It is well known that FSGS can lead to chronic renal failure. In Japan, approximately 60 patients under 20 years are annually diagnosed with ESRF requiring renal replacement therapy (dialysis or transplant). Primary FSGS is a major cause of ESRF and renal transplantation (Hattori et al. 2002), in agreement with results previously reported from the USA (Seikaly 2004). Primary FSGS is prevalent, and recurrence of the disease in the transplanted kidney is also widely recognized (Hattori et al. 2002; Fujisawa et al. 2002; Seikaly 2004). The recurrence rate in children after renal transplantation was 14-50% in first time allograft recipients (Fujisawa et al. 2002; Seikaly 2004). The risk factors for recurrence include recipient age, age at onset of FSGS, treatment-resistance or rapidly progressive native kidney disease, and histological features such as mesangial expansion or prominence (Fujisawa et al. 2002; Olio et al. 2006).

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our experience will contribute to the management and treatment of patients suffering from a similar disease.

Nephrotoxicity of calcineurine inhibitors is also widely recognized, and attention should be paid to drug dose and other side effects after organ transplantation. As regarding cyclosporine, it has been shown that the nephrotoxicity correlates both with dose and with peak level after the oral dose (Ruggenenti et al. 1993). It is important clinically to differentiate cyclosporine-induced renal dysfunction from acute rejection, and histopathological examination is the only definitive test. However, there are no specific pathological findings induced acutely by cyclosporine (Kopp and Klotman 1990). Commonly acute cyclosporine nephrotoxicity is reversible with cessation of therapy (Lamas 2005). Therefore nephrotoxicity is strongly suspected when the reversibility of renal dysfunction with drug cessation concomitantly no cellular nor vascular rejection are observed. As concerns chronic nephrotoxicity, long-term cyclosporine exposure was associated with an increased risk of graft dysfunction, although the factors responsible for chronic nephrotoxicity were not well understood. Several short-term studies showed that low doses of cyclosporine might not lead to renal dysfunction. However the secure long-term dose of cyclosporine is still controversial because of lack of the controlled prospective trials (Novick et al. 1986; Ekberg et al. 2007; Tostivint et al. 2007).

In the present patient, the first biopsy revealed acute rejection and suspected drug-induced nephropathy. Thereafter, the recipient was treated with low-dose cyclosporine, and other episode, indicating rejection or drug-induced nephropathy, was not observed until 51 months after renal transplantation. However, a drastic change occurred on 52 months after renal transplantation without visible findings that accounted for the increase in s-Cre. The efficacy of steroid pulse therapy and decreased value of trough level of cyclosporine suggests that the dose of administration should be increased. Obviously, drug-induced nephropathy was apprehensive, but he did not manifest hypertension, hyperuricemia and hyperkalemia, markers for cyclosporine nephrotoxicity. Furthermore, recurrence of FSGS was the most noteworthy event in his clinical course. Therefore, trough level of cyclosporine was maintained between 100 and 200 ng/mL.

In conclusion, we describe a young SBS patient with ESRF due to FSGS that underwent LRRTx. The patient has been maintained with oral immunosuppressive therapy for over five years. The regimen of cyclosporine was decided, based on pre-operative pharmacokinetic studies. We hope our experience will contribute to the management and treatment of patients suffering from a similar disease.

References


