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LETTER TO THE EDITORS

Tacrolimus for the treatment of focal segmental glomerulosclerosis resistant to cyclosporine A

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Sir,
We read with great interest the article by Loeffler et al. [1] referring to the efficacy of tacrolimus (TL) in children with refractory nephrotic syndrome (NS). However, there is little published information on TL treatment of childhood focal segmental glomerulosclerosis (FSGS) [1, 2]. In this letter, we report on two pediatric patients with cyclosporine A (CsA)-resistant FSGS in whom successful and rapid clinical remission and reduction in the dose of prednisolone (PSL) were achieved following TL treatment.

Case 1 A 9-year-old Japanese boy was referred to our hospital with a 2-month history of unremitting steroid-resistant proteinuria. A percutaneous renal biopsy revealed lesions characteristic of FSGS. Despite aggressive immunosuppressive therapy, such as methylprednisolone pulse therapy (MPT), and therapy with cyclophosphamide (CPM), mizoribine (MZR) and CsA at the dose of 5.0 mg/kg daily [3], the heavy proteinuria persisted for the next 6 months. The trough blood level of CsA remained between 111 and 316 ng/ml. Intermittent low-density lipoprotein (LDL) apheresis, followed by oral PSL at the dose of 1.0 mg/kg daily in combination with CsA, proved to be partially effective. However, the patient developed severe steroid toxicity, including obesity, short stature, cataract, and osteoporosis.

Case 2 An 11-year-old Japanese girl was brought to a regional hospital with an 8-day history of generalized edema. Urinalysis revealed a urinary protein excretion level of 1,153 mg/dl without hematuria. A percutaneous renal biopsy revealed lesions characteristic of FSGS. Although MPT was administered followed by oral PSL combined with CsA at the dose of 3.0 mg/kg daily, heavy proteinuria persisted for the next 4 months. The trough blood level of CsA remained between 120 and 257 ng/ml. The patient was thereafter referred to our hospital for further examinations. A second renal biopsy revealed lesions of mild CsA-related nephrotoxicity in about 5% of the interstitium. Therefore, CsA was stopped and replaced by high-dose intermittent MZR [4]. LDL-apheresis was also initiated, which proved to be partially effective. However, another relapse of heavy proteinuria occurred 6 months after the admission. The patient subsequently developed severe steroid-induced osteoporosis.

TL treatment After obtaining approval from the ethics committee at our institution, both patients were treated with TL. The initial TL dose was 4 mg daily, administered in two divided dose (0.1 mg/kg in case 1 and 0.08 mg/kg in case 2). Timing of the commencement of TL from the onset of NS was 3 years in case 1 and 18 months in case 2. The trough blood level of TL remained in the range of between 4.6 and 13.3 ng/ml in case 1, while in case 2, the trough blood level of TL remained in the range of between 4.3 and 6.5 ng/ml, despite the TL dose was subsequently increased to 6 mg (0.12 mg/kg).

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Response to TL treatment

Case 1 Complete remission was achieved within 50 days of the start of TL administration, despite gradual tapering of the PSL. No significant change in the estimated value of GFR was observed (127 ml/min per 1.73 m^2 pre- and 110 ml/min per 1.73 m^2 post-TL treatment). At present, 24 months after the commencement of TL, the patient remains free from proteinuria, and the PSL dose has been tapered to 0.36 mg/kg on alternate days without recurrence of proteinuria. Repeat renal biopsy performed 18 months after the commencement of TL revealed no evidence of TL-related nephrotoxicity.

Case 2 A rapid decrease in the urinary protein excretion was observed within 80 days of the start of TL administration, with no adverse effects of the drug. No significant change in the estimated value of GFR was observed (121 ml/min per 1.73 m^2 pre- and 140 ml/min per 1.73 m^2 post-TL treatment). At present, 3 months after the commencement of TL, her urinary protein excretion level decreased to 0.5 g/day and the PSL dose has been tapered to 0.8 mg/kg on alternate days.

In the present cases, aggressive immunosuppressive therapy consisting of MPT followed by oral PSL combined with CPM, MZR and CsA proved ineffective in terms of the anti-proteinuric effect. We therefore treated the patients with TL as an alternative drug in place of CsA, and adjusted the drug dose to maintain the trough blood level of TL in the range of 5 to 10 ng/ml [5]. Following the start of this treatment with TL, a rapid decrease in the urinary protein excretion was observed within 3 months in both cases, despite gradual tapering of the PSL dose. Segarra et al. [5] reported that combined therapy with TL and PSL was effective and safe in 68% of 25 adult patients with CsA-resistant FSGS. Loeffler et al. [1] reported that 13 of 16 pediatric patients with refractory NS showed satisfactory response to TL therapy. McCauley et al. also [2] reported on the efficacy of TL in seven patients, including four children with steroid-resistant FSGS, without any severe adverse effects of the drug being observed during the follow-up period. Considering the reports in the literature and our own patients' clinical courses, we suggest that treatment with TL might be beneficial in selected patients, even children, with refractory FSGS resistant to conventional immunosuppressive agents, including CsA. However, the long-term efficacy and safety of TL for the treatment of childhood FSGS resistant to CsA remain unclear.

References

1. Loeffler K, Gowrishankar M, Yiu V (2004) Tacrolimus therapy in pediatric patients with treatment-resistant nephrotic syndrome. Pediatr Nephrol 19:281–287
2. McCauley J, Shapiro R, Ellis D, Igdal H, Tzakis A, Starzl TE (1993) Pilot trial of FK 506 in the management of steroid-resistant nephrotic syndrome. Nephrol Dial Transplant 8:1286–1290
3. Tsugawa K, Tanaka H, Nakahata T, Ito E (2004) Effective therapy of a child case of refractory nephrotic syndrome with tacrolimus. Tohoku J Exp Med 204:237–241
4. Tanaka H, Tsugawa K, Nakahata T, Kudo M, Onuma S, Kimura S, Ito E (2005) Mizoribine pulse therapy for a pediatric patient with steroid-resistant nephrotic syndrome. Tohoku J Exp Med 205:87–91
5. Segarra A, Vila J, Pou L, Majo J, Arbos A, Quiles T, Piera L (2002) Combined therapy of tacrolimus and corticosteroids in cyclosporine-resistant or -dependent idiopathic focal glomerulosclerosis: a preliminary uncontrolled study with prospective follow-up. Nephrol Dial Transplant 17:655–662