Effective Therapy of a Child Case of Refractory Nephrotic Syndrome with Tacrolimus

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TSUGAWA, K., TANAKA, H., NAKAHATA, T. and ITO, E. Effective Therapy of a Child Case of Refractory Nephrotic Syndrome with Tacrolimus. Tohoku J. Exp. Med., 2004, 204 (3), 237-241 —— We report here the case of a 9-year-old Japanese boy with nephrotic syndrome caused by focal segmental glomerulosclerosis, which was refractory to treatment. Although aggressive immunosuppressive therapy consisting of methylprednisolone pulse therapy combined with cyclosporine A (CsA) and intermittent low density lipoprotein apheresis was effective in overcoming his steroid-resistant state, the child became persistently steroid-dependent, that is, more than 0.75 mg/kg per day of prednisolone combined with CsA was required to maintain a negative test for proteinuria. Since adverse effects of prednisolone, such as short stature, obesity, osteoporosis and cataract, were noted, CsA in his treatment regimen was replaced with tacrolimus at the dose of 0.1 mg/kg per day, with the trough blood level of the drug maintained at around 10 ng/ml. Within 4 months of the inclusion of tacrolimus in the treatment regimen, complete remission was achieved, with no recurrence of the proteinuria, while the prednisolone dose could be tapered to 0.3 mg/kg per day. No adverse effects of tacrolimus were observed. These clinical results suggest that tacrolimus may be the drug of choice in selected patients with refractory nephrotic syndrome, even if pediatric-onset cases, at least those in whom the steroid-sparing effects of CsA is unsatisfactory. ——— focal segmental glomerulosclerosis; refractory nephrotic syndrome; steroid-sparing effect; tacrolimus

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Aggressive immunosuppressive therapy, such as intravenous high-dose steroid therapy combined with an alkylating agent, has been reported to be somewhat effective for the treatment of refractory nephrotic syndrome (NS) caused by focal segmental glomerulosclerosis (FSGS) (Mendoza et al. 1990). Recently, cyclosporine A (CsA) has also been successfully used for the treatment of FSGS (Ponticelli et al. 1993). However, a proportion of patients with FSGS exhibits refractory NS that is resistant to even such aggressive immunosuppressive therapy. In this context, several investigators have tested and demonstrated the efficacy and safety of tacrolimus (FK506), a newly developed calcineurin inhibitor, for the treatment of refractory NS (McCauley et al. 1990, 1993; Schweda et al. 1997; Segarra et al. 2002; Pennesi et al. 2003; Loeffler et al. 2004). However, the efficacy and safety of tacrolimus for the treatment of refractory FSGS in pediatric patients remains to be established.

We encountered a Japanese boy with refractory NS caused by FSGS. Aggressive immunosuppressive therapy consisting of intravenous methylprednisolone pulse therapy (MPT) followed by oral prednisolone (PSL) combined with cyclophosphamide, mizoribine and CsA with a blood trough level of this drug of approximately 100 ng/ml, was useful for overcoming his steroid-resistant state. However, when the PSL dose was reduced to 30 mg/day (approximately 0.75 mg/kg per day), frequent relapse of proteinuria occurred, and the child developed features of severe steroid toxicity. We therefore treated the child with tacrolimus as an alternative drug in place of CsA, and noted the rapid steroid-sparing effect of this agent.

CASE REPORT

A 9-year-old boy with a 2-month history of generalized edema associated with persistent proteinuria was diagnosed to have NS, and referred to Hirosaki University Hospital because the NS proved to be steroid-resistant. Laboratory examination at presentation revealed the following results: serum total protein 3.4 g/100 ml; serum albumin 1.6 g/100 ml; serum total cholesterol 391 mg/100 ml; blood urea nitrogen 18 mg/100 ml; serum creatinine 0.5 mg/100 ml and urinary protein excretion, 24.6 g/liter. A percutaneous renal biopsy revealed lesions characteristic of FSGS. Although aggressive immunosuppressive therapy was initiated with MPT, followed by oral PSL in combination with several immunosuppressive agents, namely, cyclophosphamide, mizoribine and CsA, the proteinuria remained unremittent for the next 6 months, except for a transient decrease in the urinary protein excretion. Although CsA was given orally once daily and its peak blood level was adjusted to approximately 800 ng/ml (Tanaka et al. 2004), the steroid-resistant nephrotic state persisted. Finally, a combination of PSL at a dose of over 30 mg per day, with CsA and intermittent low density lipoprotein (LDL) apheresis (Muso et al. 2001) allowed his steroid-resistant state to be overcome (Fig. 1A). However, the patient developed severe steroid-induced clinical toxicity, such as short stature, obesity, cataract and osteoporosis.

METHODS

After obtaining informed consent from the child’s parents and the approval of the ethics committee at our institution, a trial of tacrolimus was started, with the drug administered at the dose of 4 mg (0.1 mg/kg) per day in two divided doses (Loeffler et al. 2004). Two weeks before the commencement of the drug, all immunosuppressive agents were stopped, except for PSL, at the dose of 30 mg/day (0.75 mg/kg per day). Repeat renal biopsy at the commencement of tacrolimus administration confirmed the absence of any CsA-induced tubulointerstitial lesions. Eventually, the PSL dose was tapered (by 2.5 mg every 2 weeks).

RESULTS

Complete remission was achieved within 50 days of the start of tacrolimus administration, even while the PSL dose was being gradually tapered (Fig. 1B). The blood trough levels of tacro-
Fig. 1.  A: Clinical course of the patient before the tacrolimus treatment. Massive proteinuria persisted without high dose steroid therapy. ■, prednisolone at mg/d; □, prednisolone at mg/alt.d; ●, ARF (acute renal failure); †, MPT (methylprednisolone pulse therapy); ★, LDL-A (LDL apheresis). B: Urine protein excretion and PSL doses after the commencement of tacrolimus. Despite the PSL tapering, rapid decrease of urine protein excretion and succeeding complete remission could be achieved within 50 days following tacrolimus treatment.
Tacrolimus ranged from 4.6 to 13.3 ng/ml. At present, 6 months after the addition of tacrolimus to the treatment regimen, the patient is free from proteinuria, and shows no adverse effects of tacrolimus. The PSL dose could eventually be tapered to 12.5 mg per day (0.3 mg/kg per day) without recurrence of proteinuria.

**DISCUSSION**

Until now, some of the treatments that have been reported to be effective for refractory NS caused by FSGS include MPT combined with alkylating agents (Mendoza et al. 1990), CsA (Ponticelli et al. 1993), intermittent LDL apheresis (Muso et al. 2001), plasmapheresis (Feld et al. 1998) and tacrolimus (McCauley et al. 1990, 1993; Schweda et al. 1997; Segarra et al. 2002; Pennesi et al. 2003; Loeffler et al. 2004). Of these, LDL apheresis and plasmapheresis are difficult to perform in a routine set-up in clinical practice, especially in pediatric patients, while CsA has generally been reported to be quite effective for the treatment of FSGS (Ponticelli et al. 1993). A proportion of patients with FSGS, however, fails to enter sustained remission following therapy with PSL or MPT in combination with CsA.

In regard to the efficacy of tacrolimus, McCauley et al. (1993) first conducted a pilot study of tacrolimus treatment in 7 patients, including 4 children with steroid-resistant NS. They reported that the drug administered at the initial dose of 0.15 mg/kg per day in two divided doses, with the blood trough levels ranging from 0.5 to 2.0 ng/ml, proved effective in 75% of the pediatric patients: the complete remission rate was 25% and the partial remission rate was 50% (McCauley et al. 1993). There have been several reports subsequently describing the successful treatment of adult patients of refractory NS with tacrolimus (Schweda et al. 1997; Segarra et al. 2002; Tang et al. 2003). On the other hand, to the best of our knowledge, there have been only a few studies on the efficacy and safety of tacrolimus in pediatric NS patients (Pennesi et al. 2003; Loeffler et al. 2004). Pennesi et al. (2003) reported a case of refractory NS in whom complete remission was achieved following tacrolimus therapy, when the drug was administered at the initial dose of 0.05 mg/kg per day and the trough levels in the blood were in the range of 8.0 to 12.0 ng/ml. Loeffler et al. (2004) recently reported their experience of tacrolimus therapy in 16 children with refractory NS. They reported that tacrolimus was highly effective and safe, that is, 81% of the treated children entered complete remission following administration of tacrolimus at an initial dose of 0.1 mg/kg per day, with the trough blood levels ranging from 4.4 to 12.8 ng/ml (Loeffler et al. 2004).

With regard to the mode of action of tacrolimus, it has been reported that this drug has inhibitory effects on cytokine production from lymphocytes, which is stronger than that of CsA (Denton et al. 1999), although it remains speculative.

In the present trial, we administered tacrolimus at the initial dose of 0.1 mg/kg per day in two divided doses, with the blood trough levels of the drug in the range of 4.6 to 13.3 ng/ml, in accordance with a recent report by Loeffler et al. (2004). Following this treatment, administered concomitantly with PSL, rapid decrease of the urinary protein excretion was observed, despite the gradual tapering of the PSL dose, and complete remission was successfully achieved within 50 days of the start of the treatment, as described above. Since unremitting proteinuria of long duration is thought to be harmful to the kidney (Tanaka et al. 2000), rapid decrease in the urine protein excretion following tacrolimus treatment is attractive for such patients with refractory NS. Although the possibility of spontaneous remission of the NS cannot be excluded in our case, the clinical course strongly suggests that tacrolimus had a beneficial role. We, therefore, conclude that tacrolimus is beneficial in selected pediatric patients with refractory NS.

It has been reported that the major adverse effect of tacrolimus, as of CsA, is nephrotoxicity. Since no randomized controlled trials comparing
Tacrolimus treatment with other immunosuppressive therapies have not been conducted until now, little is known concerning the long-term efficacy and safety of tacrolimus, including the potential long-term nephrotoxicity in difficult cases of NS. Although further studies are needed to confirm our clinical findings, we propose that tacrolimus may be an effective treatment option for selected cases of refractory NS.

References