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Original Article

Complete remission induced by tacrolimus and low-dose prednisolone in adult minimal change nephrotic syndrome: A pilot study

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Abstract

Background: Few clinical trials have examined the replacement of steroids with other immunosuppressive drugs as a primary treatment modality for minimal change disease (MCD) in adults. We studied the efficacy of tacrolimus to induce complete remission (CR) in adults with MCD.

Methods: We enrolled 14 adults with MCD and nephrotic-range proteinuria. All patients were treated with oral tacrolimus 0.05 mg/kg twice daily and prednisolone 0.5 mg/kg/day. CR was defined as a urine protein to creatinine ratio of < 0.2 g protein/g creatinine (g/g cr). The primary outcome was cumulative percentage of CR during 16 weeks.

Results: The mean urine protein to creatinine ratio at enrollment was 10.9 g/g cr (range: 4.2–18.1 g/g cr). The trough tacrolimus level was maintained at 5.99 ± 2.63 ng/mL. CR was achieved by 13/14 (92.8%) patients within 8 weeks. The cumulative CR rate was 7.7% (1/14), 64.2% (9/14), 71.3% (10/14), and 92.9% (13/14) at 1 week, 2 weeks, 4 weeks, and 8 weeks, respectively. The one remaining patient achieved CR at 20 weeks after treatment, who was followed up for a further 4 weeks. The mean time to achieve CR in the 14 patients was 4.64 ± 5.11 (1–20) weeks. Three cases suffered adverse events of abdominal pain, diarrhea, or new-onset diabetes mellitus.

Conclusion: Tacrolimus and low-dose prednisolone therapy induced CR rapidly (71.3% by 4 weeks and 100% by 20 weeks) and effectively in adult patients with MCD.

Introduction

Minimal change disease (MCD) is the most common cause of childhood nephrotic syndrome and is also responsible for 10–15% of the adult idiopathic nephrotic syndrome [1,2] in western reports. In Korea, MCD is present in more than one-third of adult cases of idiopathic nephrotic syndrome [3]. The mainstay for MCD treatment is corticosteroids in both adults and children. However, most of the data on the efficacy of corticosteroids in MCD come from pediatric samples [4,5]. In 2009, the Cochrane Collaboration issued the paucity of randomized controlled trials for MCD treatment in adults [6]. Although the complete remission (CR) rate with cortico-

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steroids is excellent in adults, such treatment poses several challenges. The response rate with corticosteroids is lower in adults than in children. Steroid dependence and resistance also provoke concern about the undesirable effects of steroids, such as avascular necrosis, myopathy, cataract, newly developed diabetes, and psychiatric disturbances [7]. The optimal type and duration of therapy for initial and relapsed cases of MCD have not been determined.

Variable corticosteroid-sparing agents such as cyclosporin, cyclophosphamide, and mycophenolate mofetil are used to introduce remission and reduce negative effects of corticosteroids [8–11]. Although cyclophosphamide and cyclosporin are widely used in MCD patients with steroid-dependent MCD [9–11], cyclophosphamide is associated with serious side effects, such as bone marrow depression, gonadal failure, and malignancy [12]. The major problems of cyclosporin treatment are frequent relapse after withdrawal and the risk of renal toxicity after long-term therapy [8]. Tacrolimus shows more potent cytokine suppression and seems to cause less toxicity than cyclosporin as a calcineurin inhibitor [13,14]. Although tacrolimus has been shown to be effective in maintaining remission in pediatric patients with steroid-dependent nephrotic syndrome, few case reports and nonrandomized trials have been conducted to investigate the effect of tacrolimus on CR induction in adult MCD patients [8,15].

The purpose of the present study was to evaluate the efficacy and safety of tacrolimus in the treatment of adult patients with MCD, as a pilot study to plan a randomized controlled trial for MCD patients with tacrolimus versus high-dose corticosteroids. The response rate to tacrolimus was faster than that reported in previous studies.

Methods

Patients

We enrolled 14 Korean adults aged ≥ 18 years with renal-biopsy-proven MCD and nephrotic-range proteinuria who were followed in a single medical center at the time of enrollment. Nephrotic-range proteinuria was defined as a urine protein to creatinine ratio (UPCR) of >3 g protein/g creatinine (g/g cr) at two or more separate examinations within 2 weeks, and a serum albumin level < 3 g/dL. The exclusion criteria were systemic disease, uncontrolled hypertension with systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg, liver function abnormalities, pregnancy, hypersensitivity to tacrolimus or macrolides, and previous therapy with cyclosporin or tacrolimus within 3 months. This study was not intended to reveal the factors related to reponse rate of therapy in MCD, so, we did not exclude MCD patients with previous chronic kidney disease. The study was approved by the Institutional Review Board of Seoul National University Hospital and informed consent was obtained from all patients. This study was notified on the web site of clinical trials (www.clinicaltrial.gov) as NCT1084980.

Definitions

MCD was diagnosed by renal biopsy. All biopsy specimens were examined by light microscopy, immunofluorescence, and electron microscopy. The histological criteria for diagnosing MCD included diffuse effacement of foot processes of podocytes on electron microscopy, absence of electron-dense deposits or thickening of basement membrane, negative immunofluorescence and absence of segmental sclerosis [7]. CR was defined as a daily UPCR < 0.2 g/g cr or negative results of repeated urine albumin dipstick test. Time to remission was the time from initiation of therapy to the first day on which remission was observed. Relapse was defined by UPCR ≥ 3.0 g/g cr or $\geq 3+$ on urine albumin dipstick in repeated measurements [7]. Steroid dependence was defined by relapse during tapering of steroids within 6 months after CR or within 14 day of cessation of steroids. Steroid resistance was defined by persistent nephrotic proteinuria despite high-dose steroid therapy ($\geq$ 1 mg/kg/day) for ≥ 12 weeks. Early CR was defined as CR within < 4 weeks. Hematuria was defined as ≥ 5 red blood cells per high-power field. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or taking antihypertensive medication to control blood pressure. Diabetes mellitus was defined as fasting blood sugar ≥ 126 mg/dL, random blood sugar ≥ 200 mg/dL, or taking antidiabetic medication to control blood sugar. Acute kidney injury (AKI) was defined as a rise of serum creatinine ≥ 0.3 mg/dL or $\geq 50\%$ compared to serum creatinine in remission.

Study protocol

All patients had tacrolimus (Prograf®, Astellas Pharma Korea Inc, Seoul, Korea) 0.05 mg/kg twice daily and prednisolone 0.5 mg/kg/day (up to 40 mg/day) until remission for 16 weeks. We performed follow-up at 1 week, 2 weeks, 4 weeks, 8 weeks, 12 weeks and 16 weeks after enrollment. At each visit, we measured complete blood counts, liver function tests, fasting blood glucose, total cholesterol, trough tacrolimus level, urinalysis including dipsticks, and UPCR. Level of serum creatinine was reported as the value of isotope dilution mass spectroscopy traceable creatinine (IDMS-CR). Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease Study (MDRD) based on IDMS-CR [16]. We also estimated creatinine clearance from serum and urinary creatinine levels.

Outcome variables

The cumulative rate of CR was calculated at each visit. We reported all types of adverse events (AEs) and AEs related to the medication.

Statistical analysis

Data were expressed as mean $\pm$ standard deviation (range) for continuous variables and as proportion for nominal data. We compared the differences of parameters at each visit and at baseline using paired Student t test for continuous variables and Pearson's χ^2 test for nominal variables. We compared the parameters using an independent Student t test between the early and late CR groups. A p value < 0.05 was considered statistically significant.

Results

Baseline characteristics

Fourteen Koreans were enrolled from May 2010 to March 2011. The mean age at enrollment was 33.8 (20–72) years and