Kidney Res Clin Pract 31 (2012) 112–117

Kidney Research and Clinical Practice

journal homepage: http://www.krcp-ksn.com
Contents lists available at ScienceDirect

Original Article

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

Yong Chul Kim [1], Tae Woo Lee [1], Hajeong Lee [1], Ho Suk Koo [2], Kook-Hwan Oh [1], Kwon Wook Joo [1,5], Suhnggwon Kim [1,4,5], Ho Jun Chin [3,4,5,*]

[1] Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea
[2] Department of Internal Medicine, Inje University College of Medicine, Busan, Korea
[3] Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul, Korea
[4] Graduate school of Immunology, Seoul National University College of Medicine, Seoul, Korea
[5] Renal Institute, Clinical Research Center, Seoul National University College of Medicine, Seoul, Korea

Article history:
Received 5 January 2012
Received in revised form
2 February 2012
Accepted 21 March 2012
Available online 3 May 2012

Keywords:
Adults
Minimal change disease
Tacrolimus

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-

* Corresponding author. Department of Internal Medicine, Seoul National University Bundang Hospital, Gumi-dong 300 Bundang-gu, SeongNam-shi, Kyeongki-do, 463–787, Korea.
E-mail address: mednep@snubh.org (HJ Chin).

2211-9132/$ - see front matter © 2012. The Korean Society of Nephrology. Published by Elsevier. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
http://dx.doi.org/10.1016/j.krcp.2012.04.321

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

Table 1. Baseline characteristics of patients

		Findings
Male/female		10/4
Age at diagnosis (yr)		25.9 ± 15.5 (5–6 1)
Age at enrollment (yr)		33.8 ± 17.4 (20–72)
Duration from diagnosis to enrollment (mo)		105.9 ± 54.0 (0–326)
Relapse before enrollment		
	none*	1
	1st	4
	2nd	1
	3rd	1
	more than 3rd	7
Diabetes mellitus		0/14
Hypertension		3/14
AKI at presentation†		0/14
SBP (mmHg)		120.9 ± 14.1 (98–141)
DBP (mmHg)		74.9 ± 10.7 (57–96)
UPCR‡		10.9 ± 4.5 (4.2–18.4)
Hematuria		1/14
Serum creatinine (mg/dL)		0.82 ± 0.21 (0.60–1.31)
Ccr (mL/min)		116.3 ± 32.4 (42.5–158.3)
eGFR by MDRD equation§		109.2 ± 30.4 (39.9–148.7)
Serum albumin (g/dL)		2.2 ±0.5 (1.4–2.9)
Serum cholesterol (mg/dL)		360 ±104 (241–562)
Blood glucose (mg/dL)		81.4 ±12.5 (60–109)

* Enrolled at the first diagnosis
† acute kidney injury defined as increase of serum creatinine ≥ 0.3 mg/dL or ≥ 50% than serum creatinine in remission
‡ g protein/g creatinine
§ estimated using isotope dilution mass spectroscopy traceable creatinine measurement (mL/min/1.73 m^2). AKI, acute kidney injury; Ccr, creatinine clearance; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; the Modification of Diet in Renal Disease Study (MDRD), SBP, systolic blood pressure; UPCR, urinary protein to creatinine ratio.

25.9 (5–6 1) years at diagnosis (Table 1). The average time from diagnosis to enrollment was 105.9 ± 54.0 (0–326) months. Three patients had been diagnosed in their childhood at 5 years, 8 years and 9 years. Thirteen patients had relapsed and seven had relapsed more than three times. The mean number of relapse times of the 13 patients was 5.69 ± 5.91 (1–20) and the mean frequency of relapses per year was 1.1 ± 0.8 (0.2–3.0). The initial treatment modality at renal biopsy in the 13 relapsed patients was mainly high-dose prednisolone (1 mg/kg/day) and one patient had high-dose prednisolone with cyclosporin (200 mg/day). The first treatment achieved CR in 12/13 patients and one patient was treated with the addition of cyclosporin and cyclophosphamide to steroids to achieve CR. The cumulative rate of CR at the first treatment in 13 patients was 7.7% (1/13) at 1 week, 15.4% (2/13) at 2 weeks, 69.2% (9/13) at 4 weeks, 84.6% (11/13) at 8 weeks, and 100.0% (13/13) at 16 weeks after treatment. At study enrollment, four patients were not taking any immunosuppressive treatment, including corticosteroids; six patients were taking prednisolone ≤ 5 mg/day or deflazacort ≤ 6 mg/day; two patients, prednisolone 7.5–10 mg/day; one patient, prednisolone 35 mg/day, who had a relapse during tapering of steroid; and one patient, 60 mg/day (1 mg/kg/day) for 12 weeks, whom we considered to have steroid resistance. Among the relapsed patients, five were defined as steroid-dependent because they relapsed during the steroid-tapering schedule. Among six patients taking ≤ 5 mg/day prednisolone, five had taken prednisolone for > 12 months (13–53 months) after the last CR and were not considered as steroid-dependent. There were no diabetic patients and three hypertensive patients were enrolled. AKI was not identified. Mean UPCR was 10.9 (4.2–18.4) g/g cr and mean serum albumin was 2.2 (1.4–2.9) g/dL. eGFR by MDRD equation using IDMS-CR was 109.2 ± 30.4 (39.9–148.7) mL/min/1.73 m^2.

Response to therapy

During 16 weeks, the mean tacrolimus trough blood level was 5.99 ± 2.63 (0.3–12.3) ng/mL and the mean tacrolimus dose was 0.096 ± 0.02 mg/kg/day. The mean prednisolone dose was 31.5 ± 6.5 mg/day (0.50 ± 0.06 mg/kg/day). The adherence rates to tacrolimus and prednisolone were 96.5 ± 4.4% (83.8–100%) and 99.9 ± 0.5% (98.2–100%), respectively. All patients completed the 16-week course of therapy and 13/14 patients (92.9%) achieved a CR. The one remaining patient showed UPCR 0.28 g/g cr at 16 weeks and achieved CR at 20 weeks after therapy, who was followed for a further 4 weeks (Fig. 1). The mean time to achieve CR was 4.64 ± 5.11 (1–20) weeks in 14 patients. The cumulative CR rate at each visit was 7.7% (1/14), 64.2% (9/14), 71.3% (10/14), 92.9% (13/14), and 100% at 1 week, 2 weeks, 4 weeks, 8 weeks and 20 weeks after therapy, respectively (Fig. 2). This CR rate was higher than that previously reported in Western or Asian countries. The response rate within 4 weeks after therapy was remarkable in this study compared to others. We calculated the slope of UPCR changes until CR from enrollment (Fig. 3). Patients with early CR within < 4 weeks after therapy showed a steep slope of UPCR changes. The mean slope of UPCR changes in patients with CR by 2 weeks after therapy was −1.03 ± 0.14 (−0.85 to −1.30) $\log_{10}$[UPCR (g/g cr)]/week. The mean value of R^2 of the estimated slope of the patients with CR within < 4 weeks after therapy was 0.933 ± 0.077 and the resulting line was very nearly linear. With increasing time to achieve CR, the slopes of

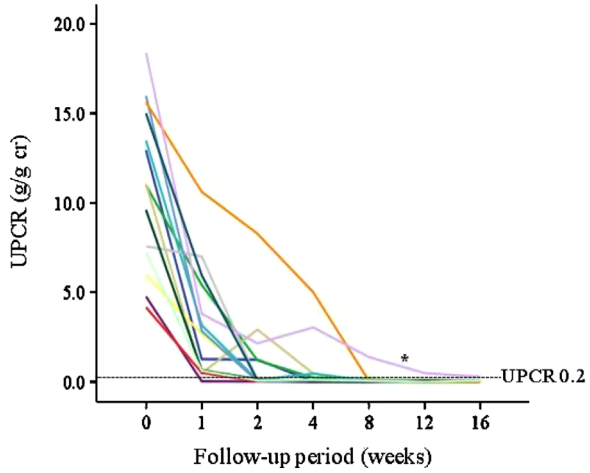

Figure 1. UPCR pattern after therapy with tacrolimus and low-dose prednisolone in adults with MCD. The asterisk-marked case did not show CR at 16 weeks with UPCR 0.28 g protein/g creatinine, but did achieve remission at 20 weeks after therapy. CR, complete remission; MCD, minimal change disease; UPCR, urine protein to creatinine ratio.

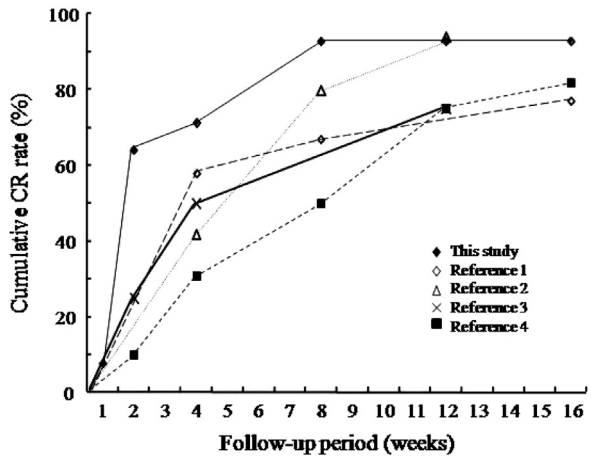

Figure 2. Cumulative CR rate of adult MCD patients in this study compared to other studies. The number on the figure is the reference number of this manuscript. CR, complete remission; MCD, minimal change disease.

the UPCR changes became lower as the linearity of the estimated line was decreased, and the mean values of R^2 for the estimated linear line were decreased.

The prednisolone dose at enrollment, relapse frequency, and steroid dependence or resistance did not predict early CR within <4 weeks after therapy but patients with early CR had higher baseline GFR than those with CR by ≥ 4 weeks after therapy (124.3 ± 17.3 mL/min/1.73m^2 vs. 82.0 ± 31.1 mL/min/1.73m^2, $p=0.034$). The mean serum albumin levels were increased, mean total cholesterol levels at 4 weeks, 8 weeks, 12 weeks and 16 weeks of treatment were decreased compared to the baseline level, and the urine protein excretion was decreased (all three changes significant; Fig. 4).

AEs

The levels of serum creatinine and eGFR were not significantly changed during the follow-up period (109.2 ± 30.4 mL/min/1.73 m^2 at baseline and 106.5 ± 8.1 mL/min/1.73 m^2 at 16 weeks

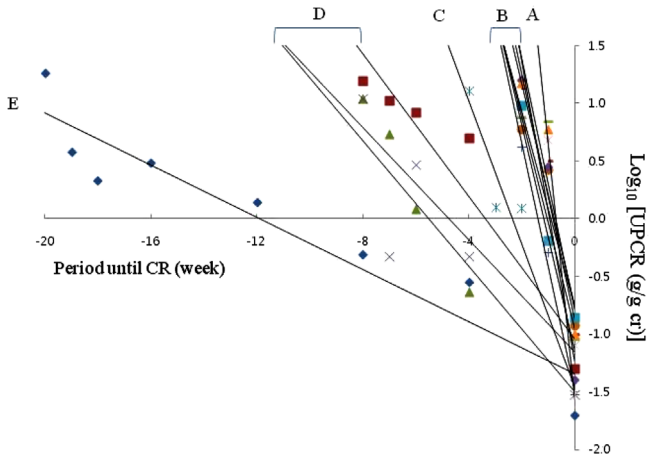

Figure 3. Each line represents the estimated curve fit for changes of UPCR until remission in each patient. The zero point on the x axis is the event period of CR. The y axis is the log value of UPCR. The A, B, C, D and E lines represent the change of UPCR of a patient who achieved CR at 1 week, 2 weeks, 4 weeks, 8 weeks and 20 weeks after therapy, respectively. CR, complete remission; UPCR, urine protein to creatinine ratio.

after therapy). There was no case of new-onset hypertension, infection, hepatotoxicity with elevation of Aspartate Aminotransferase (GOT) or Alanine Aminotransferase (GPT), anemia, or leukopenia. One patient had severe abdominal pain with tacrolimus. After decreasing the tacrolimus dose from 6 mg/day to 4 mg/day, the patient felt better and could take tacrolimus without further problems. Diabetes mellitus developed at 8 weeks after therapy in another patient, and one patient had mild diarrhea that resolved spontaneously. No patient needed to stop medication.

Discussion

In this pilot study, tacrolimus and prednisolone therapy (0.5 mg/kg/day), lower dose of conventional prednisolone dose (1 mg/kg/day), induced CR rapidly and effectively for 14 patients with MCD. The distinctive finding was that CR was induced rapidly (71.3% of patients by 4 weeks, and completely, in 100% of patients by 20 weeks after therapy), and the slope of the decrease of UPCR was constantly rapid in patients with CR in 2 weeks. With comparing the cumulative CR rate in the first treatment, the response rate of this trial was more rapid, especially CR rate at 2 weeks after treatment (15.4% vs 64.2%, χ^2 test with Yates' correction, $p=0.028$).

Among the 14 study patients, one was steroid-resistant to prednisolone at 1 mg/kg/day for 12 weeks, and five were considered steroid-dependent because they relapsed during tapering of steroids within 6 months after CR. Steroid dependency is not well defined but is considered to be indicated by a relapse on tapering steroid therapy or within 2–4 weeks of discontinuing steroids, and a need for long-term maintenance steroids [7,8]. We defined steroid dependency as relapse within 6 months during tapering of steroids or within 2 weeks after steroid cessation. In our clinic, steroids are tapered for relatively longer duration compared to other studies, and it takes >6 months after CR. Sometimes prednisolone is used for >12 months at a dose of ≤ 5 mg/day for routine care, although no concrete evidence has been presented to prove the efficacy of long-term steroid use in routinely preventing relapse. Therefore, we did not include the

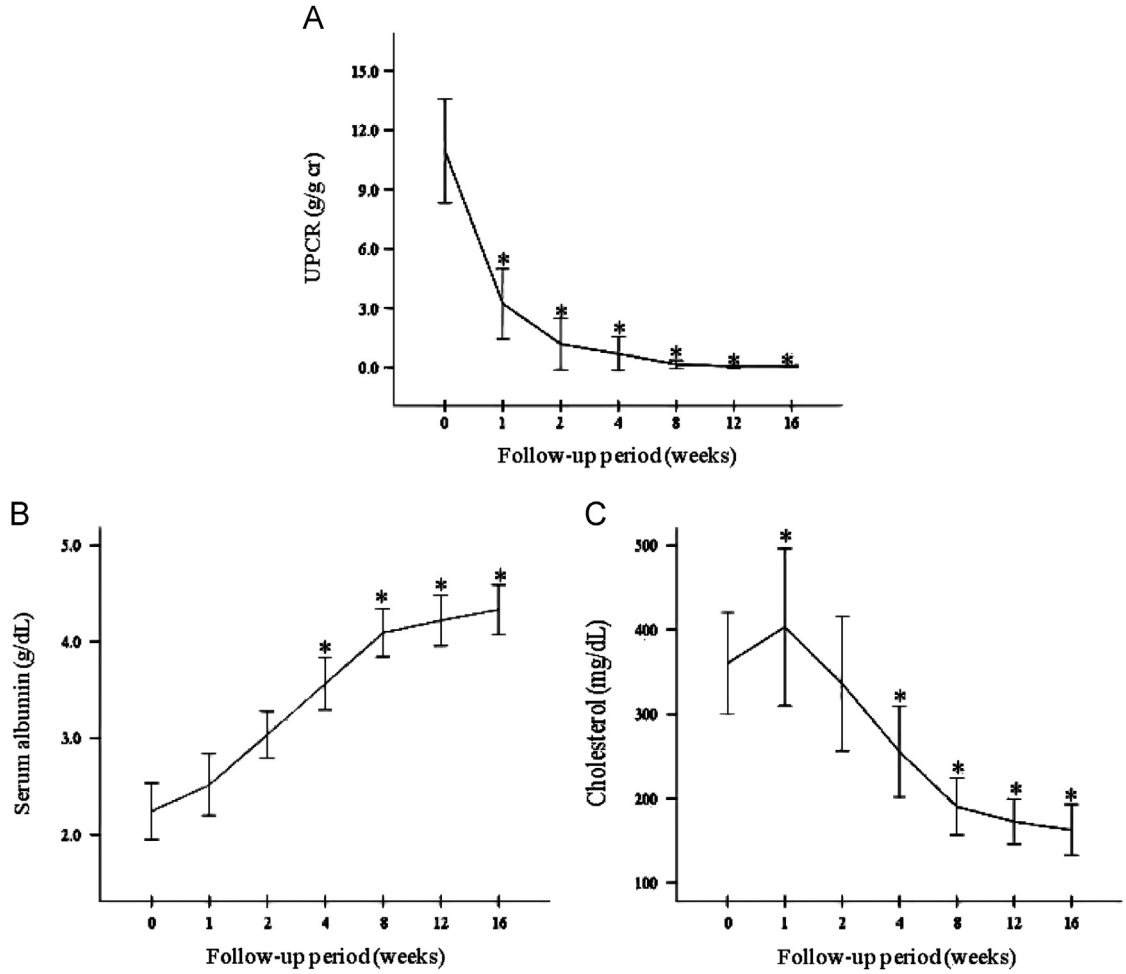

Figure 4. Changes of UPCR (a), serum albumin (b), and total cholesterol (c) in adult MCD patients. The vertical bar shows the 95% confidence interval of the mean value. ∗: difference of levels of parameters between that at each visit and at baseline, $p < 0.05$ by paired t test. MCD, minimal change disease; UPCR, urine protein to creatinine ratio.

criterion of needing to maintain steroids for > 12 months as steroid dependency. Five patients in this study had taken ≤ 5 mg/day prednisolone for > 12 months without relapse.

The overall rate of response (100% by 20 weeks after therapy) to this therapy with tacrolimus and low-dose prednisolone was remarkable compared to previous studies, especially the early response rate within 4 weeks (71.3%) after therapy. Cumulative CR rates of nearly 30% by 4 weeks and around 75% by 13 weeks have been reported by Waldman in the United States [7], 42% by 4 weeks and 94% by 12 weeks in Taiwan [17], and 58% by 4 weeks and 77% by 16 weeks in Japan [18]. The CR rate in our study was similar to that in children; 50% of whom respond within 2 weeks and almost all within 8 weeks [19,20]. We could not definitively explain this rapid response rate to tacrolimus and low-dose prednisolone. One possible explanation is the long-term use of prednisolone at a minimal dose of ≤ 5 mg/day. Despite the lack of strong evidence about the long-term effect of steroids at minimal dose on the responsiveness to further therapy for relapse and the prevention of relapse, one study has reported that the long-term use of steroids might be helpful to prevent relapse [21]. Among eight patients in the present study without steroid dependency or resistance, five had been taking a minimal prednisolone dose for > 12 months at study enrollment. Second, there were no patients with AKI related to MCD in this study. AKI is reported in around 15% of adult MCD patients [7] and is related to late response to therapy [18]. Actually, relatively low eGFR was related to late response in the present study, although lower eGFR was due to aging rather than AKI. Third, the rapid response may have been due to the effect of tacrolimus. Although no randomized controlled trials have been conducted to verify the effect of tacrolimus on adult MCD, a few reports have been published about the effect of tacrolimus on MCD. One case with steroid- and cyclosporin-resistant MCD achieved a CR with high-dose prednisolone and tacrolimus at 10 day after therapy [15]. In a Chinese study of 12 adults with steroid-dependent MCD, tacrolimus with 0.5 mg/kg/day prednisolone induced CR in nearly 25% of patients by 2 weeks, 50% by 4 weeks, and 75% by 12 weeks, which was more effective than cyclophosphamide-based therapy, [8]. As reviewed in other reports, the effect of tacrolimus in MCD treatment might be related to its immunosuppressive effect [22] and its potent inhibitory effect on the release of cytokines [23]. The response rate in the present study was rapid, even within 2 weeks, and the rate of decrease of proteinuria in patients with CR within 2 weeks was almost exactly linear. This suggests that the effect of tacrolimus in inducing a CR was not only due to immunosuppression because of rapid response time, but also resulted from the nonimmune manner of stabilization of the actin skeleton in

podocytes [24]. Calcineurin inhibitor improved foot process motility and prevented podocyte-loss-related proteinuria by inhibiting the dephosphorylation of synaptopodin, which is one of the initial steps needed for cathepsin-L-medicated degradation of synaptopodin [25].

The AEs related to tacrolimus in the present study were tolerable. One patient needed to stop medication for 2 weeks due to severe abdominal pain but then continued taking it at reduced dose without problems. Diabetes mellitus developed in a 72-year-old patient at 8 weeks after therapy. No patient needed to stop their medication.

This was a pilot open-label study and limited by its small sample size and being performed only in a single center. Although the analysis was based on a short-term follow-up of only 16 weeks to reveal the CR rate in adult MCD patients, we followed up all patients and could obtain the findings of MCD by 45 weeks after treatment. Three of 14 (21.4%) patients had relapsed at 31 weeks, 36 weeks and 40 weeks after treatment. The period from CR to relapse was 23 weeks, 28 weeks and 38 weeks, respectively. The other limitation to verify the efficacy of tacrolimus would be that this study was not a comparative study. We only compared the efficacy of tacrolimus with low-dose steroid to that of previous studies but not to the other therapeutic group.

In summary, our results showed that tacrolimus and low-dose prednisolone treatment induced CR rapidly and effectively in Korean adults with MCD, including six cases of steroid dependency or resistance. Our results suggest the need for further investigation into the role of tacrolimus as the first-line therapy of MCD in anticipation of rapid CR with a lower rate of AEs. They also provide a clue to explain the mechanism of tacrolimus in terms of the correction of podocytopathy in MCD.

Conflict of interest

No conflict of interest.

Acknowledgments

Astellas Pharma Korea Inc. supplied tacrolimus for patients. There was no financial or other conflict of interest.

References

[1] Cameron JS: Nephrotic syndrome in the elderly. *Semin Nephrol* 16:319–329, 1996
[2] Zech P, Colon S, Pointet P, Deteix P, Labeeuw M, Leitienne P: The nephrotic syndrome in adults aged over 60: etiology, evolution and treatment of 76 cases. *Clin Nephrol* 17:232–236, 1982
[3] Chang JH, Kim DK, Kim HW, Park SY, Yoo TH, Kim BS, Kang SW, Choi KH, Han DS, Jeong HJ, Lee HY: Changing prevalence of glomerular diseases in Korean adults: a review of 20 years of experience. *Nephrol Dial Transplant* 24:2406–2410, 2009
[4] Tune BM, Mendoza SA: Treatment of the idiopathic nephrotic syndrome: regimens and outcomes in children and adults. *J Am Soc Nephrol* 8:824–832, 1997
[5] Bargman J.M.: Management of minimal lesion glomerulonephritis: evidence-based recommendations. Kidney Int Suppl 70:S3–S16, 1999
[6] Palmer SC, Nand K, Strippoli GF: Interventions for minimal change disease in adults with nephrotic syndrome. *Cochrane Database Syst Rev*. CD001537
[7] Waldman M, Crew RJ, Valeri A, Busch J, Stokes B, Markowitz G, D'Agati V, Appel G: Adult minimal-change disease: clinical characteristics, treatment, and outcomes. *Clin J Am Soc Nephrol* 2:445–453, 2007
[8] Li X, Li H, Chen J, He Q, Lv R, Lin W, Li Q, He X, Qu L, Suya W: Tacrolimus as a steroid-sparing agent for adults with steroid-dependent minimal change nephrotic syndrome. *Nephrol Dial Transplant* 23:1919–1925, 2008
[9] Inoue Y, Iijima K, Nakamura H, Yoshikawa N: Two-year cyclosporin treatment in children with steroid-dependent nephrotic syndrome. *Pediatr Nephrol* 13:33–38, 1999
[10] Prasad N, Gulati S, Sharma RK, Singh U, Ahmed M: Pulse cyclophosphamide therapy in steroid-dependent nephrotic syndrome. *Pediatr Nephrol* 19:494–498, 2004
[11] Ponticelli C, Edefonti A, Ghio L, Rizzoni G, Rinaldi S, Gusmano R, Lama G, Zacchello G, Confalonieri R, Altieri P: Cyclosporin versus cyclophosphamide for patients with steroid-dependent and frequently relapsing idiopathic nephrotic syndrome: a multicentre randomized controlled trial. *Nephrol Dial Transplant* 8: 1326–1332, 1993
[12] Latta K, von Schnakenburg C, Ehrich JH: A meta-analysis of cytotoxic treatment for frequently relapsing nephrotic syndrome in children. *Pediatr Nephrol* 16:271–282, 2001
[13] Falkiewicz K, Kaminska D, Nahaczewska W, Boratynska M, Owczarek H, Klinger M, Wozniak M, Patrzalek D, Szyber P: Renal function and tubular phosphate handling in long-term cyclosporine- and tacrolimus-based immunosuppression in kidney transplantation. *Transplant Proc* 38:119–122, 2006
[14] Denton MD, Magee CC, Sayegh MH: Immunosuppressive strategies in transplantation. *Lancet* 353:1083–1091, 1999
[15] Schweda F, Liebl R, Riegger GA, Krämer BK: Tacrolimus treatment for steroid- and cyclosporin-resistant minimal-change nephrotic syndrome. *Nephrol Dial Transplant* 12:2433–2435, 1997
[16] Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F: Chronic Kidney Disease Epidemiology Collaboration: using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 145:247–254, 2006
[17] Huang JJ, Hsu SC, Chen FF, Sung JM, Tseng CC, Wang MC: Adult-onset minimal change disease among Taiwanese: clinical features, therapeutic response, and prognosis. *Am J Nephrol* 21:28–34, 2001
[18] Nakayama M, Katafuchi R, Yanase T, Ikeda K, Tanaka H, Fujimi S: Steroid responsiveness and frequency of relapse in adult (–) onset minimal change nephrotic syndrome. *Am J Kidney Dis* 39:503–512, 2002
[19] Report of the International Study of Kidney Disease in Children: The primary nephrotic syndrome in children. Identification of patients with minimal change nephrotic syndrome from initial response to prednisone. A report of the International Study of Kidney Disease in Children. *J Pediatr* 98:561–564, 1981
[20] Report of the International Study of Kidney Disease in Children: Nephrotic syndrome in children. A randomized trial comparing two prednisone regimens in steroid-responsive patients who relapse early. Report of the international study of kidney disease in children. *J Pediatr* 95:239–243, 1979
[21] Siegel N.J.: Minimal change nephrotic syndrome. In: Primer on Kidney Disease, 3rd edition. San Diego: Academic Press, 145–146, 2001
[22] Gummert JF, Ikonen T, Morris RE: Newer immunosuppressive drugs: a review. *J Am Soc Nephrol* 10:1366–1380, 1999
[23] Sasakawa Y, Sakuma S, Higashi Y, Sasakawa T, Amaya T, Goto T: FK506 suppresses neutrophil chemoattractant production by peripheral blood mononuclear cells. *Eur J Pharmacol* 403: 281–288, 2000
[24] Faul C, Donnelly M, Merscher-Gomez S, Chang YH, Franz S, Delfgaauw J, Chang JM, Choi HY, Campbell KN, Kim K, Reiser J, Mundel P: The actin cytoskeleton of kidney podocytes is a direct target of the antiproteinuric effect of cyclosporine A. *Nat Med* 14:931–938, 2008