Mycophenolate Mofetil Treatment in Primary Glomerular Disease: One-Year Follow-Up in Steroid Dependent and Resistant Nephrotic Syndrome

Adis Tasanarong MD*,
Supachai Thitiarchakul MD*

** Nephrology Division, Faculty of Medicine, Thammasat University*

Objective: *Treatment of primary nephrotic syndrome (NS) with steroid and cyclophosphamide may be unsuccessful and have much toxicity. Therefore, the authors evaluated the outcome of mycophenolate mofetil (MMF) treatment in these patients.*

Material and Method: *Fourteen primary NS patients who had failure to steroid and/or cyclophosphamide therapy were treated by MMF for at least 3 months as alternative treatment. Median ± SD (range) of urine protein to creatinine index (UPCI), serum albumin, serum creatinine, serum cholesterol and dose of prednisolone at the start, 1mo, 3 mo, 6mo, and 12 mo after MMF therapy were compared.*

Results: *In the study group, the mean of UPCI decreased significantly from 2.79 ± 8.1 to 1.81 ± 1.54 (p = 0.02) at 12 months after the MMF therapy with no significant change in the mean serum creatinine from 1.14 ± 0.45 to 1.27 ± 0.67 mg/dL. The mean serum albumin increased significantly from 2.87 ± 0.56 to 3.46 ± 0.76 g/dL (p = 0.05) and the mean of prednisolone dosage decreased significantly from 34.64 ± 19.16 to 11.11 ± 8.58 mg/day (p = 0.004). For patients with IgM Nephropathy (IgMN), one of three steroid dependent patients presented with improved renal function. One of two patients with focal segmental glomerulosclerosis (FSGS) had a complete remission and one of two patients with IgA nephropathy (IgAN) had improved renal function with partial remission.*

Conclusion: *MMF therapy in NS patients with primary glomerular disease was well tolerated and safe. These efficacies can improve NS, stabilize renal function, and achieve steroid withdrawal.*

Keywords: *Steroid dependent and resistant nephrotic syndrome, Mycophenolate mofetil, primary glomerular disease*

J Med Assoc Thai 2006; 89 (Suppl 2): S218-27
Full text. e-Journal: *http://www.medassocthai.org/journal*

Nephrotic syndrome (NS) is a common disorder, characterized by alterations of permselectivity and structure at the glomerular capillary wall, resulting in its inability to restrict the urinary loss of protein. Common treatment with steroid in some patients with NS is unresponsive or relapses. Therefore, advance in understanding the pathogenesis and treatment of glomerular diseases has progressed to develop new immunosuppressive drugs[1-3]. Many immunosuppressive regimens used in solid organ transplantation have established their efficacy and safety in glomerular diseases including lupus nephritis. mycophenolate mofetil (MMF) is a new immunosuppressive drug and has been widely used in reducing the incidence of acute rejection in renal allograft[4,5]. It also demonstrated its efficacy in the treatment of lupus nephritis[6,7]. In addition, an increasing number of publications have reported favorable responses to MMF in experimental models of glomerular diseases[8-11], and several clinical trials in patients with primary glomerular disease[12-14].

The purpose of the present study was to determine the efficacy as an alternative treatment in a group of patients with primary glomerular disease with

Correspondence to : Tasanarong A, Nephrology Division, Faculty of Medicine, Thammasat University, Bangkok 12120, Thailand.

steroid and/or cyclophosphamide dependence or resistant NS.

Material and Method

Patients

Fourteen Thai adult patients with idiopathic NS who attended the outpatient nephrology clinic of Thammasat Chalerm Prakiat Hospital between 2004 and 2005 and met the criteria of steroid dependence or resistance were studied. Steroid dependence was defined by the need of steroids to maintain the state of complete remission but relapse as soon as the steroid dosage was tapered. Steroid resistance was defined by proteinuria >3 g/day even though the patient had received conventional steroid therapy for more than 16 weeks.

Renal biopsy was performed in ten patients, and proved to be glomerulonephritis prior to cytotoxic treatment. Patients with secondary causes of glomerulonephritis were excluded from the present study. All patients received at least three months of treatment with MMF. The two most common indications for initiating the MMF adjunctive therapy in these patients were steroid dependent or steroid resistant nephrotic syndrome. Other indications included cyclophosphamide dependent or resistant nephrotic syndrome or serious side effects from or intolerance of steroid or cyclophosphamide, and deteriorating renal function.

Treatment of patients

The present study was designed as a retrospective analysis. The enrolled patients were initiated with MMF with the dosage of 0.25 to 0.5 g BID and increased to the dosage of 0.5 to 1.0 g BID as appropriate or tolerated. The MMF dose was decreased by 25 to 33% or split into 4 divided doses per day in patients who had persistent or moderate to severe gastrointestinal symptoms. MMF was discontinued temporarily if the total white blood cell (WBC) in complete blood count (CBC) decreased less than 4000/ L or if the patient developed a febrile illness or unacceptable gastrointestinal symptoms. It was discontinued permanently if evidence of malignancy was detected.

At the initiation of MMF therapy, all patients received a variable dose of prednisolone ranging from a very low dose to high dose daily (1 mg/kg/day). In the absence of relapse, an effort was made to taper and, if possible, discontinue the steroid over the first 4 to 6 months of MMF therapy.

In hypertensive patients, one or more antihypertensive agents were prescribed and the dosage was adjusted in an attempt to achieve the target blood pressure of $\leq$ 130/80 mm Hg. Almost all patients received either an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin II receptor blocker (ARB) therapy prior to the initiation of MMF. In most of those patients, who did not receive either agent, they actually received one of them before but discontinued due to their side effects. All patients were advised on appropriate dietary restrictions including a low sodium (2 g/day) diet. Almost all patients received HMG CoA reductase inhibitors in an attempt to achieve the target LDL level of $\leq$ 100 mg/dL

Follow-up

Assessment of clinical and laboratory parameters were monitored and recorded on a monthly basis for the initial three months of MMF treatment, and variable intervals afterwards. Laboratory parameters included CBC, urine analysis (UA), serum creatinine (SCr), blood urea nitrogen (BUN), serum albumin, fasting lipid profiles (cholesterol, triglycerides, and HDL). urine for protein and creatinine index (UPCI) were measured from spontaneously voided or 'spot' morning urine samples. The samples were collected from the patient during the clinic visit and approximately the same time of day throughout the study period. In addition, the data of using ACEI/ARB and HMG CoA reductase inhibitors were collected from the medical records, where there was a definite comment whether or not those medications were used.

Outcome measures

The present study showed the outcome with the consecutive treatment course with MMF and provides additional information about the clinical course. The primary outcomes compared the change in the UPCI and SCr, between the levels at the beginning and the end of the MMF treatment period. These were also assessed at the months 1, 3, 6, and 12. For proteinuria, a complete remission was defined as a reduction in UPCI to $\leq$ 0.3; a partial remission was defined as a reduction of $\geq$ 50% in UPCI, but with the end result of UPCI still $\geq$ 0.3; stable proteinuria was defined as the end result of UPCI was $\geq$ 0.3 and with $\leq$ 50% reduction of UPCI, a deterioration was defined as any increase in the UPCI over a baseline value that was $\geq$ 0.3.

Responses in renal function, in these patients were assessed based on changes in SCr before and at the end of treatment. Renal insufficiency was defined as a SCr > 1.4 mg/dL for men and > 1.2 mg/dL for women. A favorable response included either a > 15% decreased

in SCr; stable renal function was defined as a change in SCr within 15% of the initial value; deterioration of renal function was defined as an increase in SCr >15% of the initial value prior to the MMF treatment.

Statistical analysis

Data analysis was assessed by time trend analysis and using box plots to identify the outlining values for a given distribution; the accuracy of the identified values was confirmed by comparison with the original clinical record. Wilcoxon signed-ranks test was used as appropriate to compare data from the start and end of the treatment period, as defined above. In cases where there was incomplete paired data, analysis was conducted on available data. In all analyses, a two-tailed I error rate of 0.05 was used. Analyses were performed using SPSS 13.0 for windows (SPSS, Inc., Cary, NC, USA). Values were presented as mean $\pm$ SD unless other statistic tools were used.

Results

Total study group

Fourteen patients (6 females, 8 males) with primary NS were included in the present study. The mean ($\pm$ standard deviation) age was 37.8 $\pm$ 15.9 years. The encountered primary glomerular diseases included IgM nephropathy (IgMN) 21.43% (n = 3), focal segmental glomerulosclerosis (FSGS) 14.3% (n = 2), membrano proliferative glomerulo nephritis (MPGN) 7.1% (n = 1), membranous nephropathy (MN) 14.3% (n = 2), IgA nephropathy (IgAN) 14.3% (n = 2), and no biopsy done 28.6% (n = 4) (Table 1). Of all patients, five (35.7%) were steroid resistant and nine were steroid dependent NS. Moreover, eight patients (57.1%) in the present study failed for prior cyclophosphamide treatment. At the time of the present study, 6 patients (42.9%) had nephrotic range proteinuria and 4 patients (28.6%) had renal insufficiency. Baseline UPCI was 2.79 $\pm$ 1.8 mg/dL and SCr was 1.14 $\pm$ 0.45 mg/dL (Table 1). All patients were basically treated with steroids in addition to MMF.

The UPCI before MMF treatment was 2.79 $\pm$ 1.8 and decreased significantly (p = 0.02) to 1.81 $\pm$ 1.54 at the end of the MMF treatment period (Fig. 1A, Table 1). Over the course of treatment, 1 patient (7.1%) had a complete remission, with 97.3% reduction of proteinuria; 4 patients (28.6%) had a partial remission, and with 61.1% reduction of proteinuria, 7 patients (50%) had stable proteinuria, and only 1 patient (7.1%) had an increase in proteinuria. Four of the six patients (66.66%) with nephrotic range proteinuria improved to non-nephrotic range proteinuria by the end of the present study.

There was no significant change in the SCr over the course of the present study. The change in SCr from 1.14 $\pm$ 0.45 before MMF treatment to 1.27 $\pm$ 0.67 mg/dL (p = 0.58; Fig. 1B, Table 1). After the MMF therapy, the renal function returned to normal in 3 of 4 patients (75%) with initial renal insufficiency, these included one with IgMN, one with MPGN, and one with IgAN. The only patient with MN had deterioration of the renal function.

The serum albumin increased significantly from 2.87 $\pm$ 0.56 g/dL before the MMF treatment to 3.46 $\pm$ 0.76 g/dL (p = 0.05; Fig. 1C, Table 1). The serum cholesterol decreased from 244.2 $\pm$ 60.2 before MMF treatment to 209.2 $\pm$ 40.7 mg/dL (p = 0.14; Fig. 1D, Table 1). Not surprisingly, there was a significant change in

Table 1. Mean values of UPCI, serum creatinine, serum albumin, serum cholesteral, and dose of prednisolone in overall group and subgroups of primary glomerular diseases before and at the end of MMF treatment

	UPCI		Serum Creatinine		Serum Albumin		Serum Cholesteral		Dose of Prednisolone	
	Prior MMF	Post MMF	Prior MMF	Post MMF	Prior MMF	Post MMF	Prior MMF	Post MMF	Prior MMF	Post MMF
Overall group (n = 14)	2.79	1.81	1.14	1.27	2.84	3.46	244.2	209.2	34.64	11.11
IgM Nephropathy (n = 3)	1.75	1.47	1.2	1.13	3.25	3.63	207	182	11.67	6.67
FSGS (n = 2)	3.16	1.2	0.9	1.2	2.55	4.05	265.5	182	15	7.5
MPGN (n = 1)	2.94	3.4	1.5	0.7	3.0	3.0	203	200	45	40
Membranous Nephropathy (n = 2)	4.76	3.57	1.4	1.77	2.85	3.15	197	174	52.5	20
IgA Nephropathy (n = 2)	1.95	1.45	1.5	1.5	2.9	3.6	244	271	45	12.5
Other Nephrotic Syndrome (n = 4)	2.79	1.86	0.8	0.4	2.7	3.2	326	229	45	15

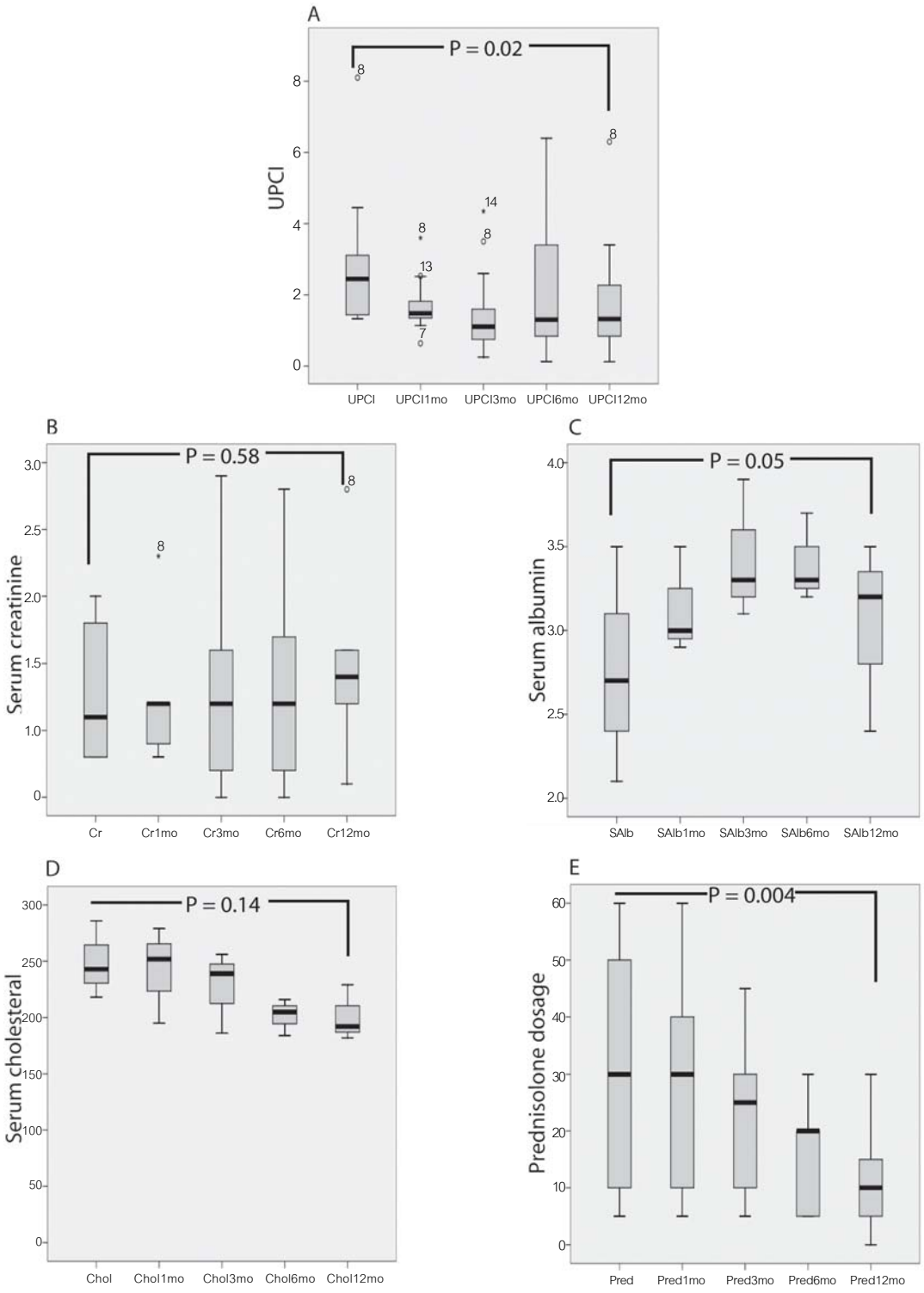

Fig. 1 Median plus interquartile range of (A) urine protein-to-creatine ratio (UPCI), (B) serum creatinine, (C) serum albumin, (D) serum cholesterol and (E) prednisolone dosage prior start MMF therapy, at 1 mo, 3 mo, 6 mo, and 12 mo after MMF therapy of the overall group

prednisolone dosage, which decreased from 34.64 ± 19.16 mg/day before the MMF treatment to 11.11 ± 8.58 mg/day (p = 0.004; Fig. 1E, Table 1) at the end of the MMF treatment period.

Steroid and cyclophosphamide resistant NS patients

Eight of fourteen patients had previously failed to respond to both steroid and cyclophosphamide. The resistant patients were: two with IgMN, two with FSGS, one with MN, one with IgAN and two that had no biopsy NS. One FSGS patient had a complete remission. The two no biopsy NS patients had partial response and four patients had stable proteinuria. Only one patient had resistance to MMF shown by increased proteinuria. In these eight patients, UPCI decreased from 3.35 ± 2.18 to 2.17 ± 1.81 at the end of the MMF treatment (p = 0.128; Fig. 2A). The serum albumin increased from 2.46 ± 0.46 g/dL to 3.31 ± 0.88 g/dL (p = 0.135; Fig. 2B) after the MMF treatment. The change in serum creatinine was from 1.01 ± 0.36 to 1.8

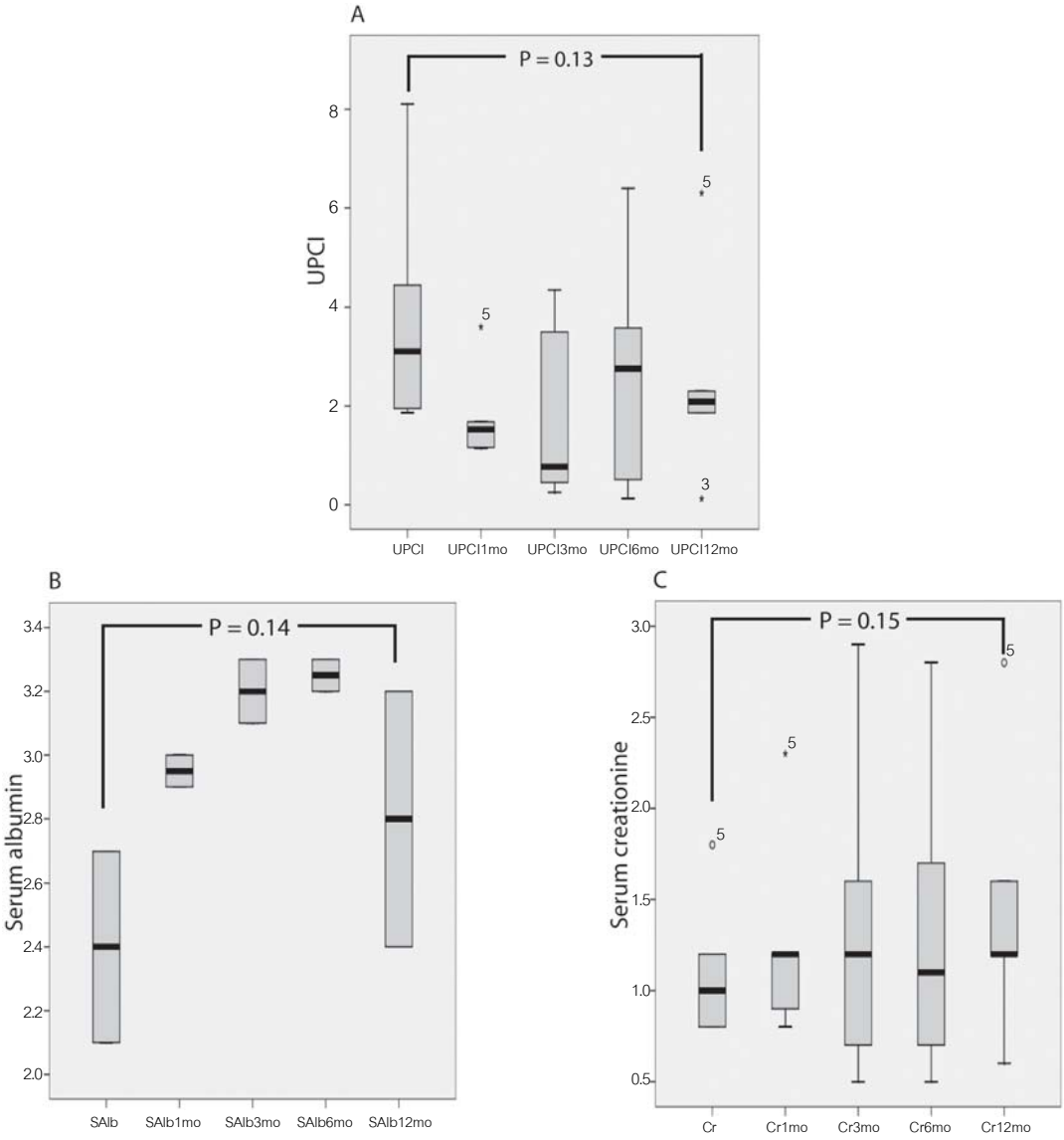

Fig. 2 Median plus interquartile range of (A) urine protein-to-creatine ratio (UPCI), (B) serum albumin, and (C) serum creatinine prior start MMF therapy, at 1 mo, 3 mo, 6 mo, and 12 mo after MMF therapy of the patient with steroid and cyclophosphamide resistant group

before the MMF treatment to 1.29 ± 0.78 mg/dL (p = 0.15; Fig. 2C) at the end of the MMF treatment.

Separate in each study subgroup

The changes of the mean values of UPCI, serum creatinine, serum albumin, serum cholesterol and dosage of prednisolone in each primary glomerular disease are demonstrated in Table 1. For the patient with IgMN, improved renal function was presented in one of three steroid dependent patients and other patient had stable renal function. All of the IgMN patients had stable proteinurea at 12 months after the MMF treatment. One of two patients with FSGS had a complete remission and the other patient showed stable renal function but increased proteinuria at the end of the present study. Only one patient with MPGN had improved renal function but increased proteinuria. Interestingly, two patients with MN had stable proteinuria but one of them had renal function deterioration. Finally, one of two patients with IgAN had improved renal function with partial remission and the other patient showed stable proteinuria and renal function.

Adverse effects

Although, many adverse effects can be found in studies of patients who received MMF, only one patient developed diarrhea in the present study. The authors divided MMF into 4 divided doses daily and diarrhea disappeared. Nobody developed evidence of malignancy or leucopenia (total WBC less than 4000/L) or a febrile illness.

Discussion

The present study evaluated the response to MMF therapy in idiopathic NS patients with both steroid and steroid/cyclophosphamide resistance. The authors enrolled patients with primary glomerular disease, predominantly IgMN, FSGS, MPGN, MN and IgAN but did not include patients with systemic diseases, eg. lupus nephritis or vasculitis. The results demonstrated that the majority of treated patients had benefited from MMF therapy, whether in terms of markedly decreased cumulative dose of steroid, complete or partial remission of proteinuria and maintained or improved renal function. Patients who responded to MMF therapy were not correlated with the degree of proteinuria. Not surprisingly, some patients failed to respond to the MMF therapy. This was similar to what happened to other immunosuppressive agents, eg. cyclosporine A, chlorambucil etc. A proportion of responsive patients were found to be MMF dependent and relapsed when MMF was discontinued.

Many mechanisms of action and immunosuppressive properties of MMF in the treatment of glomerular diseases have been proposed. mycophenolic acid (MPA) is an active metabolite of MMF that inhibits T and B lymphocyte proliferation, B lymphocyte antibody production, as well as the glycosylation and expression of adhesion molecules[15-18]. Further more, MPA has been shown to inhibit vascular smooth muscle cell, mesangial cell proliferation[19], and induces apoptosis in activated T cells[20]. Combination of these actions could be observed in the amelioration of various experimental models of glomerular disease, including hyperfiltration injury in the kidney[8-10], mesangial proliferative nephritis[21], Heymann nephritis[22], and murine lupus nephritis[23,24]. These same mechanisms are likely to be effective in the amelioration of the inflammation and/or slowing the progression in glomerular diseases.

IgMN may be a variant of minimal change disease. Treatment with steroids can induce complete remission in only 20 to 30% of patients[25]. Both steroid dependent and resistant IgMN are problematic because of the need for repeated high dose steroid. There has been less information in immuno-suppressive agents in this condition. In the present study, two of three IgMN patients with steroid and cyclophosphamide resistance had stable renal function after treatment with MMF. One in this condition had renal insufficiency before MMF treatment and improved SCr level after MMF treatment. All IgMN patients were shown to have stable proteinuria after treatment and also had steroid sparing effects. These results suggested that MMF therapy was effective and safe in IgMN patients. A more prolonged course of MMF treatment may ultimately lead to complete or partial remission and improve renal function.

FSGS is the most common cause of primary glomerular disease leading to end-stage renal disease (ESRD). Nephrotic range proteinuria and decrease in renal function are independent risk factors for progression to ESRD. Spontaneous remission rate is very low but remission of NS in patients with FSGS predicts long term renal outcome. In adults with FSGS, steroid and cyclosporine A are effective in inducing complete remission and maintaining stable renal function[26,27]. There have been few clinical trials of MMF treatment in FSGS. However, MMF has been shown to be effective in some patients who were resistant to other therapies demonstrated by a decrease of about 50% in proteinuria and the capability to maintain stable renal

function[28,29]. Similar to the present study, one of two patients with FSGS responded to complete remission but the other had progressive proteinuria after the MMF treatment. Fortunately, stable renal function could be maintained in both of them. Therefore, MMF therapy seems to be more effective in IgMN than FSGS patients.

MN remains the most common form of NS in adults[30]. MN is often complicated by NS with moderate to severe edema/anasarca. However, treatment in MN has been problematic in patients who had risk factors for progressive loss of renal function[31]. Treatment considerations are quite controversial in steroid therapy. In some clinical trials, patients generally respond suboptimally to steroids, and often manifest steroid dependency. Cyclosporine A and chlorambucil have been reported to be effective, but usually associated with dependency[32,33]. MMF was found to be effective in improving nephrotic proteinuria by more than 50% without a decline in renal function and marked clinical improvement[34,28]. In the present study, both patients with MN showed stable proteinuria after MMF treatment as in other studies. However, one of two patients with MN had stable renal function but the other one had progressive loss of renal function. Interestingly, this patient also had risk factors for progressive loss of renal function since starting the MMF therapy. Nevertheless, MMF had steroid-sparing effects in the majority of patients. From these data, treatment with MMF in MN patient should be effective if the patient does not have risk factors for progressive loss of renal function.

IgAN is the most common cause of all glomerular diseases worldwide[35,36]. The role of immunosuppressive therapy in this condition is unclear. Steroids and cytotoxic agents have demonstrated their efficacy and safety in some clinical trials, however, MMF therapy in IgAN still has few publications. MMF has shown benefits in non-progressive IgAN patients for greater reduction in proteinuria and improved renal function[37,38], but not different from placebo in the Belgium clinical trial[39]. In progressive IgAN patients, treatment with MMF showed a 50% increase in baseline SCr and progressed to ESRD. In the present study, one of two patients with IgAN had partial remission and the other had stable proteinuria after treatment with MMF. Furthermore, one of two patients with IgAN had improved renal function and the other had stable renal function. So, the responsiveness to MMF therapy in IgAN patient seems to be good, similar to IgMN patients.

In general, the presented patients tolerated very well to the MMF dosage that the authors used. Only one patient had adverse effects from MMF, similar to those identified in organ transplant recipients. The most common adverse effects were gastrointestinal complaints of some nausea/vomiting and/or loose stool and were improved after prescribing divided doses.

In summary, the results from the present study in a substantial number of patients firmly establish the efficacy of MMF in the treatment of primary glomerular diseases, especially for steroid/cyclophosphamide resistant IgMN, FSGS, and IgAN. However, for proper treatment of glomerular diseases with MMF, further prospective, well-designed clinical trials with an appropriate study population have to be conducted. The clinical improvement of patients occurred with the combination of MMF and variable dosages of steroid. Furthermore, the present results demonstrated that MMF also has major steroid sparing effects. Given the lack of nephrotoxicity, hemodynamic and metabolic effects, MMF represents a suitable alternative agent to the calcineurin-inhibitors and other immuno-suppressive drugs for the treatment of many glomerular diseases.

References

1. Appel GB. Glomerulonephritis. In: Goldman L, Ausiello D, Bennett JC, Cecil RL, editors. Cecil textbook of medicine. 22nd ed. Philadelphia: WB Saunders; 2004: 726.
2. Appel GB, Radhakrishnan J, D'Agati V. Secondary glomerular diseases. In: Brenner, B, Levine SA, eds. Brenner & Rector's the kidney. 7th ed. Philadelphia: Elsevier Press; 2004: 1381-482.
3. Zimmerman R, Radhakrishnan J, Valeri A, Appel G. Advances in the treatment of lupus nephritis. Annu Rev Med 2001; 52: 63-78.
4. The Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group. A blinded, randomized clinical trial of mycophenolate mofetil for the prevention of acute rejection in cadaveric renal transplantation. Transplantation 1996; 61: 1029-37.
5. Halloran P, Mathew T, Tomlanovich S, Groth C, Hooftman L, Barker C. Mycophenolate mofetil in renal allograft recipients: a pooled efficacy analysis of three randomized, double-blind, clinical studies in prevention of rejection. The International Mycophenolate Mofetil Renal Transplant Study Groups. Transplantation 1997; 63: 39-47.
6. Dooley MA, Cosio FG, Nachman PH, Falkenhain ME, Hogan SL, Falk RJ, et al. Mycophenolate

mofetil therapy in lupus nephritis: clinical observations. J Am Soc Nephrol 1999; 10: 833-9.
7. Chan TM, Li FK, Tang CS, Wong RW, Fang GX, Ji YL, et al. Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. Hong Kong-Guangzhou Nephrology Study Group. N Engl J Med 2000; 343: 1156-62.
8. Fujihara CK, Malheiros DM, Zatz R, Noronha ID. Mycophenolate mofetil attenuates renal injury in the rat remnant kidney. Kidney Int 1998; 54: 1510-9.
9. Romero F, Rodriguez-Iturbe B, Parra G, Gonzalez L, Herrera-Acosta J, Tapia E. Mycophenolate mofetil prevents the progressive renal failure induced by 5/6 renal ablation in rats. Kidney Int 1999; 55: 945-55.
10. Remuzzi G, Zoja C, Gagliardini E, Corna D, Abbate M, Benigni A. Combining an antiproteinuric approach with mycophenolate mofetil fully suppresses progressive nephropathy of experimental animals. J Am Soc Nephrol 1999; 10: 1542-9.
11. Corna D, Morigi M, Facchinetti D, Bertani T, Zoja C, Remuzzi G. Mycophenolate mofetil limits renal damage and prolongs life in murine lupus autoimmune disease. Kidney Int 1997; 51: 1583-9.
12. Nowack R, Birck R, van der Woude FJ. Mycophenolate mofetil for systemic vasculitis and IgA nephropathy. Lancet 1997; 349: 774.
13. Chandra M, Susin M, Abitbol C. Remission of relapsing childhood nephrotic syndrome with mycophenolate mofetil. Pediatr Nephrol 2000; 14: 224-6.
14. Miller G, Zimmerman R III, Radhakrishnan J, Appel G. Use of mycophenolate mofetil in resistant membranous nephropathy. Am J Kidney Dis 2000; 36: 250-6.
15. Eugui EM, Almquist SJ, Muller CD, Allison AC. Lymphocyte-selective cytostatic and immunosuppressive effects of mycophenolic acid in vitro: role of deoxyguanosine nucleotide depletion. Scand J Immunol 1991; 33: 161-73.
16. Allison AC, Eugui EM, Sollinger HW. Mycophenolate mofetil (RS-61443): Mechanism of action and effects in transplantation. Transplant Rev 1993; 7: 129-39.
17. Allison AC, Kowalski WJ, Muller CJ, Waters RV, Eugui EM. Mycophenolic acid and brequinar, inhibitors of purine and pyrimidine synthesis, block the glycosylation of adhesion molecules. Transplant Proc 1993; 25: 67-70.
18. Blaheta RA, Leckel K, Wittig B, Zenker D, Oppermann E, Harder S, et al. Mycophenolate mofetil impairs transendothelial migration of allogeneic CD4 and CD8 T-cells. Transplant Proc 1999; 31: 1250-2.
19. Hauser IA, Renders L, Radeke HH, Sterzel RB, Goppelt-Struebe M. Mycophenolate mofetil inhibits rat and human mesangial cell proliferation by guanosine depletion. Nephrol Dial Transplant 1999; 14: 58-63.
20. Cohn RG, Mirkovich A, Dunlap B, Burton P, Chiu SH, Eugui E, et al. Mycophenolic acid increases apoptosis, lysosomes and lipid droplets in human lymphoid and monocytic cell lines. Transplantation 1999; 68: 411-8.
21. Ziswiler R, Steinmann-Niggli K, Kappeler A, Daniel C, Marti HP. Mycophenolic acid: a new approach to the therapy of experimental mesangial proliferative glomerulonephritis. J Am Soc Nephrol 1998; 9: 2055-66.
22. Penny MJ, Boyd RA, Hall BM. Mycophenolate mofetil prevents the induction of active Heymann nephritis: association with Th2 cytokine inhibition. J Am Soc Nephrol 1998; 9: 2272-82.
23. McMurray RW, Elbourne KB, Lagoo A, Lal S. Mycophenolate mofetil suppresses autoimmunity and mortality in the female NZB x NZW F1 mouse model of systemic lupus erythematosus. J Rheumatol 1998; 25: 2364-70.
24. Van Bruggen MC, Walgreen B, Rijke TP, Berden JH. Attenuation of murine lupus nephritis by mycophenolate mofetil. J Am Soc Nephrol 1998; 9: 1407-15.
25. Alexopoulos E, Papagianni A, Stangou M, Pantzaki A, Papadimitriou M. Adult-onset idiopathic nephrotic syndrome associated with pure diffuse mesangial hypercellularity. Nephrol Dial Transplant 2000; 15: 981-7.
26. Korbet SM. Treatment of primary focal segmental glomerulosclerosis. Kidney Int 2002; 62: 2301-10.
27. Cattran DC, Appel GB, Hebert LA, Hunsicker LG, Pohl MA, Hoy WE, et al. A randomized trial of cyclosporine in patients with steroid-resistant focal segmental glomerulosclerosis. North America Nephrotic Syndrome Study Group. Kidney Int 1999; 56: 2220-6.
28. Choi MJ, Eustace JA, Gimenez LF, Atta MG, Scheel PJ, Sothinathan R, et al. Mycophenolate mofetil treatment for primary glomerular diseases. Kidney Int 2002; 61: 1098-114.
29. Cattran DC, Wang MM, Appel G, Matalon A, Briggs W. Mycophenolate mofetil in the treatment of focal segmental glomerulosclerosis. Clin

Nephrol 2004; 62: 405-11.
30. Glassock RJ. Diagnosis and natural course of membranous nephropathy. Semin Nephrol 2003; 23: 324-32.
31. Cattran DC. Membranous nephropathy: quo vadis? Kidney Int 2002; 61: 349-50.
32. Cattran DC, Appel GB, Hebert LA, Hunsicker LG, Pohl MA, Hoy WE, et al. Cyclosporine in patients with steroid-resistant membranous nephropathy: a randomized trial. Kidney Int 2001; 59: 1484-90.
33. Ponticelli C, Altieri P, Scolari F, Passerini P, Roccatello D, Cesana B, et al. A randomized study comparing methylprednisolone plus chlorambucil versus methylprednisolone plus cyclophosphamide in idiopathic membranous nephropathy. J Am Soc Nephrol 1998; 9: 444-50.
34. Miller G, Zimmerman R, III, Radhakrishnan J, Appel G. Use of mycophenolate mofetil in resistant membranous nephropathy. Am J Kidney Dis 2000; 36: 250-6.
35. Donadio JV, Grande JP. IgA nephropathy. N Engl J Med 2002; 347: 738-48.
36. D'Amico G. Natural history of idiopathic IgA nephropathy: role of clinical and histological prognostic factors. Am J Kidney Dis 2000; 36: 227-37.
37. Chen X, Chen P, Cai G, Wu J, Cui Y, Zhang Y, et al. A randomized control trial of mycophenolate mofeil treatment in severe IgA nephropathy. Zhonghua Yi Xue Za Zhi 2002; 82: 796-801.
38. Tang S, Leung JC, Tang AW. The Hong Kong IgA Study Group. A prospective randomized case controlled trial on the efficacy of MMF in IgA nephropathy patients with persistent proteinuria despite angiotensin blockade [Abstract]. Paper presented at: American Society of Nephrology; November 12-17, 2003; San Diego, CA.
39. Maes BD, Oyen R, Claes K, Evenepoel P, Kuypers D, Vanwalleghem J, et al. Mycophenolate mofetil in IgA nephropathy: results of a 3-year prospective placebo-controlled randomized study. Kidney Int 2004; 65: 1842-9.

ผลการรักษา 1 ปี ด้วยยาไมโคฟีโนเลท โมฟีทิล ในผู้ป่วยโรคทางโกลเมอรูลัสชนิดปฐมภูมิ ที่มีภาวะ เนฟโฟรติกชนิดที่ไม่ตอบสนองต่อการรักษาด้วยยาสเตียรอยด์

อดิศว์ ทัศณรงค์, ศุภชัย ฐิติอาชากุล

วัตถุประสงค์: การรักษาผู้ป่วยภาวะเนฟโฟรติก ด้วยยาสเตียรอยด์และไซโครฟอสฟาไมด์ ในบางครั้งอาจจะไม่ประสบผลสำเร็จ และอาจจะมีภาวะแทรกซ้อนหลายอย่าง ดังนั้นทางคณะผู้วิจัยจึงได้ทำการวิเคราะห์ผลของการรักษาด้วยยาไมโคฟีโนเลท โมฟีทิล ในผู้ป่วยเหล่านี้

วัสดุและวิธีการ: ผู้ป่วยภาวะเนฟโฟรติก ที่ไม่ตอบสนองต่อการรักษาด้วยยาสเตียรอยด์และไซโครฟอสฟาไมด์ จำนวน 14 คน ได้เข้าร่วมการศึกษานี้ โดยรับการรักษาด้วยยาไมโคฟีโนเลท โมฟีทิล นานคนละอย่างน้อย 3 เดือน ผู้ป่วยทั้งหมดได้รับการตรวจวัด อัตราส่วนของโปรตีนและครีเอตินินในปัสสาวะ (UPCI), ระดับอัลบูมิน, ครีเอตินินและโคเลสเตอรอลในกระแสเลือด รวมทั้งได้จดบันทึกขนาดของยาสเตียรอยด์ ตั้งแต่ขณะที่เริ่มต้นรักษาด้วยยาไมโคฟีโนเลท โมฟีทิลที่ 1 เดือน, 3 เดือน, 6 เดือน และ 12 เดือน หลังการรักษาด้วยยาไมโคฟีโนเลท โมฟีทิล

ผลการศึกษา: ในผู้ป่วยทั้งหมด พบว่า ค่าเฉลี่ยของ UPCI ลดลงอย่างมีนัยสำคัญทางสถิติ จาก 2.79 $\pm$ 8.1 เป็น 1.81 $\pm$ 1.54 ($p = 0.02$) ที่ 12 เดือนหลังการรักษาด้วยยาไมโคฟีโนเลท โมฟีทิล รวมทั้งไม่พบการเปลี่ยนแปลงของค่าเฉลี่ยของซีรัมครีเอตินิน คือ 1.14 $\pm$ 0.45 เทียบกับ 1.27 $\pm$ 0.67 มล./ดล. ค่าเฉลี่ยของซีรัมอัลบูมินมีค่าเพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติจาก 2.87 $\pm$ 0.56 เป็น 3.46 $\pm$ 0.76 มล./ดล. ($p = 0.05$) และค่าเฉลี่ยของขนาดของยา เพรดนิโซโลนลดลงอย่างมีนัยสำคัญทางสถิติจากขนาด 34.64 $\pm$ 19.16 เหลือ 11.11 $\pm$ 8.58 มก./วัน ($p = 0.004$) สำหรับผู้ป่วย IgM nephropathy พบว่าผู้ป่วย 1 ราย ใน 3 ราย ที่มีภาวะไตเสื่อม ตั้งแต่เริ่มการรักษามีหน้าที่การทำงานของไตดีขึ้น ผู้ป่วย focal segmental glomerulosclerosis 1 ใน 2 ราย หลังการรักษาเข้าสู่ภาวะ complete remission และ 1 ใน 2 รายของผู้ป่วย IgA nephropathy มีหน้าที่การทำงานของไตดีขึ้นร่วมกับปริมาณโปรตีนในปัสสาวะลดลงมากกว่าร้อยละ 50

สรุป: การรักษาผู้ป่วยภาวะเนฟโฟรติกที่เกิดจากโรคทางโกลเมอรูลัส ด้วยยาไมโคฟีโนเลท โมฟีทิลมีความปลอดภัย ประสิทธิภาพของยานี้สามารถที่จะทำให้ภาวะเนฟโฟรติกดีขึ้น โดยการลดปริมาณโปรตีนในปัสสาวะ, คงค่าระดับซีรัมครีเอตินินในกระแสเลือดและลดขนาดของการใช้ยาสเตียรอยด์