Efficacy and Safety of Mycophenolate Mofetil in Children with Steroid Dependent Nephrotic Syndrome

Taek Jin Lim, M.D.,
Seong Heon Kim, M.D.,
Su Young Kim, M.D.

Department of Pediatrics, Pusan
National University Children's Hospital,
Yangsan/Gyeongnam, Republic of
Korea

Corresponding author:

Su Young Kim, M.D.
Department of Pediatrics, Pusan National
University Children's Hospital, 20, Geumo-
ro, Mulgeum-eup, Yangsan, Gyeongnam,
Republic of Korea
Tel: +82-55-360-2180
Fax: +82-55-360-2181
E-mail: suyung@pusan.ac.kr

Received: 20 September 2015

Revised: 13 October 2015

Accepted: 25 October 2015

Purpose: Steroid dependent nephrotic syndrome (SDNS) is a chronic illness in childhood hard to treat. Steroid sparing drugs are often used, because long-term steroid therapy can cause severe side effects. We studied to compare efficacy between MMF and other drugs including cyclosporine and levamisole.

Methods: This study was performed retrospectively on patients with SDNS, who were treated at Pusan National University Children's hospital. MMF group included 11 patients who were treated with MMF for at least six months between June 2012 and July 2014. As control groups, cyclosporine group (n=15) and levamisole group (n=18) included patients treated between January 2008 and July 2014. Number of relapse was analyzed in patients treated more than six months, and relapse free for one year was analyzed in patients treated more than one year.

Results: In MMF group, ten were boys and mean age at onset was 5.8 years. Mean age at starting of MMF was 8.6 years. Number of relapse in MMF group was reduced significantly after treatment from 3.4 /year to 0.2 /year ($P=0.003$). There was no significant difference in number of relapse among groups (MMF: 0.2 /year, cyclosporine: 0.5 /year, levamisole: 0.5 /year). Comparing the early relapse within six months after treatment levamisole group was significantly higher than the other two groups ($P=0.04$).

Conclusions: MMF which is used in SDNS significantly reduced the relapse and side effects were rare. In addition, MMF did not show any significant difference in comparison with the other two groups in number of relapse and relapse free for one year.

Key words: Steroid dependent nephrotic syndrome, MMF, Cyclosporine, Levamisole

Introduction

Of children with nephrotic syndrome, 80–85% are known to have the minimal change disease and more than 90% respond to steroids¹. Of these patients, 10–20% experience relapse 3–4 times, and about 50% have frequent relapse or show steroid-dependency². The long-term use of steroids can cause severe side effects including excessive weight gain, Cushing syndrome, high blood pressure, growth disturbance, glucose intolerance, cataract, mood disorder, bone mineral density loss, acne and hirsutism³. In steroid dependent nephrotic syndrome, several drugs such as cyclosporine, tacrolimus, levamisole and cyclophosphamide are used as steroid sparing drugs. Cyclosporine was

This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/bync/3.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Table 1. Patient characteristics of steroid dependent nephrotic syndrome

	MMF	CsA	Levamisole	P value
Patients	11	15	18	
Sex (male)	10 (90.9%)	12 (80%)	16 (88.9%)	0.633
Age at diagnosis (years)	5.82±3.03	5.56±3.95	4.60±2.44	0.560
Age at treatment (years)	8.55±2.62	6.52±3.97	8.15±3.71	0.155
Treatment duration (months)	15.27±3.13	17.33±9.12	13.61±10.80	0.357

Abbreviations: MMF, Mycophenolate mofetil; CsA, Cyclosporine

first used by Hoyer et al.⁴⁾ in 1986 and has become widely used over the past 30 years. Levamisole which was first used by Tanphaichitr et al.⁵⁾ in 1980 also continues to be in use. Mycophenolate mofetil (MMF) which is used relatively frequently at present was approved for kidney transplantation by the Food and Drug Administration (FDA) in 1995⁶⁾. Since 2000, several small-sized studies have reported the effects of MMF on nephrotic syndrome. We compared the efficacy between MMF and other drugs including cyclosporine and levamisole. We also examined the safety profile of MMF.

Materials and methods

The study subjects were patients under 18 years of age who had been diagnosed with steroid dependent nephrotic syndrome from June 2012 to August 2014 at Pusan National University Children's Hospital and had taken MMF for more than six months in the same hospital, as well as patients under 18 who had been diagnosed with steroid dependent nephrotic syndrome from January 2008 to August 2014 at Pusan National University Hospital and Pusan National University Children's Hospital and had taken cyclosporine and levamisole. We retrospectively analyzed their medical records. Based on the patients' records, their sex, age of onset, age of the first drug administration, treatment period, administration period, administration history, side effects and other factors were analyzed. The dose of MMF was 40 mg/kg/day #2, and prednisolone 0.2 mg/kg was also used. Steroid dependent nephrotic syndrome was defined when relapse in the middle of reducing steroid or two relapse occurrences in a row within a month after the completion of steroid treatment.

The efficacy of treatment was analyzed in three areas. The first was the number of relapse that occurred in the

patients who had taken the drug for more than six months. The second was the relapse free for one year of patients who had taken the drug more than one year. Finally, the third was the early relapse within six months after treatment.

For statistical analysis, the IBM SPSS Statistics 22(Chicago, IL) program was applied. To determine the significance of a reduction in the relapse rate in the drug administration group, the Wilcoxon signed rank test was conducted. To compare the number of relapse and relapse free for one year between three groups, the Kruskal–Wallis test and Freeman–Halton extension of Fisher's exact test were applied. P-value less than 0.05 was defined as significant.

Results

Of 11 patients who had received MMF, six patients had MMF administered first as a secondary drug and five patients had the history of 1–2 years of cyclosporine treatment among whom three patients had a history of rituximab use. For each drug, there was a six-month administration interval. Fifteen and 18 patients had received cyclosporine and levamisole, respectively. The three groups were analyzed in terms of sex-based frequency, onset age, the age of first administration of a relevant drug, the frequency of relapse before treatment, and the treatment period. As the result of the analysis, the three groups demonstrated no significant difference (Table 1).

The MMF group's number of relapse was 3.0 /year before treatment. After MMF treatment, the group had 0.24 /year (Table 2). Therefore, in this group, the number for relapse was significantly reduced ($P=0.003$; Fig. 1). The cyclosporine group had 2.8 /year before treatment and 0.5 /year after treatment (Table 3). The levamisole group had 2.6 /year before treatment and 0.6 /year after treatment (Table 4). In both two groups, numbers of relapse were significantly

Table 2. MMF group (treatment over 6 months)

Patient	Treatment duration (months)	Number of relapse before Tx (/year)	Number of relapse during Tx (/year)
1	21	2	0.57
2	12	5	0
3	12	4	0
4	18	3	0
5	12	2	0
6	17	3	0.71
7	18	3	0.67
8	17	4	0.71
9	15	2	0
10	12	3	0
11	14	2	0
Mean	15.27	3	0.24

Abbreviation: Tx, Treatment

Fig. 1. Changes in number of relapse (Mycophenolate mofetil)
 * 3 patients, † 2 patients
 Abbreviation: Tx, Treatment

reduced (Fig. 2, Fig. 3). Nevertheless, with regard to the extent of the reduction in numbers of relapse before and after treatment, the three groups showed no significant difference ($P=0.27$; Table 5).

Regarding the rate of relapse free for one year after treatment, the MMF group's rate was 63.6% (7 out of 11 patients), that of the cyclosporine group was 58.3% (7/12), and that of the levamisole group was 41.7% (5/12). There was no significant difference between the three groups ($P=0.59$; Table 5). In terms of the rate of early relapse within 6 months

after treatment, the rate of the levamisole group was 50% (9 out of 18 patients), that of the MMF group was 9.1% (1/11), and that of the cyclosporine group was 13.3% (2/15). Therefore, the levamisole group showed a significantly higher rate than the other two groups ($P=0.04$).

No patient had any complaint of MMF administration side effects, including stomachache and diarrhea. In the observation period, there were no hematologic side effects like myelosuppression, but one patient had herpes zoster infection.

Discussion

Patients with steroid dependent nephrotic syndrome who had taken steroids on a long-term basis have been found to have some side effects. For this reason, various drugs to replace steroids have been used to maintain remission. Such drugs are metabolic suppression drugs, alkylating agents, cyclosporine, levamisole and others^{2,6}.

It has been extensively reported that in nephrotic syndrome, treatment with cyclosporine has such benefits as a reduction in the steroid dose and a decreased relapse rate. As a result, cyclosporine is used widely for treatment of steroid dependent nephrotic syndrome⁷⁻¹². This study conducted a comparative analysis before and after cyclosporine treatment. The difference in the number of relapse before and after treatment was 2.3 /year, which represents a significant reduction. However, because of nephroto-

Table 3. Cyclosporine group (treatment over 6 months)

Patient	Treatment duration (months)	Number of relapse before Tx (/year)	Number of relapse during Tx (/year)
1	24	2	0
2	27	4	0
3	24	2	0.5
4	27	3	2.2
5	26	3	1
6	24	3	0.5
7	25	2	0
8	15	3	0
9	18	4	2
10	18	4	0
11	12	2	0
12	12	2	0
Mean	21.0	2.83	0.52

Abbreviation: Tx, Treatment

Table 4. Levamisole group (treatment over 6 months)

Patient	Treatment duration (months)	Number of relapse before Tx (/year)	Number of relapse during Tx (/year)
1	14	1	0
2	26	2	0.92
3	12	3	0
4	11	4	1.09
5	8	2	1.5
6	28	3	0.42
7	22	3	1.1
8	37	2	0
9	13	2	0
10	13	4	0
11	25	3	0.48
12	22	2	0.54
Mean	19.3	2.58	0.50

Abbreviation: Tx, Treatment

xicity, which is cyclosporine's main side effect, it is not advisable to administer the drug over the long term¹³⁻¹⁸.

Since the first use of levamisole in 1980, several reports have revealed that the drug is effective in induction and a reduction in the relapse rate¹⁹⁻²³. According to our study, the difference in the number of relapse before and after treatment was 2.0 /year, which represents a significant reduction. Levamisole is inexpensive and causes no significant side effects other than neutropenia^{12,24}. However, like with other drugs, most patients tend to experience relapse when they stop taking this drug^{19,22,24-26}. In our study, the levamisole group had more early relapses (relapse within 6 months after treatment) than the other groups ($P=0.04$).

Unfortunately, we don't know exactly if this result comes from characteristics of levamisole itself. Most patients who had early relapse stopped receiving levamisole treatment, but three had had no relapse up to 24 months after a relapse within six months. Therefore, it is considered that even if there is early relapse, it may be possible to continue with the treatment more.

After MMF was approved by the FDA in 1995, several small-sized studies in the early 2000s demonstrated its effects in nephrotic syndrome²⁶⁻³³. In our study, the difference in the number of relapse before and after treatment was 2.8 /year, which represents a significant reduction. MMF is known to have no nephrotoxicity which is fatal to

Fig. 2. Changes in number of relapse (Cyclosporine)
* 4 patients, † 2 patients
Abbreviation: Tx, Treatment

Fig. 3. Changes in number of relapse (Levamisole)
* 2 patients
Abbreviation: Tx, Treatment

Table 5. Comparison of relapses

	MMF	Cyclosporine	Levamisole	P value
Δ Number of relapse (/year)	2.76±1.04	2.32±0.94	2.08±0.99	0.27
Relapse free for 1yr	7/11 (63.6%)	7/12 (58.3%)	5/12 (41.7%)	0.59
Early relapse*	1/11 (9.1%)	2/15 (13.3%)	9/18 (50%)	0.04

Abbreviation: MMF, Mycophenolate mofetil
*relapse within six months after treatment

patients with nephrotic syndrome³¹⁾. In addition, according to a recent report, it has low drug dependence characteristics³⁴⁾. Nevertheless, many studies that have been conducted so far have limitations, such as that the research was carried out at a single institution or a short period of administration was used for a small number of study subjects. To overcome such limitations, Banerjee et al.³³⁾ studied 46 patients with steroid dependent nephrotic syndrome at multiple institutions with mean follow-up period of 3.6±1.8 years. These researchers found that after one year of MMF administration, 32 of the patients (70%) had stopped taking steroids or were taking a reduced dose. At the last follow-up, 56% (14/25) patients were off regular medication in MMF group and only 10.5% (2/21) patients did in the other group. These results were statistically significant. Recently, Gellermann et al.³⁵⁾ conducted a randomized crossover study to compare the effects of cyclosporine with those of MMF. According to their research, cyclosporine was more effective in preventing relapse, but when MMF

was used, cystatin clearance, estimated glomerular filtration rate (GFR), and hemoglobin level were significantly high. Given the results, it was considered that MMF would become a less-nephrotoxic treatment option. Like previous studies, our study revealed that the MMF group showed a significant reduction in the number of relapse and that there was no significant difference from the groups that took other drugs. Among the subjects of this study, no severe side effect was found in any patients in the MMF group except for one patient who was infected with herpes zoster. Therefore, it is considered that MMF can be used with relative safety. This study has several limitations. One is that it was conducted at a single institution respectively and not controlled study. Another is that we changed the drug at early relapse, so we could not determine the effect of long-term administration of the drug. In conclusion, in the case of steroid dependent nephrotic syndrome, MMF showed no significant difference in its

remission maintenance effect from other drugs such as cyclosporine and levamisole; moreover, it exhibited a low frequency of severe side effects. This drug does not cause nephrotoxicity, and thus it can be used for long-term treatment. In this respect, it is considered that MMF is effective in maintaining long-term remission of steroid dependent nephrotic syndrome.

Conflict of interest

Authors have no relevant financial relationships to disclose or conflict of interest to we solve.

References

1. Primary nephrotic syndrome in children: Clinical significance of histopathologic variants of minimal change and of diffuse mesangial hypercellularity. A report of the international study of kidney disease in children. *Kidney Int* 1981;20:765-71.
2. Cheong WY. Recent advance in nephrotic syndrome. *J Korean Soc Pediatr Nephrol* 2002;6:15-24.
3. Siegel NJ, Goldberg B, Krassner LS, Hayslett JP. Long-term follow-up of children with steroid-responsive nephrotic syndrome. *J Pediatr* 1972;81:251-8.
4. Hoyer PF, Krull F, Brodehl J. Cyclosporin in frequently relapsing minimal change nephrotic syndrome. *Lancet* 1986;2:335.
5. Tanphaichitr P, Tanphaichitr D, Sureeratanan J, Chatasingh S. Treatment of nephrotic syndrome with levamisole. *J Pediatr* 1980;96:490-3.
6. Moudgil A, Bagga A, Jordan SC. Mycophenolate mofetil therapy in frequently relapsing steroid-dependent and steroid-resistant nephrotic syndrome of childhood: Current status and future directions. *Pediatr Nephrol* 2005;20:1376-81.
7. Ponticelli C, Edefonti A, Ghio L, Rizzoni G, Rinaldi S, Gusmano R, et al. Cyclosporin versus cyclophosphamide for patients with steroid-dependent and frequently relapsing idiopathic nephrotic syndrome: A multicentre randomized controlled trial. *Nephrol Dial Transplant* 1993;8:1326-32.
8. Inoue Y, Iijima K, Nakamura H, Yoshikawa N. Two-year cyclosporin treatment in children with steroid-dependent nephrotic syndrome. *Pediatr Nephrol* 1999;13:33-8.
9. 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.
10. Ishikura K, Yoshikawa N, Hattori S, Sasaki S, Iijima K, Nakanishi K, et al. Treatment with microemulsified cyclosporine in children with frequently relapsing nephrotic syndrome. *Nephrol Dial Transplant* 2010;25:3956-62.
11. Tanaka R, Yoshikawa N, Kitano Y, Ito H, Nakamura H. Long-term cyclosporin treatment in children with steroid-dependent nephrotic syndrome. *Pediatr Nephrol* 1993;7:249-52.
12. Hino S, Takemura T, Okada M, Murakami K, Yagi K, Fukushima K, et al. Follow-up study of children with nephrotic syndrome treated with a long-term moderate dose of cyclosporine. *Am J Kidney Dis* 1998;31:932-9.
13. Fujinaga S, Kaneko K, Muto T, Ohtomo Y, Murakami H, Yamashiro Y. Independent risk factors for chronic cyclosporine induced nephropathy in children with nephrotic syndrome. *Arch Dis Child* 2006;91:666-70.
14. Iijima K, Hamahira K, Tanaka R, Kobayashi A, Nozu K, Nakamura H, et al. Risk factors for cyclosporine-induced tubulointerstitial lesions in children with minimal change nephrotic syndrome. *Kidney Int* 2002;61:1801-5.
15. Nakamura T, Nozu K, Iijima K, Yoshikawa N, Moriya Y, Yamamori M, et al. Association of cumulative cyclosporine dose with its irreversible nephrotoxicity in japanese patients with pediatric-onset autoimmune diseases. *Biol Pharm Bull* 2007;30:2371-5.
16. Sairam VK, Kalia A, Rajaraman S, Travis LB. Secondary resistance to cyclosporin A in children with nephrotic syndrome. *Pediatr Nephrol* 2002;17:842-6.
17. Habashy D, Hodson E, Craig J. Interventions for idiopathic steroid-resistant nephrotic syndrome in children. *Cochrane Database Syst Rev* 2004;(2):CD003594.
18. Niaudet P, Habib R, Tete MJ, Hinglais N, Broyer M. Cyclosporin in the treatment of idiopathic nephrotic syndrome in children. *Pediatr Nephrol* 1987;1:566-73.
19. Han JH, Lee KJ, Lee YM, Kim JH, Kim PK. The effect of levamisole in steroid-dependent nephrotic syndrome in children. *J Korean Soc Pediatr Nephrol* 2001;5:109-16.
20. Bagga A, Sharma A, Srivastava RN. Levamisole therapy in corticosteroid-dependent nephrotic syndrome. *Pediatr Nephrol* 1997;11:415-7.
21. Neuhaus TJ, Fay J, Dillon MJ, Trompeter RS, Barratt TM. Alternative treatment to corticosteroids in steroid sensitive idiopathic nephrotic syndrome. *Arch Dis Child* 1994;71:522-6.
22. Lim HS, Noh US, Choe BH, Koh CW, Koo JH. Therapeutic effects of cytotoxic agents (cyclophosphamide and chlorambucil), cyclosporine and levamisole in children with steroid-dependent nephrotic syndrome. *Korean J Nephrol* 1997;16:246-53.
23. Dayal U, Dayal AK, Shastry JC, Raghupathy P. Use of levamisole in maintaining remission in steroid-sensitive nephrotic syndrome in children. *Nephron* 1994;66:408-12.
24. Niaudet P, Drachman R, Gagnadoux MF, Broyer M. Treatment of idiopathic nephrotic syndrome with levamisole. *Acta Paediatr Scand* 1984;73:637-41.
25. Levamisole for corticosteroid-dependent nephrotic syndrome in childhood. british association for paediatric nephrology.

- Lancet 1991;337:1555-7.
26. Montane B, Abitbol C, Chandar J, Strauss J, Zilleruelo G. Novel therapy of focal glomerulosclerosis with mycophenolate and angiotensin blockade. *Pediatr Nephrol* 2003;18:772-7.
27. Chandra M, Susin M, Abitbol C. Remission of relapsing childhood nephrotic syndrome with mycophenolate mofetil. *Pediatr Nephrol* 2000;14:224-6.
28. Bagga A, Hari P, Moudgil A, Jordan SC. Mycophenolate mofetil and prednisolone therapy in children with steroid-dependent nephrotic syndrome. *Am J Kidney Dis* 2003;42:1114-20.
29. Gellermann J, Querfeld U. Frequently relapsing nephrotic syndrome: Treatment with mycophenolate mofetil. *Pediatr Nephrol* 2004;19:101-4.
30. Barletta GM, Smoyer WE, Bunchman TE, Flynn JT, Kershaw DB. Use of mycophenolate mofetil in steroid-dependent and -resistant nephrotic syndrome. *Pediatr Nephrol* 2003;18:833-7.
31. Ulinski T, Dubourg L, Said MH, Parchoux B, Ranchin B, Cochat P. Switch from cyclosporine A to mycophenolate mofetil in nephrotic children. *Pediatr Nephrol* 2005;20:482-5.
32. Zhao M, Chen X, Chen Y, Liu Z, Liu Y, Lu F, et al. Clinical observations of mycophenolate mofetil therapy in refractory primary nephrotic syndrome. *Nephrology (Carlton)* 2003;8:105-9.
33. Banerjee S, Pahari A, Sengupta J, Patnaik SK. Outcome of severe steroid-dependent nephrotic syndrome treated with mycophenolate mofetil. *Pediatr Nephrol* 2013;28:93-7.
34. Mendizabal S, Zamora I, Berbel O, Sanahuja MJ, Fuentes J, Simon J. Mycophenolate mofetil in steroid/cyclosporine-dependent/resistant nephrotic syndrome. *Pediatr Nephrol* 2005;20:914-9.
35. Gellermann J, Weber L, Pape L, Tonshoff B, Hoyer P, Querfeld U, et al. Mycophenolate mofetil versus cyclosporin A in children with frequently relapsing nephrotic syndrome. *J Am Soc Nephrol* 2013;24:1689-97.