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Immunosuppressive regimens containing generic mycophenolate mofetil (Myfenax) in *de novo* renal transplant recipients – preliminary results of 6-month observation

Bolesław Rutkowski[ACDE], Beata Bzoma[BCEF], Alicja Dębska-Ślizień[ABCDE], Andrzej Chamienia[BDE]

Department of Nephrology, Transplantology and Internal Medicine, Medical University of Gdansk, Gdansk, Poland

Summary

Background: The aim of the findings presented below is to show the preliminary outcomes of transplantation in patients treated with the generic formulation of mycophenolate mofetil (Myfenax, Teva).

Material/Methods: Over the past 2 years 34 patients received generic mycophenolate mofetil (Myfenax) after renal transplantation at the Gdansk Transplantology Center. During the same time period another 127 kidney transplantations were performed in our Department and these patients were treated with other formulations of mycophenolate (CellCept, Myfortic or Mycophenolate mofetil Apotex) as a part of the immunosuppressive scheme. Fifteen of the Myfenax patients received a pair of kidneys from the same donor and received original mycophenolate mofetil Cell-Cept.

Results: The outcomes of the renal transplants in both groups (Myfenax *vs.* pair) were good; with satisfactory function of grafts, and no instances of graft loss were reported. There was no difference in the incidence of acute renal graft rejection (AR) in either group. Moderate adverse reactions to immunosupression were observed in both groups.

On the other hand, a comparison between the 34 patients with Myfenax and the 127 other patients with other formulations of mycophenolate revealed no differences in the incidence of AR, delayed graft function (DGF), graft loss and death.

Conclusions: There were no differences in the incidence of AR, DGF, graft loss and death in patients with Myfenax *vs.* original CellCept and other formulations of mycophenolate.

In order to confirm its complete biological and pharmacokinetic equivalence with the reference medicine, long-term, randomized observations carried out on larger renal transplant patients groups are needed.

Key words: kidney transplantation • Myfenax • mycophenolate mofetil

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Author's address: Boleslaw Rutkowski, Department of Nephrology, Transplantology and Internal Medicine, Gdansk Medical University, Debinki 7 St., 80-211 Gdansk, Poland, e-mail: bolo@amg.gda.pl

Background

Kidney transplantation is the best form of renal replacement therapy; it extends life expectancy, improves quality of life and is more cost-effective than hemodialysis. Post-renal transplant immunosuppressive treatment is based on simultaneous administration of several medications according to regimens dependent on the degree of immunological risk, severity of metabolic disorders, comorbid conditions and graft function. Typically, triple immunosuppression with steroids, calcineurin inhibitors and mycophenolic acid derivates is used. The adjunctive use of mycophenolate mofetil (MMF) with calcineurin inhibitors lowers the percentage of acute rejection episodes and the related rates of kidney graft loss [1–4], improves both one-year and multi-year survival of patients with a functioning renal graft [5], and reduces the risk of chronic graft failure, irrespective of the decrease in acute rejection incidence [6]. On the other hand, some studies failed to confirm a beneficial influence of MMF on the reduction of AR and chronic allograft dysfunction in comparison to azathioprine [7,8].

In some cases, MMF permits reduction of doses of calcineurin inhibitors [9], and reduction or withdrawal of glucocorticosteroids [10,11]. The clinical studies underlying the above-mentioned observations were conducted using the reference medicine containing mycophenolate mofetil (CellCept, Roche). An increasing number of generics are currently entering the market. This is also true for medicines used in immunosupression following renal transplantation [12]. Simple comparison of pharmacokinetic properties may not necessarily equate to therapeutic equivalence [13]. The aim of the present study was to show the preliminary outcomes of transplantation in patients treated with the generic formulation of mycophenolate mofetil (Myfenax, Teva).

Material and Methods

Between 24 April, 2009 and 19 January, 2011, in the Department of Nephrology, Transplantology and Internal Medicine of Gdansk Medical University, 161 kidney transplantations were performed, and 34 patients received generic mycophenolate mofetil (Myfenax) as one of the immunosuppressants used. Fifteen of them received a pair of kidneys from the same donor and received original MMF Cell-Cept. The follow-up period after transplantation was 6–26 months. Generally, patients were hospitalized at least for 2 weeks after kidney transplantation and then during the next month ambulatory control was performed every week, later twice monthly, and after three months every month.

Statistical analysis – categorical data were compared with the Fisher test, while continuous data were compared with Student's T test or the Mann-Whitney U test (when variances were not homogenous on the basis of Levene test).

Characteristics of all patients treated with Myfenax (n=34)

The average age of the kidney donors for the whole group treated with Myfenax in our centre (34 patients) was 45 years (range, 18–71). The donors were 22 men and 12 women. The causes of donor death were 18 craniocerebral traumas and 16 cerebrovascular causes. Mean number of HLA mismatches (MM) in the Myfenax group was 2.88 (1–5), the mean warm ischemia time was 28 minutes (range, 15–44), and the mean total ischemia time (TIT) was 851 minutes (range, 310–1707). During the same time, 127 other patients were transplanted in our centre and received Cell-Cept, Myfortic or Mycophenolate mofetil Apotex. We established that Myfenax is given to about 20% of patients transplanted in our Department; patients were randomized to particular groups with mycophenolate. The characteristics of patients on Myfenax therapy are presented below (Table 1). Data concerning donor characteristics, ischemia times and number of MM were comparable to the rest of the group of patients (n=127) transplanted in our unit during the above-mentioned period of time (detailed data not presented).

Characteristics of patients on Myfenax therapy who received a pair of kidneys from the same donor, receiving original mycophenolate mofetil Cell-Cept

The average age of the kidney donors for the above mentioned 15 recipients was 50 years (range, 25–71). Donors were 8 men and 7 women. The causes of donor death were 5 craniocerebral traumas, 10 cerebrovascular causes. The mean number of HLA mismatches in the Myfenax group was 2.9 (range, 2–5), the mean warm ischemia time was 27 minutes (range 15–35), and the mean TIT was 891 minutes (range, 395–1692). In the Cell-Cept group the mean number of HLA mismatches was 3.9 (range, 2–5), the mean warm ischemia time was 27 minutes (range, 17–38), and the mean TIT was 839 minutes (range, 347–1465).

Table 1. The clinical characteristics of patients on Myfenax therapy (n=34).

Age (years)	28–72 (mean 50.7)
Sex	12f/22m
Cause of ESRD	11 GN primary/secondary 7 ADPKD 7 HN 4 DM 2 congenital defect 3 unknown
Prior renal replacement therapy	28 HD 4 DO 2 PREE
Time on dialysis (months)	0–124 (mean 33.1)
2nd kidney transplantation	1 female patient
Immunosuppression	1 – ATG steroids tacrolimus Myfenax 1 – Simulect steroids tacrolimus Myfenax 1 – Simulect steroids cyclosporine Myfenax 22 – steroids tacrolimus Myfenax 9 – steroids tacrolimus Myfenax
Mean serum creatinine concentrations/eGFR	On 3rd month after transplantation 1.3 mg%/57 ml/min/1.73 m^2 On 6th month after transplantation 1.28 mg%/60 ml/min/1.73 m^2

Results

Analysis of incidence of AR and delayed graft function (DGF) in all patients treated with Myfenax (n=34) *vs.* patients on Cell-Cept, Myfortic, Mycophenolate mofetil Apotex (n=127) – 6-month observation

During 6 months of observation there were no differences in the incidence of AR, DGF, graft loss and death in patients with Myfenax (n=34) *vs.* patients with other formulations of mycophenolate (n=127) (Table 2).

Table 2. The incidence of acute rejection (AR), delayed graft function (DGF), graft loss and death in all patients treated with Myfenax (n=34) *vs.* patients on other formulation of mycophenolate (n=127).

	Myfenax		Others		Fisher test
AR	7/34	(21%)	36/127	(28%)	NS
DGF	12/34	(35%)	46/127	(36%)	NS
Graft loss	0/34	(0%)	4/127	(3%)	NS
Death	1/34	(3%)	1/127	(0.8%)	NS

Analysis of patients on Myfenax therapy who received pair of kidneys from the same donor, receiving original mycophenolate mofetil Cell-Cept – 6-month observation

No instances of graft loss were reported. AR was observed in 4 patients (26.6%) receiving Myfenax. In 3 patients AR was diagnosed on the bases of clinical manifestations, in 1 patient the diagnosis was confirmed by biopsy (Banff IIA), basal immunosupression was in 3 cases – steroids, tacrolimus, Myfenax and in 1 case – steroids, cyclosporin, Myfenax. AR was treated successfully with boluses of methylprednisolone. In Cell-Cept patients acute rejection occurred in 3 patients (20%) and in 2 cases were confirmed histopathologically (Banff IA), in 1 - diagnosis based on clinical symptoms. In all cases basal immunosuppression was tacrolimus, steroids, Cell-Cept, treatment of AR boluses of methylprednisolone. There was no statistical difference between the incidence of AR in the Myfenax group and Cell-Cept group (Fisher Test, $p>0.05$).

Delayed graft function (DGF), defined as the need for dialysis in the first week after transplantation, was observed more often in the Myfenax group than in the Cell-Cept group (6/15–40% *vs.* 3/15–20%), but it was not significant (Fisher Test, $p>0.05$).

The clinical characteristics and comparison of the investigated groups of kidney recipients are presented below in Table 3.

Table 3. Characteristics and comparison of investigated kidney recipients (Myfenax *vs.* the same kidney donor pair).

	Myfenax	Pair	
Sex	5f 10m	4f 11m	
Cause of ESRD	4 ADPKD 5 GN 3 HA 1 DM 1 congenital defect 1 unknown	4 ADPKD 5 GN 3 HA 2 interstitial nephritis 1 unknown	
Prior renal replacement therapy	13 HD 2 PD	14 HD 1 PD	
BMI	28.1 (20–33.6)	26 (20–34)	NS
Age years (min–max)	54.1 (28–71)	49 (21–66)	NS
Time on dialysis (months)	33.4 (7–64)	42 (4–108)	NS
MM	2.7	3.9	Test U Mann-Witney $p<0.05$
PRA last	1–41% 14–0%	1–53% 1–10% 13–0%	
TIT min (min-max)	891 (395-1692)	839 (347-1465)	NS
Immunosuppression	1 – Simulect, steroids, Prograf, Myfenax 10 – steroids, Prograf, Myfenax 4 – steroids, Neoral, Myfenax	1 – Simulect, steroids, Prograf, CellCept 1 – Simulect, steroids, Neoral, CellCept 12 – steroids, Prograf, CellCept 1 – steroids, Neoral, CellCept	
2nd transplantation	0	1 male patient	
History of pre-transplant cardiovascular complications	2 – stroke 1 – myocardial infarct, PTCA 1 – coronary heart disease 1 – aortic valve defect 15 – HA	1 – coronary hart disease 14 – HA	

Immunosuppressive adverse effects occurring in the investigated group within 6 months of the kidney transplantation are presented in Table 4. The incidence of gastrointestinal adverse effects was equal – 2/15 (13.3%) in both groups.

Overall, the dose of Myfenax was reduced in 8/15 patients and Cell-Cept in 11/15 patients, on the basis of high mycophenolic acid (MPA) level (mean C0 before reduction – 6.7mg/l in the Myfenax group and mean C0 7.15 mg/l in the Cell-Cept group; target level 1–3.5 mg/l [14]) and adverse reactions in the form of diarrhea, anemia, vomiting/nausea, mucosal lesions, and acute infection (UTI, respiratory truck infections, CMV, herpes zoster). One patient in the Myfenax group and 2 patients in the Cell-Cept group required reoperation, including a peritoneal fenestration to treat lymphocele formation.

Mean serum creatinine concentrations, eGFR and levels of cyclosporine or tacrolimus on days 14 and month 3 and 6 are presented in Table 5.

Discussion

The outcomes of the renal transplants in both groups (Myfenax *vs.* pair) were good; after 6 months mean creatinine levels were 1.29 mg/dl (eGFR 61 ml/min/1.73m^2) and 1.36 mg/dl (eGFR 47.4 ml/min/1.73 m^2), respectively. There were no differences in AR during 6-month observation after renal transplantation in patients receiving Myfenax in comparison with their pairs receiving Cell-Cept and in comparison with all patients transplanted in our Department in the same period of time (treated with other formulations of mycophenolate). The frequency of AR in selected patients on Myfenax (these having their

Table 4. Complications in renal transplant patients.

Complication	Myfenax		Pair		
AR	4	(26.6%)	3	(20%)	NS
Biopsy	1		2		NS
DGF	6	(40%)	3	(20%)	NS
ATN	4	(26.6%)	3	(20%)	NS
infections	7	(46.7%)	7	(46.7%)	NS
UTI	5	(353.3%)	6	(40%)	NS
CMV	0		6	(40%)	Fisher Test p<0.05
Gastrointestinal symptoms	2	(13.3%)	2	(13.3%)	NS
Lymphocele fenestration	1		2		NS
PTDM	4		1		NS
Graft loss	0		0		NS
Death	1		1		NS
Reduction of MMF	8		11		NS

Table 5. Mean serum creatinine concentrations, eGFR (4 points MDRD) and levels of cyclosporine or tacrolimus on days 14 and months 3 and 6.

Groups	Parameter	Day 14	Month 3	Month 6
Myfenax	creat [mg/dl]	2.36	1.3	1.3
	eGFR	48.0	61.0	63.0
	Tac [ug/l]	12.7	11.9	7.3
	CsA [ug/l]	196.1	227.1	205.5
CellCept	creat [mg/dl]	2.06	1.45	1.36
	eGFR	40.7	55.3	58.3
	Tac [µg/l]	13.0	9.9	10.79
	CsA [µg/l]	187.9	160.6	Data unknown
	Significance	NS	NS	NS

donor pairs, n=15) was 26.6%, in all, 34 patients treated with Myfenax in our Department – 21%. General frequency of AR in our Department during the study period was 28.6% (43/161).

The majority of diagnosis of AR was performed on the basis of clinical symptoms (reduction of diuresis, decreasing of GFR, data from Doppler ultrasonography of graft), and good response to the methylprednisolone treatment was the confirmation of AR. In the investigated groups (Myfenax *vs.* kidney donor pair with Cel-Cept), biopsy was performed once in the Myfenax group (Banff IIA) and twice in the Cell-Cept group (both IA). In the literature, the frequency of acute rejection diagnosis up to 6 months after renal transplantation is reported to be in the range of 10–35% [6,15].

DGF (defined as the need for dialysis during the first week after kidney transplantation) occurred in almost 40% of patients receiving Myfenax (6/15) and in 20% of those receiving Cell-Cept (3/15). Although the difference was not significant (Fisher Test, >0.05), we should stand that patients with Myfenax (n=15) had higher cardiovascular morbidity and it could have influenced more frequent development of DGF. Analyzing the whole group treated with Myfenax (n=34) *vs.* others (n=127), there was no difference in DGF (35% *vs.* 36%).

We did not observe graft loss in pair analysis (n=15). In the Cell-Cept group and the Myfenax group there was 1 lethal case in each group. In the Myfenax group 1 female patient died 3 months after renal transplantation due to *Pseudomonas*

aeruginosa sepsis, following several vascular procedures because of *Candida albicans* arteritis of the renal graft anastomosis. This is a particularly rare complication, occurring in 1/1000 renal grafts [15] and it is difficult to know whether it was related to the immunosupression regimen applied. In the Cell-Cept group (n=15) the death was caused in a male patient 2 weeks after transplantation by rapid hemorrhage from arterial anastomosis of the kidney graft, also connected with candida arteritis. Both patients had received kidney transplantation from the same multiorgan donor.

Complications of the mycophenolate in pair analysis did not differ. The most common were infections, mainly urinary tract infections (UTIs) (43% and 50%) which are the most common infection in renal graft recipients. The incidence of UTIs after renal transplantation varies from 36% to 60% [17,18]. A significant difference was observed in CMV infection – it was diagnosed in 6 patients in the Cell-Cept group, but there were no such case in the Myfenax group.

Gastrointestinal symptoms (diarrhea, vomiting/nausea, abdominal pain) requiring reduction of the dose of mycophenolate occurred in 2 cases in both groups. Gastrointestinal symptoms in the course of mycophenolate mofetil therapy have been reported at 20–40% [18–20].

Conclusions

Summarizing the above analysis of the preliminary treatment outcomes, we can conclude there were no differences in the incidence of AR, DGF, graft loss and death in patients with Myfenax *vs.* original CellCept (pairs n=15) and there were no differences in the incidence of AR, DGF, graft loss and death in patients with Myfenax (n=34) *vs.* patients with other formulations of mycophenolate (n=127).

At the same time, it must be emphasized that in order to confirm its complete biological and pharmacokinetic equivalence with the reference medicine, long-term, randomized observations carried out on larger renal transplant patient groups are needed.

References:

1. European Mycophenolate Mofetil Study group: Placebo-controlled study of mycophenoate mofetil combined with cyclosporine and corticosteroids for prevention of acute rejection. Lancet, 1995; 345: 1321–25
2. 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
3. US Renal Transplant Mycophenolate Mofetil Study Group, Sollinger H: Mycophenolate Mofetil for acute rejection in primary cadaveric renal allograft recipients. Transplantation, 1995; 60: 225–32
4. The International Mycophenolate Mofetil Renal Trasplant Study Groups, Halloran P, Mathew T, Tomlanovich S et al: Mycophenolate mofetil in renal allograft recipients: a polled efficacy analysis of three randomized, double-blind clinical studies in prevention of rejection. Transplantation, 1997; 63: 39–47
5. Mycophenolate Mofetil Acute Renal Rejection Study Group: Mycophenolate mofetil for the treatment of a first acute renal allograft rejection. Transplantation, 1998; 65: 235–41
6. Ojo A, Meier-Kriesche H, Hanson J et al: Mycophenolate mofetil reduces late renal allograft loss independently of acute rejection. Transplantation, 2000; 69(11): 2405–9
7. Remuzzi G, Lesti M, Gotti E et al: Mycophenolate mofetil versus azatioprine for prevention of acute rejection in renal transplantation (MYSS): A randomized trial. Lancet, 2004; 354: 503–12
8. Remuzzi G, Cravedi P, Costantini M et al: Mycophenolate mofetil versus azathioprine for prevention of chronic allograft dysfunction in renal transplantation: the MYSS follow-up randomized, controlled clinical trial. J Am Soc Nephrol, 2007; 18: 1973–85
9. Ekberg H, Tedesco-Silva H, Demirbas A et al: ELITE-Symphony Study. Reduced exposure to calcineurin inhibitors in renal transplantation. N Engl J Med, 2007; 357(25): 2562–75
10. Squifflet J, Vanrenterghem Y, van Hooff J et al: Safe withdrawal of corticosteroids or mycophenolate mofetil: results of a large, prospective, multicenter study. Transplantation Proceedings, 2002; 34(5): 1584–86
11. Matas AJ, Ramcharan T, Paraskevas S et al: Rapid discontinuation of steroids in living donor kidney transplantation: a pilot study. Am J Transplant, 2001; 1(3): 278–83
12. Masri MA, Andrysek T, Rizk S et al: The Role of Generics in Transplantation: TM-MMF Versus Cellcept in Healthy Volunteers. Transplantation Proceedings, 2004; 36: 84–85
13. Holt D: Generic Formulations of Immunosuppressive. Is it always safe to swith? Ann Transplant, 2009; 14(Suppl.1): 11
14. KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients. Am J Transpl, 2009; 9(Suppl.3): s20

15. Gonwa T, Johnson C, Ahsan N et al: Randomized trial of tacrolimus + mycophenolate mofetil or azathioprine versus cyclosporine + mycophenolate mofetil after cadaveric kidney transplantation: results at three years. Transplantation, 2003; 75(12): 2048–53
16. Albano L, Bretagne S, Mamzer-Bruneel MF et al: Evidence that graft-site candidiasis after kidney transplantation is acquired during organ recovery: a multicenter study in France. Clin Infect Dis, 2009; 48(2): 194–202
17. Sorto R, Irizar SS, Gelgadilo G et al: Risk factors for urinary tract infections during the first year after kidney transplantation. Transplant Proc, 2010; 42: 280–81
18. Veroux M, Giuffrida G, Corona D et al: Infective complications in renal allograft recipients: epidemiology and outcome. Transplant Proc, 2008; 40: 1873–76
19. Hardinger K, Brennan D, Lowell J et al: Long-term outcome of gastrointestinal complications in renal transplant patients treated with mycophenolate mofetil. Transpl Int, 2004; 17(10): 609–16
20. Pelletier R, Akin B, Henry M et al: The impact of mycophenolate mofetil dosing patterns on clinical outcome after renal transplantation. Clin Transplant, 2003; 17(3): 200–5
21. Tierce J, Porterfield-Baxa J, Petrilla A et al: Impact of mycophenolate mofetil (MMF)-related gastrointestinal complications and MMF dose alterations on transplant outcomes and healthcare costs in renal transplant recipients. Clin Transplant, 2005; 19(6): 779–84