The effect of conversion from enteric-coated mycophenolate sodium to mycophenolate mofetil (MMF) among renal transplant patients – comparison of brand name MMF and generic (Myfenax)

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Objective. To examine the safety of conversion from enteric-coated mycophenolate sodium (EC-MPS) to mycophenolate mofetil (MMF) among renal transplant patients. Comparison of generic MMF (Myfenax, Teva) and brand name MMF (CellCept, Roche).

Methods. This 12 months open observational study analyzed the outcomes of conversion therapy from EC-MPS to MMF (brand name and generic) due to social-economical reason.

Results. We analyzed 37 recipients of cadaveric renal transplants of mean age 50.5 ± 11 years including 24 male and 13 females. Our patients had stable renal function with mean creatinine of 1.32 ± 0.05 mg/dl. Baseline treatment included cyclosporine-EC-MPS-prednisone (35%), tacrolimus-EC-MPS (2.7%) and tacrolimus-EC-MPS-prednisone (62.3%). Bioequivalent conversion was carried out at 32± 18 months posttransplantation. 22 patients were converted to Myfenax and 15 to CellCept. After 12 months renal function remained stable in both groups; there were no episodes of rejection and severe infection.

Conclusion. Conversion from EC-MPS to MMF was safe among renal transplant recipients during 12 months observation. Use of generic MMF (Myfenax) provided safe and effective immunosuppressive therapy compared with brand name MMF. However, as the duration of the study was short, these results need to be confirmed in a long-term study.

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Key words:
• kidney transplantation
• immunosuppressant treatment
• mycophenolate mofetil

Wyniki konwersji leczenia immunosupresyjnego z soli sodowej kwasu mykofenolowego na preparaty mykofenalu mofetylu u pacjentów po przeszczepieniu nerek – porównanie preparatu oryginalnego i generycznego (Myfenax)

Cel. Określenie bezpieczeństwa zmiany leczenia z soli sodowej kwasu mykofenolowego (Myfortic) na preparaty mykofenolanu mofetylu (MMF) u pacjentów po przeszczepieniu nerek. Ponadto porównanie wyników leczenia preparatami MMF generycznym (Myfenax, Teva) i oryginalnym (CellCept, Roche).

Metody. 12 miesięczne badanie obserwacyjne podczas którego poddano analizie efekty zmiany leczenia z przyczyn społeczno-ekonomicznych z Myforticu na MMF.

Wyniki. Przeanalizowano 37 biorców przeszczepów nerek ze zwłok, średnia wieku chorych wynosiła 50,5 ± 11 lat, było to 24 mężczyzn i 13 kobiet. Pacjenci mieli stabilną funkcję nerek ze średnią wartością kreatyniny 1,32 ± 0,05 mg / dl. Przed konwersją 35% pacjentów przyjmowało cyklosporynę-Myfortic-prednizon, 2,7% takrolimus-Myfortic i 62,3% takrolimus-Myfortic-prednizon. Zmiana leczenia została przeprowadzona w 32 ± 18 miesięcy po zabiegu transplantacji. 22 pacjentów otrzymało Myfenax i 15 CellCept zamiast Myforticu.

Grupy nie różniły się istotnie pod względem ilości niezgodności HLA, struktury płci, wieku, BMI oraz przyczyn niewydolności nerek. Po 12 miesiącach funkcja nerek była stabilna oraz nie stwierdzono różnic w przeżyciu pacjentów i nerek w obu grupach. Nie obserwowano istotnych działań niepożądanych, nie wystąpiły epizody odrzucenia i ostrej infekcji.

Wnioski. Zmiana leczenia immunosupresyjnego przeprowadzona pod nadzorem lekarza transplantologa była procedurą bezpieczną i nie wpłynęła istotnie na losy poddanych jej chorych podczas 12 miesięcznej obserwacji. Nie stwierdzono różnic pomiędzy grupami leczonymi preparatami MMF oryginalnym i generycznym. Czas obserwacji był stosunkowo krótki, otrzymane wyniki wymagają potwierdzenia w badaniach długoterminowych.

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Słowa kluczowe:
• przeszczepienie nerki
• leczenie immunosupresyjne
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Immunosuppressant treatment with mycophenolate mofetil (MMF) has improved renal transplantation outcomes [1]. Nowadays prodrugs containing mycophenolic acid constitute a backbone of modern immunosuppression in kidney transplant recipient. However, MMF can produce gastrointestinal side effects, such as diarrhea, nausea and vomiting. Enteric-coated mycophenolate sodium (EC-MPS) has been developed to improve MPA-related gastrointestinal tolerability [2-5]. Among adult kidney transplant recipients, EC-MPS has been shown to be therapeutically equivalent to MMF with a similar pharmacokinetic profile [6,7]. The new regulations introduced in Poland the 1st of January 2012 concerning reimbursement for many drugs have led to changes in availability of certain therapies, also immunosuppressive. Socio-economical situation was the reason for the conversion of transplant patients from EC-MPS to MMF therapy. The 12 months' observation of this group of patients was the basis of the study.

Table I

Patient characteristics at baseline.

Wyjściowa charakterystyka pacjentów.

Parameter	
Gender: female/male (n)	13/24
Age (years)	50.5 ± 11
Serum creatinine (mg/dl)	1.321±0.05
Creatinine clearance-Cockcroft-Gault formula (ml/min)	67.37 (62.11-82.59)
Body mass index - BMI (kg/m^2)	26.98 (25.12-29.89)
systolic blood pressure (mm Hg)	133.5 (130.05-137.95)
diastolic blood pressure (mm Hg)	78.6 (76.27-81.73)
Hemoglobin (g/dl)	13.9±0.31
Myfortic (mg/day)	846.3 (792.19-957)
MMF (mg/day after conversion)	1073.6 (1006.85-1221.26)
Cyclosporine (mg/day) n=13	173.83 (157.95-195.89)
Tacrolimus (mg/day) n=24	4.33±0.59
Steroids (mg/day) n=36	5.2±0.54
HLA A+B+DR mismatches	3.36±0.22

Data are expressed as mean ± SEM or geometric mean (95% confidence interval).

Table II

Laboratory results and clinical data 3 months after conversion.

Wyniki laboratoryjne i dane kliniczne 3 miesiące po konwersji.

	CellCept		Myfenax		p<0.05
	Conversion day	3 months after conversion	Conversion day	3 months after conversion	
serum creatinine (mg/dl)	1.28±0.11	1.29±0.1	1.35±0.26	1.34±0.06	NS
MMF dose (mg/day)	1144.7 (998.6-1368.1)	1144.7 (998.6-1368,1)	1027.6 (928.5-1205)	1024.1 (929.1-1184.5)	NS
systolic blood pressure (mm Hg)	129.4 (123.2-136.7)	135,7 (126.3-147.1)	136.5 (132-141.7)	138.5 (132.2-146.1)	NS
diastolic blood pressure (mm Hg)	77.3 (72.9-82.5)	78.1 (72.9-84.3)	79.6 (76.4-83.4)	81.6 (77.4-86.9)	NS
hemoglobin (g/dl)	13.6±0.63	13.6±0.6	14.1±0.3	13.7±1.1	NS
Steroids dose (mg/day)	6.1±1.2	5.37±0.75	5.46±0.39	5.0±0.16	NS
Cyclosporine dose (mg/day)	165 (119-221)	165 (119-221)	179.5 (159-203)	173.2 (152.6-197.3)	NS
Cyclosporine trough concentration (ng/ml)	127±14	71.8±15.3	123.9±5.4	87.8±4.3	NS
Tacrolimus dose (mg/day)	5.15±1.1	4.65±0.93	3.8±0.65	3.43±0.49	NS
Tacrolimus trough concentration (ng/ml)	10.3±1.8	10.26±0.95	7.4±0.4	6.94±0.64	NS

Data are expressed as mean ± SEM or geometric mean (95% confidence interval).

Table III

Laboratory results and clinical data 12 months after conversion.

Wyniki laboratoryjne i dane kliniczne 12 miesięcy po konwersji.

	CellCept		Myfenax		p<0.05
	Conversion day	12 months after conversion	Conversion day	12 months after conversion	
serum creatinine (mg/dl)	1.28±0,11	1.3±0.1	1.35±0.26	1.36±0.1	NS
creatinine clearance [CG] ml/min	74.8 (62.4-99.4)	74.35 (63.33-94.28)	62.1 (53.7-77.7)	59.7 (53.2-72.3)	NS
systolic blood pressure (mm Hg)	129.4 (123-136.7)	140.4 (130.6-152.5)	136.5 (132-141.7)	141.5 (133.9-150.8)	NS
diastolic blood pressure (mm Hg)	77.3 (72.9-82.5)	84.3 (78.7-91.5)	79.6 (76.4-83.4)	83.5 (78.3-90.2)	NS
Hemoglobin (g/dl)	13.6±0.63	14.1±0.76	14.1±0.3	13.7±0.3	NS
MMF dose (mg/day)	1144.7 (998.6-1368)	1166.9 (1002-1431.6)	1027.6 (928.5-1205)	992.3 (896-1172.2)	NS

Data are expressed as mean ± SEM or geometric mean (95% confidence interval). CG – Cockcroft-Gault formula

Table IV
Laboratory results 3 and 12 months after conversion.
Wyniki badań laboratoryjnych w 3 i 12 miesiącu po konwersji.

	CellCept		Myfenax		p<0.05
	3 months after conversion	12 months after conversion	3 months after conversion	12 months after conversion	
Δ serum creatinine (mg/dl)	0.02±0.03	0.02±0.02	-0.005±0.0028	0.02±0.005	NS
Δ creatinine clearance [CG] ml/min	-1.23 (-15 – 25.6)	-2.09 (-16.8 – 21.8)	2.46 (-4.6 – 20.68)	0.69 (-19.2 – 11.53)	NS

Data are expressed as mean ± SEM or geometric mean (95% confidence interval). CG – Cockcroft-Gault formula

Methods

We retrospectively collected data from 37 kidney recipients of mean age 50.5 ± 11 years found to be receiving generic MMF (Myfenax, Teva) or brand name MMF (CellCept, Roche) after conversion from EC-MPS (Myfortic, Novartis) due to social-economics problems. Data were collected on recipient primary diagnosis, age at transplant, current age, time since transplant, donor source, concomitant medications and post-transplant course. We also collected data on immunosuppressant treatment dose, trough drug (tacrolimus and cyclosporine) levels, blood pressure, hemoglobin level, serum creatinine and calculated glomerular filtration rate (eGFR) by Cockcroft-Gault formula. Results are presented as means ± SEM. Differences in variable changes between treatment with brand name and generic MMF were assessed using Student's *t*-test. Differences in variables measured more than twice were assessed using ANOVA. *P* less than 0.05 (2-tailed) were considered statistically significant. Data were evaluated using Statistica (version 7.1; StatSoft Inc, Tulsa, OK) software package.

Results

Details of patients characteristics are provided in Table I. All 37 patients completed the 12 months observation. Results of the whole study population and subgroup analyses are summarized in Tables II-IV. We didn't find any significant differences between the groups.

Discussion

The development of MMF resulted in improved outcomes of renal transplantation. Nevertheless, the use of this drug is limited by a series of well recognized gastrointestinal side effects. MMF dose adjustment is associated with an increased risk of rejection [8-10] and graft loss [11,12]. EC-MPS at 720 mg twice a day is therapeutically equivalent to MMF at 1000 mg twice a day with a comparable safety profile. It has been demonstrated that conversion of maintenance renal transplant patients from MMF to EC-MPS is a safe option [13,14]. In the present study, the conversion of EC-MPS to MMF therapy was caused by the new regulations concerning the reimbursement. The EC-MPS therapy became related with significant cost for a patient – 113 Polish Zloty (PLN) and 216 PLN (about 54 EUR) for a package of 180 mg tablets and 360 mg respectively. Due to that, this type of treatment became unavailable for the majority of patients and the conversion to MMF therapy had to be performed. Some patients received brand name MMF and generic MMF in equivalent dose. The experience of our department suggests comparable clinical outcomes when adult patients received generic MMF (Myfenax) de novo after renal transplantation [15]. Fifteen of the Myfenax patients received a pair of kidneys from the same donor and received original MMF (CellCept). 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 in either group. Our results were similar to the overall results reported in other studies [16,17].

Increased health care costs and the burdens of copayments are substantial for transplant recipients. A survey of all U.S. kidney transplant programs found that the authors of 47% of programs reported more than 40% of their patients difficulties in paying for their immunosuppressive drugs [18]. Furthermore, 68% reported deaths and graft losses attributable to cost-related immunosuppressive nonadherence. Although the cost savings associated with generic MMF may be offset in the short term by increased monitoring, it is possible that savings would be incurred in the long run and may lead to improved adherence to immunosuppression and better health outcomes for transplant recipients. As additional generic immunosuppressants become available on the market, pharmacoeconomic analyses are needed to determine the true costs associated with generic conversion.

Conclusion

On the basis of the center experience it can be confirmed now that immunosuppressive conversion, performed under supervision of transplantologist, can be a safe procedure and do not influence the fate of patients during 12 months' observation. Moreover, no significant differences were found between the groups treated with the brand name and the generic MMF. However, as the duration of the study was short, these results need to be confirmed in a long-term study.

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