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ORIGINAL ARTICLE

Conversion from azathioprine to mycophenolate mofetil in patients with kidney transplantation taking triple drug immunosuppression

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The purpose of this study was to evaluate the effect and safety of azathioprine (AZA) replacement with mycophenolate mofetil (MMF) in a triple drug immunosuppression protocol on kidney transplant recipients. Fifty patients (35 men), 34 year – old (range 15 – 60 years) were included in the study. The replacement of AZA with MMF was done 5.24 ±2.43 years from transplantation (range 1.47 – 10.56 years) because of a serum creatinine rise and / or proteinuria. The patients had received triple or quadruple induction therapy with Cyclosporine A (CsA), methylprednizolone, AZA and antilymphocyte globulin. Forty patients had received a kidney graft from living related donor (LRD).

Serum creatinine (Cr), total protein (Pt), SGPT levels, WBC, platelet count and Ht were recorded every two months for a period of one year before and one year after conversion. At the same time period infections were recorded. Proteinuria (12 patients) was recorded at the time of conversion and six months later. Statistical analysis was done with ANOVA for repeated measures and paired t test.

Serum Cr was 1.31±0.35 mg/dl, 1.41±0.38 mg/dl, 1.35±0.38 mg/dl, 1.37±0.35 mg/dl, 1.45±0.38 mg/dl, 1.45±0.38 mg/dl και 1.47±0.40 mg/dl 12, 10, 8, 6, 4, 2 and 0 months before the conversion respectively (p=0.0005), and 1.54±0.41 mg/dl, 1.50±0.41 mg/dl, 1.54±0.47 mg/dl, 1.60±0.49 mg/dl, 1.56±0.44 mg/dl, 1.66±0.57 mg/dl 2, 4, 6, 8, 10 and 12 μήνες after conversion respectively (p=NS). Proteiuria was 0.59±0.64 g/24h before and 0.64±0.69 g/24h one year after conversion (p=NS). The infections per patient year were 0.44±0.54 before and 0.42±0.53 one year after the conversion (p=NS). WBC, platelets and Ht, the serum Pt and SGPT did not show significant difference during time before and after the conversion.

In conclusion the shift from AZA to MMF retarded the graft function deterioration in patients with a history of acute rejection episode and/or chronic allograft nephropathy and allowed the lowering of cyclosporine dose in patients with cyclosporine toxicity and grafts from aged donors. This conversion was not accompanied by new acute rejection episodes, new cases of chronic allograft nephropathy and there was no patient or graft loss.
Hippokratia 2002, 6 (4): 177-185

MMF is a prodrug of mycophenolic acid, an immunosuppressant, which inhibits inosine monophosphate dehydrogenase, an enzyme for the de novo synthesis of guanosine nucleotides in T and B – lymphocytes and smooth muscle cells[1, 2].

MMF inhibits the proliferation of lymphocytes and smooth muscles, the cytotoxic T lymphocyte response to allogenic cells, the production of antibodies induced by mitogens and antigens, and suppresses the production of antibodies against the anti – lymphocyte globulins[3-6].

The main cause of chronic allograft nephropathy is the occurrence of acute rejection episodes[7-9]. It is known that MMF in combination with steroids and CsA reduces the occurrence of acute allograft rejection compared with the AZA, steroids and CsA triple drug immunosuppressive protocol[10-12]. Recent evidence suggest that the use of MMF is connected with better long-term patient and graft survival when compared with immunosuppressive scheme containing AZA[13].

The information concerning the effect of MMF

on grafts with ongoing allograft nephropathy is scarce[14]. Having in mind the above and the fact that MMF may inhibit chronic rejection in animal studies[15, 16], we decided to investigate the safety and effectiveness of substitution of MMF for AZA in cases with ongoing allograft nephropathy - dysfunction.

Patients and methods

Fifty patients were evaluated. Their demographic data are shown in table 1. The conversion from AZA to MMF (table 2) was done 5.24±2.43 years from transplantation time (range 1.47 – 10.56 years) because of a serum creatinine rise and / or proteinuria (> 0.25 g/24 h). The patients had received triple or quadruple induction therapy with CsA, methylprednizolone, AZA and antilymphocyte globulin. Forty patients had received a kidney graft from LRD and ten from a cadaveric one. MMF was given by mouth in a daily dose of 20 – 30 mg / Kg divided in two. During the time of follow up the MMF dose was adjusted according to the behavior of each patient (leukocyte count, infections).

Serum creatinine (Cr), total protein (Pt), albumin SGPT, alkaline phosphatase levels, WBC and platelet count, and Ht were recorded every two months for a period of one year before and one year after conversion. Infections were recorded at the same time. Proteinuria (12 patients) and cyclosporine levels were recorded at the time of conversion and one year later. AZA and MMF doses were recorded 12 months before, at conversion and 12 months after conversion. Statistical analysis was done with ANOVA for repeated measures and paired t test. Regression analysis was used for serum creatinine curve and slope estimation. A p value less than 0.05 was considered to be significant. These patients were divided into two groups: Group A (19 patients) with an acute or chronic rejection history, documented by a kidney biopsy and group B (31 patients) with an aged graft implanted (> 55 years old donor) or a CsA toxicity history (biopsy proved or clinically suggested because of serum creatinine fall after reduction of the cyclosporine dose).

Results

In table 3 the mean serum creatinine level of the whole sample (50 pts) presented a significant raise one year before conversion while there was no significant change after conversion. In group A (19 pts) there was a significant raise of serum creatinine level before conversion while there was no significant change after conversion. In group B (31 pts) there was a raise of serum creatinine levels but it was not

Table 1. Demographic data

Patients	:	50	**Primary renal disease**	
Men	:	35	Chronic glomerulonephritis	21
Women	:	15	Polycyctic kidneys	5
Age	:	34.47 ± 11.20 years	Interstitial nephritis /	
range	:	15 – 60 years	pyelonephritis	8
Donor age	:	50.5±14.8	Angitis	4
range	:	from 12.22 to 77.45	Other congenital diseases	2
			Hypertensive nephrosclerosis	1
			Unknown	9

Table 2. Clinical Data

LRD : 40	CD : 10	Patients with CAN:	8
Conversion time :	5.24 ± 2.43 έτη	Patients with acute rejection:	11
(from Rt)		Patients with proteinuria:	12
range :	1.47 - 10.56 έτη	Patients with CsA toxicity	6
Immunosuppression		(clinical picture)	
Triple :	40	Patients with CsA toxicity	5
Quadruple :	10	(biopsy)	
		Patients with aged grafts	20

CAN = Chronic allograft nephropathy CD: Cadaveric donor

Table 3. Serum creatinine changes of the whole patient sample, in patients with acute rejection, and in patients without rejection before and after conversion

Time	Whole patient sample (50)	Patients without rejection (31)	Patients with rejection (19)	Patients with CsA toxicity (biopsy in 5)
		Serum creatinine (mg/dl)		
12 months before	1.31 ± 0.35°	1.27 ± 0.30	1.37 ± 0.42[1]	1.32 ± 0.58
10 »	1.41 ± 0.38°	1.34 ± 0.33	1.52 ± 0.43[1]	1.46 ± 0.57
8 »	1.35 ± 0.38°	1.29 ± 0.36	1.44 ± 0.39[1]	1.38 ± 0.56
6 »	1.37 ± 0.35°	1.29 ± 0.30	1.49 ± 0.39[1]	1.36 ± 0.52
4 »	1.45 ± 0.38°	1.34 ± 0.34	1.61 ± 0.39[1]	1.50 ± 0.47
2 »	1.45 ± 0.38°	1.37 ± 0.31	1.58 ± 0.45[1]	1.46 ± 0.54
0 conversion	1.47 ± 0.40°	1.35 ± 0.32	1.64 ± 0.47[1]	1.40 ± 0.50
2 months after	1.54 ± 0.41	1.42 ± 0.35	1.61 ± 0.46	1.50 ± 0.49
4 »	1.50 ± 0.41	1.46 ± 0.39	1.65 ± 0.55	1.36 ± 0.45
6 »	1.54 ± 0.47	1.46 ± 0.41	1.78 ± 0.54	1.40 ± 0.40
8 »	1.60 ± 0.49	1.49 ± 0.37	1.66 ± 0.50	1.40 ± 0.46
10 »	1.56 ± 0.44	1.52 ± 0.40	1.82 ± 0.73	1.46 ± 0.55
12 »	1.66 ± 0.57	1.47 ± 0.40	1.85 ± 0.78	1.44 ± 0.52

° p=0.0005 repeated measures analysis of variance

[1] p=0.011 repeated measures analysis of variance

significant neither the year before nor the year after MMF conversion. The serum creatinine of patients with CsA toxicity, confirmed by graft biopsy, showed a raise of serum creatinine before MMF conversion, while after MMF conversion there was no change. The number of these patients was too small to draw any conclusion. No change was noticed the period before and after conversion regarding the total serum protein, serum albumin, alkaline phosphatase and transaminase levels (table 4). Also, fairly stable remained the WBC, Ht and platelet number before and after conversion (table 5). There was no change of 24-hour proteinuria and the number of infections remained stable during the two year follow up (table 6). No new case of proteinuria was traced after conversion from AZA to MMF.

Table 4. Serum total protein, albumin, transaminase and alkaline phosphatase levels before and after the conversion from AZA to MMF in the whole patient sample

Time (months)	Total protein g/dl	Albumin g/dl	Transaminase (GPT) iu/l	Alkaline posphatase iu/l
-12	7.42 ± 0.53	4.76 ± 0.39	20.45 ± 10.91	84.58 ± 33.9
-10	7.58 ± 0.63	4.75 ± 0.45	29.93 ± 20.32	88.27 ± 27.5
-8	7.51 ± 0.58	4.74 ± 0.44	21.83 ± 17.84	94.51 ± 36.0
-6	7.56 ± 0.59	4.65 ± 0.55	23.96 ± 19.25	83.68 ± 33.3
-4	7.52 ± 0.63	4.73 ± 0.44	27.74 ± 33.23	85.82 ± 34.3
-2	7.51 ± 0.63	4.66 ± 0.47	23.00 ± 13.29	84.92 ± 39.3
0	7.57 ± 0.73	4.72 ± 0.50	22.54 ± 12.49	81.03 ± 32.4
+2	7.41 ± 0.56	4.62 ± 0.47	26.55 ± 22.35	86.63 ± 34.6
+4	7.65 ± 0.69	4.73 ± 0.58	25.33 ± 22.08	86.81 ± 32.2
+6	7.57 ± 0.57	4.79 ± 0.57	21.29 ± 11.15	81.81 ± 34.9
+8	7.55 ± 0.70	4.80 ± 0.51	23.25 ± 8.64	83.04 ± 35.7
+10	7.56 ± 0.66	4.72 ± 0.61	21.22 ± 7.39	76.18 ± 28.1
+12	7.46 ± 0.67	4.83 ± 0.55	21.62 ± 9.08	78.54 ± 37.3

p: NS in all cases

Table 5. WBC, platelet and Ht levels during the period of follow up before and after conversion in the whole patient sample

Time (months)	WBC /mm^3	Ht %	Platelets /mm^3
-12	8202 ± 2076	40.5 ± 5.8	224638 ± 62258
-10	8335 ± 2003	40.7 ± 5.2	228888 ± 58785
-8	8390 ± 2196	40.7 ± 5.1	225883 ± 57394
-6	8010 ± 2037	40.3 ± 4.9	226880 ± 54807
-4	7935 ± 1752	40.3 ± 5.4	218138 ± 52003
-2	8080 ± 2029	40.6 ± 5.5	213722 ± 46806
0	7860 ± 1852	40.3 ± 5.7	209527 ± 51772
+2	7646 ± 1832	39.1 ± 5.4	212821 ± 59797
+4	8210 ± 1849	39.0 ± 5.8	211214 ± 59850
+6	8033 ± 2019	39.6 ± 5.0	221178 ± 75900
+8	7796 ± 1993	40.0 ± 5.0	206714 ± 62391
+10	8313 ± 2274	39.8 ± 5.2	193285 ± 57189
+12	8343 ± 2218	39.4 ± 4.8	212714 ± 45378

p: NS

Table 6. Proteinuria (24 hour) at time of conversion and one year later and infection rate one year before and one year after conversion

Time	on conversion	one year later
Proteinuria (g/24h)	0.59 ± 0.64	0.64 ± 0.69
	the year before	the yare after
Infections (/ year)	0.44 ± 0.54	0.42 ± 0.53

p=NS, t test για μη ζεύγη τιμών

The azathioprin dose (mg/d) showed a not significant tendency to rise during the year before conversion. The mycophenolate mofetil (g/d) dose was reduced significantly (p= 0.0005) from the time of conversion to the end of the year (table 7) mainly due to infection adjustment. At the same time there was a significant reduction of the cyclosporine level in the group B (p= 0.024, table 8). There was no acute allograft rejection or patient death after conversion. Also, there was no new case of chronic allograft nephropathy. The slope and curve of serum creatinine is shown in table 9 and fig. 1, 2, 3, 4.

Discussion

It is known that the addition of MMF to schemes of cyclosporine and steroids reduces the acute rejection episodes[11,12,17,18]. It has been shown that MMF in triple drug protocols is connected with lower rates of acute allograft rejection compared with AZA triple drug immunosuppressive protocols[10-12]. Also, the use of MMF is connected with better long-term patient and graft survival when compared with immunosuppressive scheme containing AZA[13].

Table 7. Azathioprine and MMF dose during the follow up period

Time	Azathioprine mg/d	Mycophenolate mofetil gr/d
-12 months	82.95 ± 25.15	-
0	84.09 ± 23.55	1.52 ± 0.47[1]
12 months	-	1,30 ± 0,36[1]

[1]p=0.0005

Table 8. CsA levels at the time of conversion and one year later in patients with or without rejection and methylprednizolone dose according to donor origin

Cyclosporine A levels (ng/ml)		
	Patients with rejection (grup A)	Patients with CsA toxicity or an aged graft (grup B)
During the conversion	91.36 ± 24.34	100.80 ± 26.44[1]
Twelve months later	84.42 ± 13.71	91.56 ± 26.15[1]
Methylprednizolone dose kidney from living related donor : 0.08 mg/d kidney from cadaveric donor : 0.10 mg/d		

[1]p=0.024

Table 9. The slope of the curve of the mean of serum creatinine levels of the whole patient sample, of the patients with and without rejection and the patients with biopsy proved CsA toxicity one year before and one year after conversion from AZA to MMF

Time	Whole patient sample	Patients with rejection	Patients without rejection	Patients with biopsy proved CsA toxicity
1 year before	0.0217	0.0450	0.0037	0.0129
1 year after	0.0221	0.0315	0.017	0.0037

The trials of switching from CsA to MMF in patients with graft dysfunction taking CsA and corticosteroids, have been connected with acute rejection episodes and graft and patient loss due to cancer or infection as a result of over - immunosuppression[19,20].

This retrospective analysis was done on 50 patients with slowly but significantly deteriorating graft function (table 3) and / or proteinuria (table 6) in whom there was a tendency to augment the AZA daily dose. Our findings indicate that a shift from AZA to MMF retards the graft function deterioration (measured by serum creatinine) in patients with chronic allograft dysfunction (table 3, figure 1). Further analysis of our results showed that the patients that may benefit from this conversion are those with a history of acute rejection and / or ongoing chronic allograft rejection (tables 3, 9, figures 3, 4). The fact that renal function deterioration is not linear in patients with chronic allograft nephropathy but accelerates during time[21] stresses the significance of MMF influence in this setting. These findings are in agreement with a pediatric study in which the substitution of MMF for AZA was connected with improvement of patients' immunosuppressive status, significant fall of serum creatinine and significant deterioration of proteinuria of patients with ongoing chronic rejection[14]. In that study T – lymphocytes did not change during MMF treatment; in contrast B – lymphocytes ($CD19^+$) were decreased only in patients treated with MMF[14]. In our study baseline proteinuria was not different from that measured one year after conversion (table 6) in disagreement with the pediatric study where there was found a significant fall[14] and the study of Ducloux [20] where there was increased proteinuria.

The conversion allowed us to reduce significantly the cyclosporine dose in patients with CsA toxicity or aged grafts (table 8). This shift was not accompanied by significant change of serum creatinine level or shift of the slope of the curve of serum creatinine during time. Further analysis of 5 patients with cyclosporine toxicity, confirmed by graft biopsy, showed that there was a slow down of the slope of serum creatinine after the switching from AZA to MMF (table 9, figure 4).

This conversion did not affect the liver enzymes measured and there was no change of the hematological patients' profile (tables 4, 5). The infections per patient year were not different compared with those of the year before conversion (table 6). The switching from AZA to MMF was not associated with graft rejection episodes, new cases of chronic al-

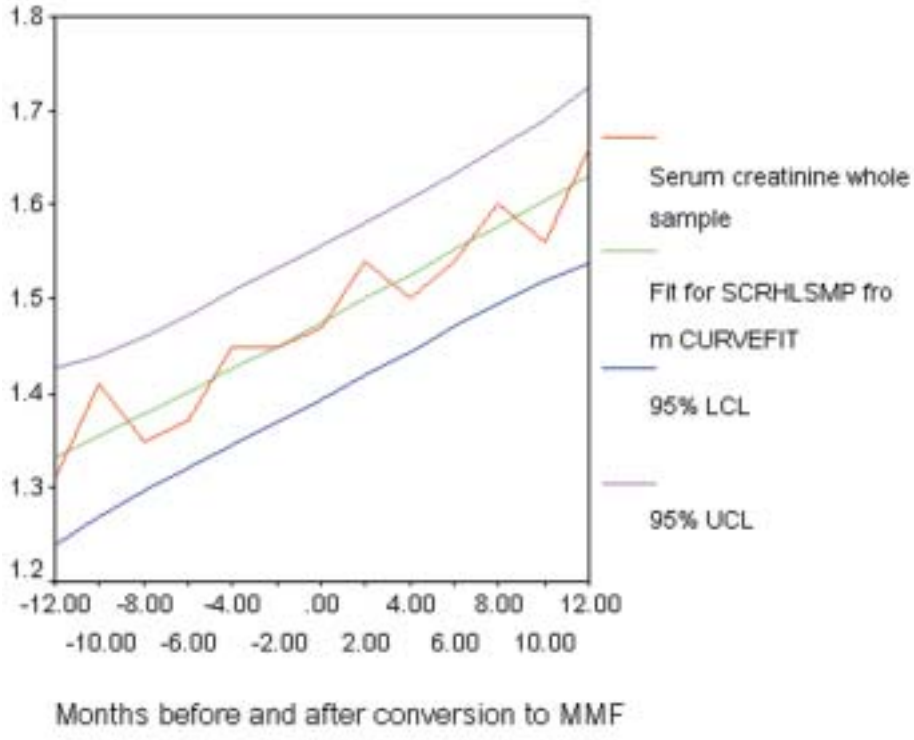

Fig. 1. The curve of serum creatinine in the whole patient sample

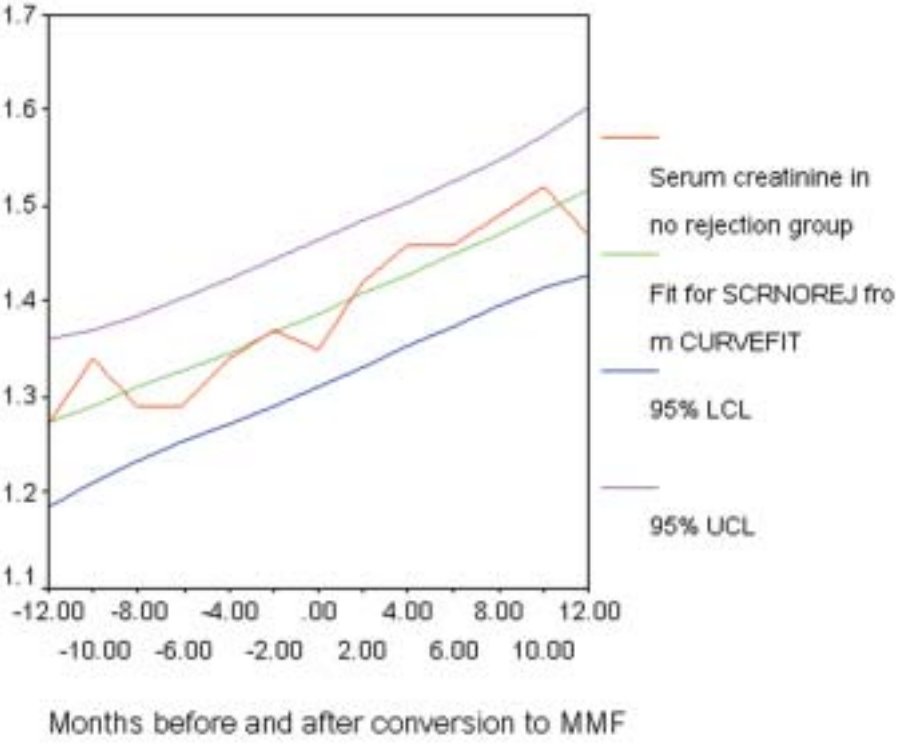

Fig. 2. The curve of serum creatinine in the group of patients with no rejection episodes

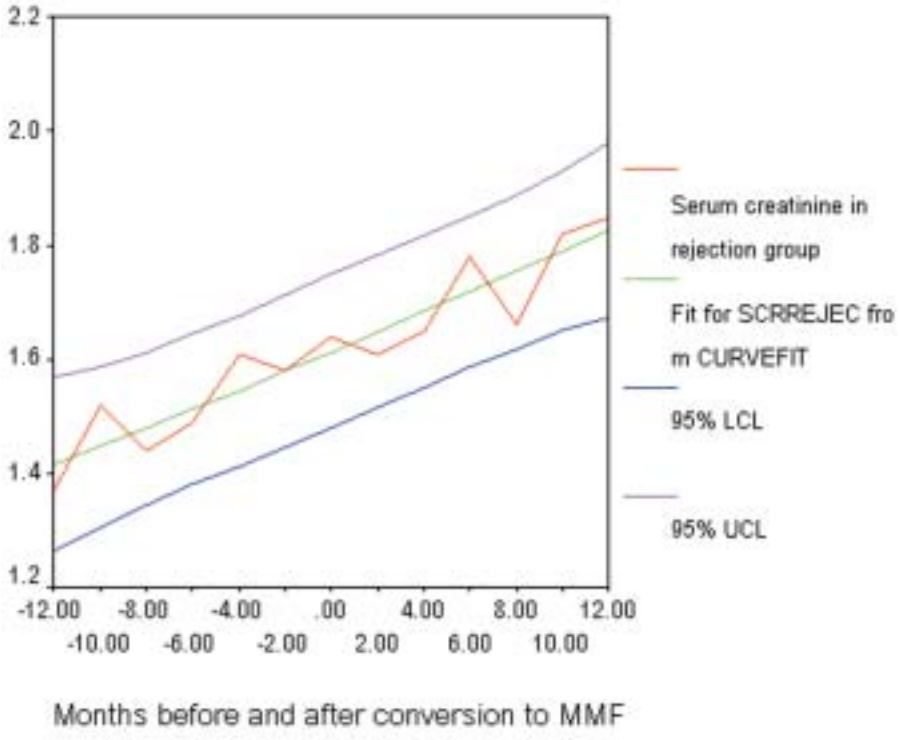

Fig. 3. The curve of serum creatinine in patients with acute rejection history or CAN

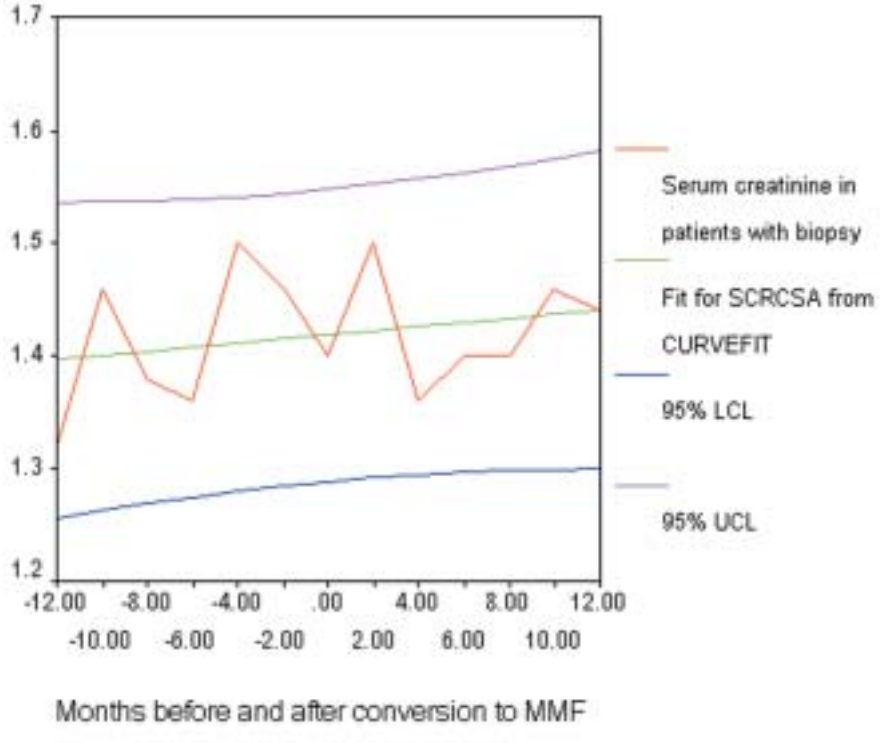

Fig. 4. The curve of serum creatinine in patients with biopsy proven CsA toxicity

lograft nephropathy, patient or graft loss during the follow up period.

In conclusion the shift from AZA to MMF retarded the graft function deterioration in patients with a history of acute rejection episode and chronic allograft nephropathy and allowed the lowering of cyclosporine dose in patients with cyclosporine toxicity and grafts from aged donors. It was safe because was not accompanied by new acute rejection episodes or new cases of chronic allograft nephropathy and there was no patient or graft loss.

Περίληψη

Γ. Βέργουλας, Γρ. Μυσερλής, Ι. Φούζας, Γ. Τρελλόπουλος, Β. Παπανικολάου, Δ. Γάκης, Ε. Ατματζίδης, Α. Αντωνιάδης. **Αντικατάσταση της αζαθειοπρίνης με mycophenolate mofetil σε ασθενείς με μεταμόσχευση νεφρού.** Ιπποκράτεια 2002, 6: 4: 177-185

Σκοπός της μελέτης ήταν να μελετήσουμε την ασφάλεια και την επίδραση της αντικατάστασης της αζαθειοπρίνης με MMF στην ανοσοκαταστολή συντήρησης μεταμοσχευμένων ασθενών. Στη μελέτη περιλήφθηκαν 50 ασθενείς (35 άνδρες), ηλικίας 34 ετών (διακύμανση 15 – 60 έτη). Η αντικατάσταση της AZA με MMF έγινε 5.24±2.43 έτη (διακύμανση 1.47-10.56 έτη) μετά τη μεταμόσχευση λόγω ανόδου της κρεατινίνης του ορού και/ή λευκωματουρίας. Οι ασθενείς είχαν πάρει τριπλή ή τετραπλή διαδοχική εισαγωγική ανοσοκαταστολή με κυκλοσπορίνη, AZA, μεθυλπρεδνιζολόνη, και αντιλεμφοκυτταρική σφαιρίνη. Σαράντα από αυτούς είχαν πάρει μόσχευμα από συγγενή ζωντανό δότη. Η κρεατινίνη ορού (Cs), το ολικό λεύκωμα του ορού (tP), τα επίπεδα της SGPT, ο αριθμός λευκών αιμοσφαιρίων και αιμοπεταλίων, και ο αιματοκρίτης (Ht) καταγράφηκαν ανά δίμηνο για διάστημα ενός έτους πριν και ενός μετά την μετατροπή. Το ίδιο χρονικό διάστημα καταγράφηκαν και οι λοιμώξεις. Η λευκωματουρία (12 ασθενείς) καταγράφηκε τη στιγμή της μετατροπής και ένα έτος αργότερα. Η στατιστική μελέτη έγινε με ANOVA για επανειλημμένες μετρήσεις και t test για ζεύγη τιμών (SPSS for Windows). Η Cs ήταν 1.31±0.35 mg/dl, 1.41±0.38 mg/dl, 1.35±0.38 mg/dl, 1.37±0.35 mg/dl, 1.45±0.38 mg/dl, 1.45±0.38 mg/dl και 1.47±0.40 mg/dl 12, 10, 8, 6, 4, 2 και 0 μήνες πριν από τη μετατροπή αντίστοιχα (p=0.0005), και 1,54±0.41 mg/dl, 1.50±0.41 mg/dl, 1.54±0.47 mg/dl, 1.60±0.49 mg/dl, 1.56±0.44 mg/dl, 1.66±0.57 mg/dl 2, 4, 6, 8, 10 και 12 μήνες μετά τη μετατροπή αντίστοιχα (p=0.35). Η λευκωματουρία ήταν 0.59±0.64 g/24h πριν και 0.64±0.69 g/24h ένα έτος μετά τη μετατροπή (p=NS). Οι λοιμώξεις ανά έτος ασθενείας ήταν 0.44±0.54 πριν και 0.42±0.53 ένα έτος μετά τη μετατροπή (p=NS). Τα λευκά αιμοσφαίρια, τα αιμοπετάλια, ο Ht, το ολικό λεύκωμα του ορού και η SGPT δεν έδειξαν σημαντική διαφορά στη διάρκεια του χρόνου πριν και μετά τη μετατροπή. Συμπερασματικά η αντικατάσταση της AZA με MMF επιβραδύνει της έκπτωση της λειτουργίας του μοσχεύματος σε ασθενείς με ιστορικό οξείας απόρριψης και / ή χρόνιας νεφροπάθειας του μοσχεύματος. Επιτρέπει την ελάττωση της δόσης της κυκλοσπορίνης σε ασθενείς με τοξικότητα από κυκλοσπορίνη ή ασθενείς που έχουν πάρει ηλικιωμένα μοσχεύματα. Η αντικατάσταση αυτή δεν συνδέθηκε με επεισόδια οξείας απόρριψης, εμφάνιση χρόνιας νεφροπάθειας μοσχεύματος ούτε με απώλεια ασθενών ή μοσχευμάτων.

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