MICOPHENOLAT MOFETIL VERSUS AZATHIOPRINE: EFFECTS ON RENAL GRAFT FUNCTION IN EARLY POSTTRANSPLANT PERIOD

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Abstract

All conventional immunosuppressive tree drugs-protocols are based on Cyclosporine; consisting of low doses of Cyclosporine (CsA), Azathioprine (AZA) or Mycophenolate Mofetil (MMF) and Prednisolone. AZA has been used in clinical transplantation for more than 30 years and was the first immunosuppressive agent to achieve widespread use in organ transplantation. MMF was introduced in clinical practice in 1995 after several clinical trials proved that it was more efficient than AZA for prevention of acute rejection episodes. Our aim was to evaluate influence of AZA and MMF on renal graft function in early post-transplant stage. Study recruited 74 patients who underwent kidney transplantation in University Clinical Centre Tuzla. All patients received CsA and corticosteroid-based immunosuppression, as a part of triple immunosuppressive regiment, 40 patients received AZA and 34 MMF. In order to assess renal graft function, following parameters were evaluated: glomerular filtration rate GFR (ml/min) creatinine clearance (CrCl) (ml/min), 24 h urine output (ml/day), and from the serum potassium, sodium, urea and creatinine (mmol/dm3). Significantly higher average values of 24 hour urine output were recorded during first seven postoperative days in patients receiving MMF compared to those treated with AZA. Serum creatinine values showed statistically significant decrease, starting with the second postoperative day, in MMF vs. AZA group (168,7±70,5 vs. 119,9±42,6; p<0,0007). GFR was significantly higher in MMF compared to the AZA group of patients. On the first post-transplant day CrCl was higher in AZA group (24,3±10 vs. 17,5±7,3; p=0,01), next six days situation is reversed CrCl is significantly higher in the MMF group (43,7±15 vs. 53, 4±22, 8 p=0,006). MMF vs. AZA therapy was associated with protective effect against worsening of renal function in first seven post-transplant days.

KEY WORDS: immunosuppression, MMF, AZA, renal graft function

Introduction

The first attempts at immunosuppression used total-body irradiation, AZA was introduced in the early 1960s, and was soon routinely accompanied by Prednisolone. The polyclonal antibody preparations antithymocyte globulin and antilymphocyte globulin became available in the mid-1970s. The situation was transformed in the early 1980s with the introduction of CsA (1). The initiation of CsA in kidney transplantation produced statistically significant amelioration in graft survival rates to greater than 80% at 1 year (2). CsA has greatly improved morbidity and mortality in transplantation patients; however its use is often accompanied by renal related unwanted side effects such as tubular atrophy, interstitial fibrosis, and focal hyalinosis of small renal arteries and arterioles (3, 4). Calcineurin-inhibitor therapy, a key component of triple immunosuppressive regiments for patients undergoing transplantation, has also been implicated as a principal cause of post-transplant renal dysfunction (5, 6).

Cyclosporine reduces renal blood flow by causing vasoconstriction of afferent arterioles and in the longer term by a variety of mechanisms including intimal thickening in blood vessels, hypertension and hyperlipidemia, and also leads to interstitial fibrosis in the kidney (7). All conventional immunosuppressive tree drugs-protocols are based on CsA; consisting of low doses of CsA, AZA or MMF and Prednisolone (8). Azathioprine has been used in clinical transplantation for more than 30 years and was the first immunosuppressive agent to achieve widespread use in organ transplantation (9). Developers of AZA, Gertrude Elion and George Hitchings, were acknowledged by a share of the 1988 Nobel Prize (10). Azathioprine is a pro-drug that releases 6-mercaptopurine which is afterwards converted into active component 6-thioinosine-5'-monophosphate. Active component of AZA interferes with production of deoxyribonucleic acid (DNA) by incorporation into cellular DNA, where it inhibits purine nucleotide creation and interferes with synthesis and metabolism of ribonucleic acid (RNA) (1, 11). When cyclosporine was introduced, AZA became second-line drug, and was used as an adjunctive agent in most circumstances. With the introduction of MMF, its use has been discontinued in many programs (12). Mycophenolate Mofetil was introduced in clinical practice in 1995 after several clinical trials proved that it was more efficient than AZA for prevention of acute rejection episodes (12,13). Mycophenolate Mofetil is an inactive prodrug that is converted to its active compound mycophenolic acid (MPA) by intestinal, liver and plasma esterase's (14). Mycophenolic acid is potent, non-competitive, reversible inhibitor of inosine-5-monophosphate dehydrogenase, an enzyme necessary for lymphocyte mitosis (15). Mycophenolic acid is relatively specific inhibitor of lymphocyte proliferation; whose inhibitory doses do not affect other proliferatory tissues, selectivity of MMF is its most important feature. Mycophenolate Mofetil inhibits proliferation of T and B lymphocytes, antibody production and generation of cytotoxic T cells. Mycophenolate Mofetil was found to be a more effective agent than AZA by virtue of its capacity to reduce the incidence of acute rejection episodes when used with cyclosporine (and later with tacrolimus) and corticosteroids (1). Various clinical studies comparing MMF to AZA have demonstrated superiority of MMF in prevention of acute rejection episodes (13, 16). Our aim was to evaluate influence of MMF and AZA on renal graft function in early post-transplant period.

Patients and Methods

This is an observational cohort study; it recruited 74 patients who underwent kidney transplantation in University Clinical Centre Tuzla. Of the patients studied 69 % were men and 31 % women, whose age at transplantation was 32,9 ± 9,7 years. All patients received CsA and corticosteroid-based immunosuppression, as a part of triple immunosuppressive regiment, 40 patients received AZA and 34 MMF. All patients were assessed as ASA IV (American Society of Anaesthesiologists) physical status. Balanced anaesthesia was used in all transplant patients. Postoperatively all patients were placed in Intensive Care Unit (ICU); length of ICU stay depended on function of transplanted kidney and general condition of the patients. Continuous monitoring of central venous pressure (CVP), arterial pressure and oxygen saturation of blood, were applied. Central venous route was insured trough sublacvian vein and was used for intravenous fluids administration and CVP measuring. Fluid resuscitation depended on CVP values. In order to assess renal graft function, following parameters were evaluated: GFR (ml/min) CrCl (ml/min), 24 h urine output, and from the serum potassium, sodium, urea and creatinine (mmol/dm3). During first seven post transplant days all parameters were assessed daily. CVP was measured every four hours; in our research were used average daily values. Glomerular filtration rate was calculated using following formula:

$$GFR = 270 \times Cr^{-1,007} \times Age^{-0,18} \times Bun^{-0,169} \times 0,755 \text{ (female)} \quad (17).$$

Creatinine clearance was calculated by using formula proposed by Cockcroft and Gault, which is formula widely used to detect onset of renal insufficiency.

$$\text{Creatinine clearance} = (140\text{-age}) \times \text{BW (kg)} / (72 \times \text{creatinine}) \quad (18).$$

Statistical analysis

The statistical analysis was performed using Student t-test, p-value of 0,05 or less was considered statistically significant.

Results

The study was conducted in University Clinical Centre Tuzla. It included 74 patients mean age 32, 9±9, 7 years, 51 were males and 23 females. Mean donor age was 49, 2±12, 2 years, 48 donors were younger then 55 years and 26 were older. All transplant patients received CsA and steroids postoperatively; besides CsA 34 patients were treated with MMF, and the rest of them with AZA. Statistical analysis shoved significantly higher average values of 24 hour urine output in a group of patients receiving MMF compared to the patients being treated with AZA (Figure 1). Average values of serum creatinine did not differ significantly on the first post-transplant day (436,5±230,1 vs. 475,5±182,2 p= 0,43). On the second postoperative day positive statistically significant decrease in serum creatinine values was observed in MMF group (168,7±70,5 vs. 119,9±42,6; p<0,0007) (Figure 2).

On the first post-transplant day there was no significant difference in glomerular filtration rate between compared groups. Following six days glomerular filtration rate was significantly higher in MMF compared to the AZA group of patients (Figure 3). Values of creatinine clearance are significantly higher in the AZA group of patients but only on first post-transplant day (24,3±10 vs. 17,5±7,3; p=0,01), next six days situation is reversed and creatinine clearance values are rising and are significantly higher in the MMF group, reaching there peak on the fifth postoperative day (43,7±15 vs. 53,4±22,8 p=0,006) (Figure 4).

Discussion

Over the last 20 years allograft and renal transplant recipient survival have considerably ameliorated, this is a result of many factors, especially improvement in efficiency and lessening in toxicity of immunosuppressive drugs. This study was undertaken in order to evaluate influence of two different immunosuppressive agents on renal graft function in first seven post-transplant

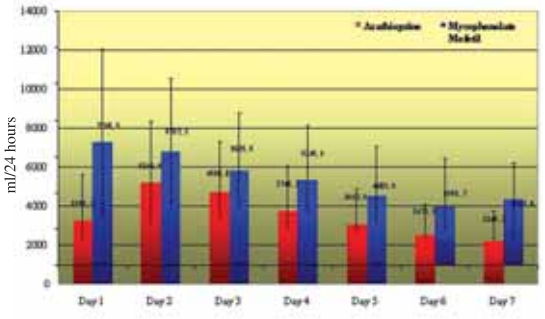

FIGURE 1. Average values of 24 hour urine output compared to the type of immunosuppressive treatment

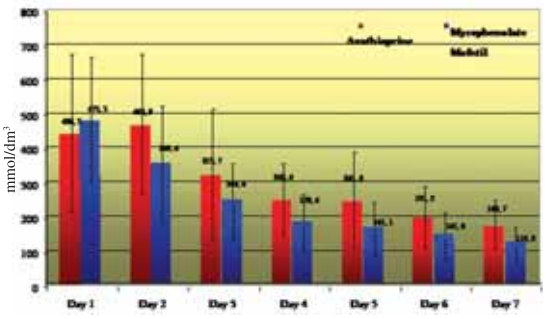

FIGURE 2. Average values of serum creatinine compared to the type of immunosuppressive treatment

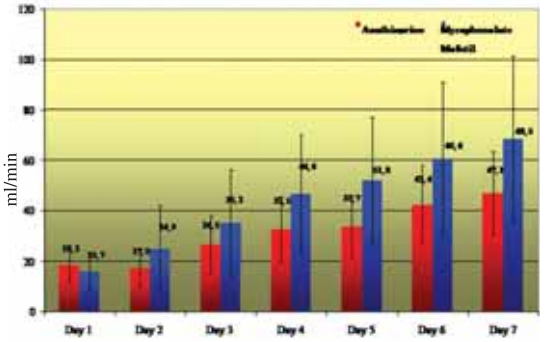

FIGURE 3. Average values of glomerular filtration rate compared to the type of immunosuppressive treatment

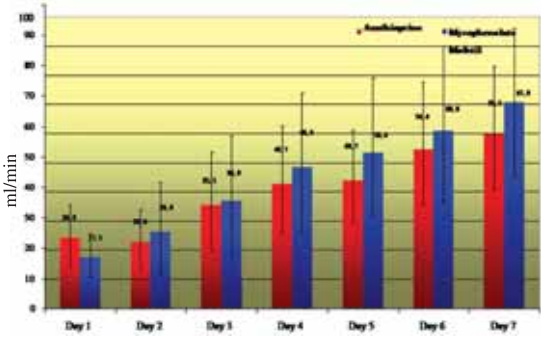

FIGURE 4. Creatinine clearance values compared to the type of immunosuppressive treatment

days. Renal function has long been recognized as a critical determinant of the probability of graft survival, and its critical role as a predictor of survival has been confirmed in the United Network for Organ Sharing (UNOS) database (19). Risk of acute kidney rejection is greatest in early post-transplant period; therefore during this period close monitoring is warranted. Assessment of renal graft function in our study, (during first seven postoperative days) was based on daily monitoring of GFR, serum creatinine levels, CrCl and 24 hour urine output, in both AZA and MMF group. The glomerular filtration rate is traditionally considered the best overall index of renal function in health and disease. Serum creatinine and calculated CrCl have been proposed as outcome measures in renal transplantation as well as in primary renal diseases (20). Forty of 74 recipients were given AZA and to 34 MMF as a part of triple immunosuppressive treatment. The patients who received MMF had significantly higher values of 24 hour urine output during observed period, compared to patients treated with AZA. Creatinine clearance was also significantly higher in MMF group (43,7±15 vs. 53,4±22,8; p=0,006), with the exception of the first post-transplant day (24,3±10 vs. 17,5±7,3; p=0,01). Sita et al. found that more stable CrCl, i.e., a lower rate of loss of CrCl, was associated with the use of MMF versus AZA, during six month post-transplant period (21). In the study conducted by Gourishankar and colleagues, a more stable creatinine clearance was associated with use of MMF versus AZA (22). In our research statistically significant decrease in average values of serum creatinine values was also observed in MMF group, after the first post-transplant day. We also found significantly higher values of GFR in the MMF group. Gill and colleagues conducted a retrospective analysis of 40,963 first kidney only transplant recipients, with allograft survival of at least 2 years. Patients were classified according to the type of maintenance Calcineurin (conventional cyclosporine, cyclosporine microemulsion, tacrolimus) and purine metabolism inhibitor (AZA, MMF) they received after transplantation. The objective of the study was to determine the effect of immunosuppressive agents on the rate of kidney allograft function loss by monitoring changes in GFR. Patients receiving MMF demonstrated slower decline in GFR than those patients receiving AZA (23). Mycophenolate Mofetil is a non-nephrotoxic immunosuppressant specific for T and B-cells. Compared with AZA, superior safety and efficacy of MMF has been demonstrated in hearth, kidney and liver transplant recipients (24, 25, 26). The use of MMF with lower cyclosporine dosages has been reported to improve renal function while maintaining adequate immunosuppression (27). Azathioprine has been used in clinical transplantation for over 40 years but MMF is a more powerful immunosuppressant associated with better short-term- and probably better long-term-outcomes (19, 28).

Conclusion

Our research analyzed influence of two different immunosuppressive treatments on renal allograft function in first seven postoperative days. Detection of renal graft deterioration in early post-transplant stage can be an important predictor of chronic rejection which is the most important cause of graft loss in long-term studies. According to our results, MMF vs. AZA therapy was associated with protective effect against worsening of renal function in first seven post-transplant days.

List of Abbreviations

AZA	-	Azathioprine
ASA	-	American Society of Anaesthesiologists
CsA	-	Cyclosporine
CrCl	-	creatinine clearance
CVP	-	central venous pressure
DNA	-	deoxyribonucleic acid
GFR	-	glomerular filtration rate
MMF	-	Mycophenolate Mofetil
MPA	-	mycophenolic acid
RNA	-	ribonucleic acid
ICU	-	Intensive Care Unit
UNOS	-	United Network for Organ Sharing

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