Freedom from Rejection and Stable Kidney Function are Excellent Criteria for Steroid Withdrawal in Tacrolimus-Treated Kidney Transplant Recipients

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Abstract:
Objectives: This prospective, randomized, multicentre study investigated the efficacy and safety of two tacrolimus-based regimens and their potential to withdraw steroids. **Methods:** In total 489 patients were randomised to receive either tacrolimus and MMF (n=243) or tacrolimus and azathioprine (n=246) concomitantly with steroids in both treatment groups. The initial oral dose of tacrolimus was 0.2 mg/kg/day, MMF dose was 1 g/day, azathioprine was administered at 1-2 mg/day. Steroids were tapered from 20 mg/day to 5 mg/day. From month 3 onwards, steroids were withdrawn in patients who were free from steroid-resistant rejection and who had serum creatinine concentrations <160 μmol/L. Study duration was 6 months. **Results:** Patient survival at month 6 was 98.3% (Tac/MMF/S) and 98.4% (Tac/Aza/S), graft survival at 6 month was 95.0% (Tac/MMF/S) and 93.5% (Tac/Aza/S). The 6-month incidences of biopsy-proven acute rejection were 18.9% (Tac/MMF/S) compared with 26.8% (Tac/Aza/S), p=0.038. The 6-month incidences of steroid-resistant acute rejection were 2.1% (Tac/MMF/S) and 4.9% (Tac/Aza/S), p=ns. At the end of month 3, steroid withdrawal was performed in 60.5% (Tac/MMF/S) and 48.8% (Tac/Aza/S) of patients, p<0.01. During months 4-6, 2.7% of patients in the Tac/MMF group had a biopsy-confirmed acute rejection compared with 0.8% of patients in the Tac/Aza group. In patients who continued to receive steroids, the incidences of biopsy-proven acute rejections during months 4-6 were 3.5% (Tac/MMF/S) and 7.1% (Tac/Aza/S). At study end, the steroid-free patients had an excellent kidney function, the median serum creatinine concentration was 119.5 μmol/L (Tac/MMF) and 115.1 μmol/L (Tac/Aza); the median serum creatinine of the total study group was 130.5 μmol/L (Tac/MMF/S) and 132.8 μmol/L (Tac/Aza/S). **Conclusion:** Both tacrolimus regimens are efficacious and safe. The combination of Tacrolimus and MMF achieved a lower rejection rate and permitted a higher proportion of steroid-free patients. The overall incidence of acute rejection was low and kidney function was good.

Key words: graft function, renal transplantation, immunosuppression

Introduction

In recent years steroid withdrawal has become a major objective in the optimisation of immunosuppression following renal transplantation. The risks of continued steroid treatment are well known and include detrimental effects on lipid metabolism, development of diabetes mellitus, worsening of hypertension, and bone demineralisation [1]. There are a number of reports demonstrating short term advantages of steroid withdrawal [2-4]. Nevertheless, there are often substantial numbers of patients who experience rejection episodes when steroids are withdrawn [5]. Therefore, one of the most difficult issues concerning the withdrawal of steroids is the question how to identify suitable patients that are likely to tolerate steroid-free regimens. By comparing the efficacy and safety of two tacrolimus-based regimens we also evaluated the potential of the two regimens to withdraw steroids.

Methods

This was a prospective, open, randomised, multicentre study conducted in 4 countries (Poland, Hungary, Czech Republic and Ireland). Study duration was 6 months.

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Patients were eligible for study entry if they were 18 years or older and candidates for primary renal transplantation or retransplantation. Patients received grafts from cadaveric or living donors of 5-65 years of age. Female patients had to maintain effective birth control during the study. Patients were excluded from participation if their PRA-grade was above 50% or if they had lost a previous graft within less than 1 year due to immunological reasons as were patients who were intolerant to any of the study drugs, HCO-60, or macrolide antibiotics. Patients who required systemic immunosuppressive medication for other reasons than transplantation, who had significant liver disease, had severe diarrhoea, had a history of malignancy, uncontrolled infections or were HIV positive could not be included into the study. Furthermore patients who were unlikely to comply or had a history of substance abuse were excluded.

Immunosuppression

In total, 489 patients were randomised to either receive a triple regimen of tacrolimus, MMF and steroids (n=243) or tacrolimus, azathioprine, and steroids (n=246). The initial oral dose of tacrolimus was 0.2 mg/kg/day. Subsequent tacrolimus doses were tapered according to whole blood trough levels of 15 ng/mL on days 0-21, 10-15 ng/mL on days 22-41, and 5-10 ng/mL on days 42-183. Mycophenolate mofetil (MMF) was administered at 1 g/day. Azathioprine dose was 1-2 mg/kg/day during the entire study period.

Steroids were tapered during months 1-3 according to the following schedule. Patients received an intraoperative bolus of 500 mg or less methylprednisolone on day 0 (day of skin closure) and 125 mg prednisolone i.v. on day 1. On days 2-14 the oral prednisone dose was 20 mg, on days 15-28 15 mg, on days 29-42 10 mg, and 5 mg on days 43 -91.

At the end of month 3 steroid withdrawal was performed in patients who did not experience a steroid-resistant acute rejection during the first 2 months of the study and who had a serum creatinine concentration below 160 μmol/L at days 84-91 post transplant. Furthermore, patients had to receive at least 1 mg/kg/day of azathioprine or 0.5 g/day of MMF.

Results

Patients

In both study arms a very high percentage of patients completed the study (93.0 % in the tacrolimus/MMF/steroids group and 91.9% in the tacrolimus/azathioprine/steroids group). In each study arm 4 patients died and the number of patients withdrawn from the study was also similar (5.8% in the Tac/MMF/steroids group and 6.5% in the Tac/Aza/steroids group). Demographics and baseline characteristics were comparable in both study groups (Table 1).

At the end of month 3, in the Tac/MMF/steroids group 147 patients (60.5%) were assigned to steroid taper compared to 120 patients (48.8%) in the Tac/Aza/steroids group, p<0.01.

Immunosuppression

In the Tac/MMF/steroids group the mean oral tacrolimus dose dropped from 0.182 mg/kg/day during week 1 to 0.089 mg/kg/day during month 6. Likewise the mean oral tacrolimus dose was 0.185 mg/kg/day during week 1 and 0.107 mg/kg/day during month 6 in the Tac/Aza/steroids group. The corresponding mean whole blood trough levels were 15.9 ng/mL during week 1 and 9.2 ng/mL during month 6 in the Tac/MMF/steroids group compared with 14.38 ng/mL (week 1) and 8.95 ng/mL (month 6) in the Tac/Aza/steroids group (Figure 1).

Table I. Demographics and baseline characteristics

	Tacrolimus/MMF/ /Steroids N=243	Tacrolimus/Aza/ /Steroids N=246
Mean patient age	43.8 years	42.1 years
Male sex	156 (64.2%)	157 (63.8%)
Number of transplants		
1st transplant	229 (94.2%)	234 (95.1%)
2nd transplant	14 (5.8%)	12 (4.9%)
Mean HLA mismatch	2.8	2.6
CMV mismatch R-/D+	30 (12.3%)	40 (16.3%)
Organ donation		
Cadaveric	234 (96.3%)	235 (95.5%)
Living	9 (3.7%)	11 (4.5%)
Mean cold ischemia time	21.0 hours	21.7 hours

Efficacy

The 6-month incidence of acute rejection confirmed by biopsy was 18.9% in the Tac/MMF/steroids group and 26.8% in the Tac/Aza/steroids group, p=0.038.

The incidence of steroid-resistant acute rejection was low in both treatment groups.

The majority of acute rejections happened during the first 3 months. During months 4-6 only very few rejection episodes were reported (Table 2). There was no difference in the incidence of acute rejections during months 4-6 between the steroid withdrawal groups and the steroid receiving groups.

At the end of month 3 the median serum creatinine concentrations in the Tac/MMF/steroids was 137 μmol/L compared with 150.5 μmol/L in the Tac/Aza/steroids group. In patients assigned to steroid withdrawal, kidney function at study end was excellent. The median serum creatinine concentrations at month 6 was 119.5 μmol/L in the Tac/MMF group and 115.1 μmol/L in the Tac/Aza group. In the patients who continued steroids the median serum creatinine concentrations were 180.5 μmol/L (Tac/MMF/steroids) and 168.2 μmol/L (Tac/Aza/steroids).

Safety

Patient survival at month 6 was 98.3% (Tac/MMF/steroids) and 98.4% (Tac/Aza/steroids), p=0.972. In the Tac/MMF/steroid group 12 grafts were

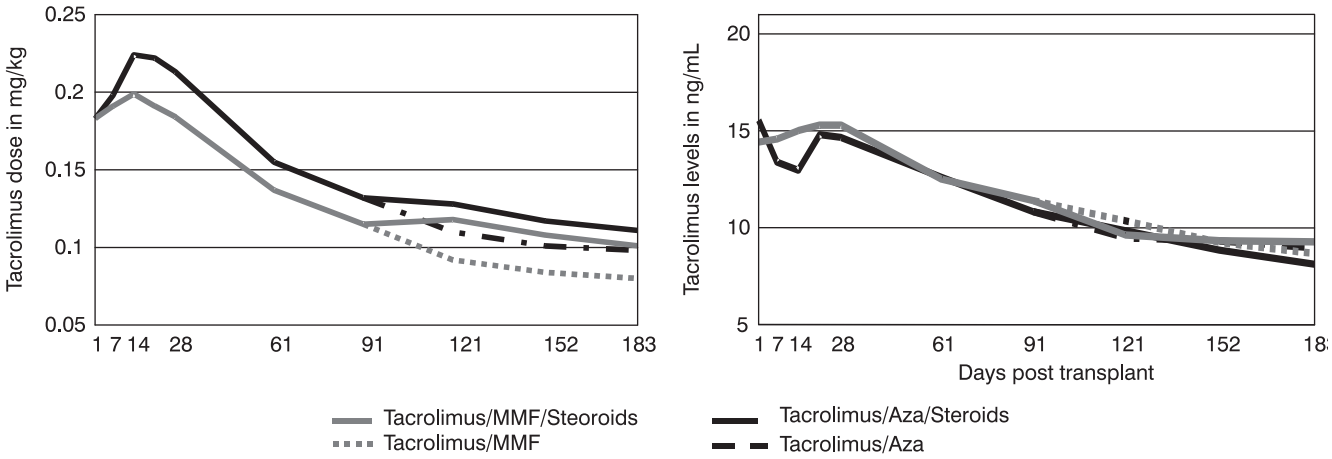

Figure 1. Mean tacrolimus dose and mean whole blood trough level

Table 2. Incidence of acute rejection confirmed by biopsy

	Tacrolimus/MMF/Steroids N=243		Tacrolimus/Aza/Steroids N=246	
Months 1-3				
Acute rejection	44 (18.1%)		64 (26.0%)*	
Steroid-resistant acute rejection	5 (2.1%)		11 (4.5%)	
Months 4-6				
	Tac/MMFN=147	Tac/MMF/SN=85	Tac/AzaN=120	Tac/Aza/SN=113
Acute rejection	4 (2.7%)	3 (3.5%)	1 (0.8%)	8 (7.1%)
Steroid-resistant acute rejection	0	0	0	2 (1.8%)

* p=0.035

Table 3. Adverse events with a significantly different incidence in the treatment groups

	Tacrolimus/MMF/Steroids N=24	Tacrolimus/Aza/ Steroids 3N=246	P-value
Abnormal kidney function	18.5%	27.2%	0.019
Kidney tubular necrosis	9.5%	15.9%	0.033
Leukopenia	2.9%	8.5%	0.001
Bronchitis	4.9%	1.2%	0.011
Herpes zoster	2.9%	0	0.007
Hypercholesteremia	2.5%	0	0.015
Gastritis	2.1%	0	0.030

lost compared with 16 grafts lost in the Tac/Aza/steroid group. Graft survival at month 6 was 95.0% (Tac/MMF/steroids) and 93.5% (Tac/Aza/steroids), p=0.472.

The incidence of adverse events was similar in both treatment groups. However, there were a number of adverse events for which significant differences between the treatment groups were observed (Table 3). Although the incidences were low, there was a tendency for more kidney function disorders in the Tac/Aza/steroids group and more infectious complications in the Tac/MMF/steroid group (Table 3).

Discussion and Conclusion

Both tacrolimus based regimens were efficacious and safe. Excellent patient and graft survival rates were

achieved. The criteria chosen for the selection of patients to undergo steroid withdrawal were successful: There were no more rejections in the steroid withdrawal groups than in the patients who continued on steroids. Kidney function in patients subjected to steroid withdrawal was very good. However, in patients remaining on steroids renal function was inferior. This was obviously a result of the selection process. Good risk patients with a good graft function and without a rejection were selected for steroid withdrawal while patients with a more difficult clinical course remained on steroids. This shows that the criteria chosen to select patients for steroid withdrawal namely the absence of a steroid-resistant rejection and a serum creatinine concentration below 160 μmol/L at month 3 post transplant were adequate. In both study groups, steroid withdrawal was performed successfully. Patients could easily be managed on a Tacrolimus/ MMF regimen as well as on a Tacrolimus/ Azathioprine regimen and the efficacy results as well as the safety data are very encouraging in both treatment groups.

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