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Benelux Experience With a Combination of Tacrolimus and Mycophenolate Mofetil: 4-Year Results

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THE PRESENT analysis was performed in a subset population of the European multicenter tacrolimus/mycophenolate mofetil (MMF) study.[1–3] The rationale for this subset analysis is that a full 4-year follow-up of all patients participating in the three Benelux centers (Maastricht, Brussels, and Leuven) is now available, that these centers had similar patient populations and donor-recipient matching policies, and that all three centers had experience using both tacrolimus and MMF.

The objectives of the follow-up were to determine whether MMF could be withdrawn in stabilized patients and to evaluate, in the longer term, the incidence of rejection and the side effects associated with the tacrolimus/corticosteroid/MMF combination. Results at 2 years have been published previously.[4]

METHODS

This prospective, randomized, multicenter trial was conducted in adult renal transplant recipients and excluded those with current or previous malignancies or liver disease or recent infection. Patients were randomized (1:1:1) to receive tacrolimus and corticosteroids (group 1, $n = 25$); tacrolimus/corticosteroids/MMF 1 g/d (group 2, $n = 25$); or tacrolimus/corticosteroids/MMF 2 g/d (group 3, $n = 23$). In all three groups, the initial recommended dose of tacrolimus was 0.2 mg/kg per day, with initial blood target levels of <15 ng/mL, with no lower limit. The corticosteroid protocol comprised methylprednisone, given as a 500 mg bolus on day 0 and a 125-mg bolus on day 1, followed by a rapid oral corticosteroid taper from 20 mg/day (days 2 to 14) to 5 mg/day (days 43 to 90) and thereafter administered at the investigator's discretion. MMF withdrawal was also left to the investigator's discretion. The initial immunosuppressive regimen excluded the use of antilymphocyte globulin as induction therapy, and treatment of rejection was by best local therapy. After the first 6 months posttransplant, changes in the immunosuppressive protocol were at the investigator's discretion.

RESULTS

Patients

All 73 patients recruited to the three Benelux centers completed at least 4 years of follow-up; patients were censored at death. No statistically significant differences in baseline characteristics were observed between the three treatment groups (Table 1), although there was a slightly higher HLA-mismatching rate in group 1 and a lower percentage of non-heart-beating donors in patients randomized to group 2.

Table 1. Patient Demographics

	Group 1 Tac/Steroids ($n = 25$)	Group 2 Tac/Steroids/ MMF 1 g ($n = 25$)	Group 3 Tac/Steroids/ MMF 2 g ($n = 23$)
Mean age (years)	45.0 ± 14.5	45.8 ± 12.4	49.0 ± 12.6
Male donors (%)	56	56	65
Mean HLA mismatch	2.80	2.16	2.30
Retransplants (%)	12	8	26
Non-heart-beating donors (%)	20	8	26

Tac = tacrolimus.

Efficacy

The overall patient survival rate at year 4 was 93.1%, with no major differences among the treatment groups (Table 2). Graft survival for the entire study population was 80.8%, and again there were no significant differences among the three treatment groups (Table 2). There were no new episodes of acute rejection between the 2- and 4-year follow-ups. Three patients died, and an additional five grafts were lost after the first year. One death was due to a cerebrovascular accident after 23 months with excellent graft function and another to carcinoma of the colon; the cause of the third death is unclear (the patient was found dead at home). The other causes of graft loss comprised hemolytic uremic syndrome ($n = 1$), chronic rejection ($n = 2$, one each in groups 1 and 2), prolonged ischemia ($n = 1$), and recurrent glomerulonephritis ($n = 1$). The overall projected graft half-life was 16.5 years.

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Table 2. Four-Year Patient and Graft Survival by Treatment Group

	Group 1 Tac/Steroids (n = 25)	Group 2 Tac/Steroids/ MMF 1 g (n = 25)	Group 3 Tac/steroids/ MMF 2 g (n = 23)
Patient survival (%)	92	92	100
Graft survival (%)	72	80	92

Tac = tacrolimus.

Tacrolimus Dosing and Immunosuppressive Regimens at 4 Years

At 4 years, 59 patients were alive with functioning grafts. Tacrolimus had been withdrawn in three patients: in one because of early graft dysfunction, in another for alopecia, and in a third for neurologic complications (polyradiculitis). Primary immunosuppressive therapy was continued with cyclosporine in two of these patients and with prednisolone/azathioprine in the third. In the remaining patients, the mean tacrolimus dose and whole-blood trough level were 0.07 ± 0.04 mg/kg and 7.7 ± 2.8 ng/mL, respectively. While there were no statistically significant differences in tacrolimus blood levels between patients who were receiving concomitant steroids (7.86 ± 3.23 ng/mL) and those who were not (7.49 ± 1.84 ng/mL), the steroid-treated group required significantly higher doses of tacrolimus (0.08 ± 0.05 mg/kg vs 0.05 ± 0.01 mg/kg, respectively; $P < .05$, Student's t test).

MMF could be withdrawn from more than 80% of the patients randomized to receive it by the end of the first year posttransplant and, by the end of the fourth year, had been withdrawn from all but 13 patients, including four who had received it as an add-on therapy.

At the end of 4 years, 15 patients (27%) were receiving tacrolimus monotherapy, 33 (59%) received dual combinations (n = 28 tacrolimus/corticosteroids, n = 5 tacrolimus/MMF), and eight (14%) received triple therapy. Immunosuppression was maintained in 20 patients (36%) without the use of corticosteroids (n = 15 tacrolimus monotherapy, n = 5 tacrolimus/MMF). Immunosuppressive regimens according to the original intent-to-treat groups are presented in Table 3.

Table 3. Immunosuppression at 4 Years

	Intention-to-treat population		
	Group 1 Tac/Steroids (n = 17)	Group 2 Tac/Steroids/ MMF 1 g (n = 19)	Group 3 Tac/Steroids/ MMF 2 g (n = 20)
Tacrolimus monotherapy	4	5	6
Tacrolimus/MMF	1	2	2
Tacrolimus/steroids/MMF	2	4	2
Tacrolimus/steroids	10	8	10

Tac = tacrolimus.

Safety and Tolerability

One patient in this subset had developed new-onset insulin-dependent diabetes mellitus at the 2-year follow-up. By 4 years, however, this patient no longer needed insulin. Three patients with impaired glucose tolerance were successfully managed with oral antidiabetic medication. Good renal function was maintained after 4 years of tacrolimus-based therapy, as shown by a mean serum creatinine concentration of 143 ± 78 μmol/L. Mean blood pressure for the entire intent-to-treat population was 137/81 mm Hg; 20 of 56 patients (36%) needed no antihypertensive medication, while a further 18 (32%) were managed with only one such agent. Lipid profiles remained excellent, as shown by mean serum total cholesterol (4.9 ± 0.9 mmol/L), low-density lipoprotein cholesterol (2.8 ± 0.6 mmol/L), and triglycerides (1.71 ± 0.97 mmol/L). Twelve of 56 patients (21%) were receiving lipid-lowering medication with statins.

There were no statistically significant differences in terms of adverse events among the three treatment groups or according to corticosteroid treatment. Patients receiving steroids had a mean serum glucose level of 5.5 ± 2.0 mmol/L compared with 6.6 ± 2.4 mmol/L for those patients no longer requiring steroids; serum creatinine was 145 ± 87 μmol/L and 140 ± 57 μmol/L, respectively, and total cholesterol was 5.1 ± 0.8 mmol/L and 4.9 ± 1.0 mmol/L. Antihyperlipidemic medication was required by 9 of 36 (25%) patients receiving steroids and by 3 of 20 (15%) patients in the steroid-free group. Mean blood pressure was also similar: 136/83 mm Hg (corticosteroid group) and 137/78 mm Hg (corticosteroid-free group).

DISCUSSION AND CONCLUSION

The long-term results of the Benelux study confirm those of the European tacrolimus/MMF multicenter study:[1–3] that is, the efficacy and safety of the combination of tacrolimus and MMF therapy for the prevention of rejection following kidney transplantation. After 4 years of follow-up, excellent long-term patient and graft survival rates were achieved, as well as stable renal function and an excellent metabolic profile.

The Benelux follow-up also clearly conveys that MMF can be withdrawn after the initial transplantation period without any deleterious effects, including an increase in rejection rate. At the end of 4 years, more than a quarter of all patients had been converted to tacrolimus monotherapy, and more than a third did not require corticosteroids for maintenance immunosuppression. The latter finding is of particular importance in terms of the potential for reducing steroid-associated adverse events such as diabetes and hyperlipidemia, which are important cardiovascular risk factors. In this analysis, however, no significant differences were observed in terms of adverse events between corticosteroid-containing and corticosteroid-free regi-

mens, perhaps due to the small numbers of patients involved.

The use of MMF is beneficial with respect to reducing the incidence of acute rejection during the initial period after transplantation, but thereafter its withdrawal can be safely accomplished in most cases, as can corticosteroid therapy, thereby enabling customization of immunosuppressive regimens to the needs of the patient.

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