Transpl Int (1998) 11 [Suppl 1]: S73–S77

I. A. Hauser
H.-N. Neumayer

Tacrolimus and cyclosporine efficacy in high-risk kidney transplantation

on behalf of the European Multicentre Tacrolimus (FK506) Renal Study Group

I. A. Hauser (✉) · H.-N. Neumayer[1]
University Erlangen-Nürnberg,
Department of Medicine IV,
Klinik Nürnberg Süd,
D-90471 Nürnberg, Germany
Fax + 49-911-8906647

A. D. Mayer · J. Dmitrewski
Queen Elizabeth Hospital,
Birmingham B15 2TH, UK

J.-P. Squifflet · T. Besse
Université Catholique de Louvain,
Cliniques Universitaires Sanit-Luc,
B-1200 Bruxelles, Belgium

B. Grabensee · B. Klein
Heinrich Heine Universität Düsseldorf,
D-40225 Düsseldorf, Germany

F. W. Eigler · U. Heemann
Universitätsklinik, D-45147 Essen,
Germany

R. Pichlmayr · M. Behrend
Medizinische Hochschule Hannover,
D-30625 Hannover, Germany

Y. Vanrenterghem · J. Donck
Universitaire Ziekenhuizen Gasthuisberg,
B-3000 Leuven, Belgium

J. van Hooff · M. Christiaans
Academisch Ziekenhuis, B-6201 BX
Maastricht, Belgium

J. M. Morales · A. Andres
Hospital Universitario '12 de Octubre',
E-28041 Madrid, Spain

R. W. G. Johnson · C. Short
Manchester Royal Infirmary,
Manchester M13 9WL, UK

B. Buchholz · N. Rehmert
Westfälische Wilhelms Universität,
D-48149 Münster, Germany

W. Land · S. Schleibner
Ludwig-Maximilians-Universität,
Klinikum Großhadern, D-81366 München,
Germany

J. L. R. Forsythe · D. Talbot
Royal Victoria Infirmary,
Newcastle-upon-Tyne NE1 4LP, UK

B.-G. Ericzon · C. Brattström · K. Claesson
Karolinska Institute, Huddinge Hospital,
S-141 86 Huddinge/Uppsala University
Hospital, S-751 85 Uppsala, Sweden

F. Mühlbacher · E. Pohanka
Allgemeines Krankenhaus, A-1090 Wien,
Austria

Present address:
[1] Universitätsklinikum Charitè,
D-10098 Berlin, Germany

Abstract The efficacy and safety of tacrolimus- and cyclosporine-based immunosuppressive regimens were compared in a prospectively defined subgroup of kidney transplant recipients from the European, open, multicentre, 2 : 1 randomised, parallel group study. Patients were stratified as high risk for immunological events if they had a panel-reactive antibodies grade greater than 80% and/or a previous transplant functional for less than 1 year. The primary efficacy variables evaluated were the incidence of acute rejection, steroid usage and patient and graft survival. Safety was assessed based on adverse events and laboratory evaluations. At 1 year, the tacrolimus group ($n = 22$) had a lower incidence of biopsy-proven acute rejection (31.8%) and a higher graft survival (86.0%) than the 11 patients in the cyclosporine group (54.5% and 72.0%, respectively). The frequencies of adverse events were similar between the two groups. The tacrolimus regimen appears more beneficial for high risk patients than cyclosporine.

Key words Tacrolimus · Cyclosporine · Kidney transplantation · High risk

Introduction

Risk factors for increased allograft rejection after cadaveric kidney transplantation include the presence of panel reactive antibodies (PRA) greater than 50%, early failure of a previous transplant and/or a donor-recipient combination in which the recipient currently lacks anti-donor leukocytotoxic antibodies (negative crossmatch), but has had such antibodies in the past (historical positive crossmatch) [9]. Patients with these risk factors not only have a longer time on the transplant waiting list [13], but have an increased frequency of rejection episodes, which tend to be more severe, and a reduced allograft survival post-transplant [9].

The treatment of this group of kidney transplant patients, traditionally classified as immunologically high risk, has become more successful with the development of potent immunosuppressive treatment regimens [4]. Immunosuppression based on cyclosporine induction protocols is commonly used in this patient population [6]. Recent clinical experience with tacrolimus in renal transplantation suggests that primary prophylaxis with tacrolimus results in graft and patient survival rates equivalent to those achieved with cyclosporine-based therapy, a lower rate of rejection episodes and reduced corticosteroid requirements [10–12].

The aim of this report is to evaluate the safety and efficacy of tacrolimus-based immunosuppression or standard cyclosporine-based treatment in a subgroup of immunologically high risk patients from the European multicentre trial. Patients were stratified as high risk for immunological events if they had a PRA grade greater than 80% and/or a previous transplant functional for less than 1 year.

Patients and methods

Study design

The European multicentre study was a 12-month, open label, parallel group study performed at 15 centres in seven European countries. Details of the study design, patient eligibility criteria, immunosuppressive regimens administered and therapeutic drug monitoring have been published previously [10]. The study was conducted in accordance with the Declaration of Helsinki and European Community Good Clinical Practice guidelines. Approval was obtained from central and local ethics committees, and informed consent was provided by each patient prior to enrolment into the study. The primary efficacy variables in the European multicentre trial were the incidence of acute rejection, steroid usage and 1-year patient and graft survival. Definitions of the efficacy variables are described in a prior publication [10]. Safety was assessed based on spontaneously reported adverse events and routine laboratory evaluations, irrespective of causal relationship to the study medication. Adverse events were classified by means of a modified COSTART [2] coding system (coding system for adverse reaction terms) and graded for severity and relationship to the study drug.

Table 1 Demographic and baseline characteristics of patients at a high risk of acute rejection

Parameter	Tacrolimus	Cyclosporine
Number of patients	22	11
Male/female	12/10	9/2
Age (years)		
Patient	37.1 (19–60)	42.6 (30–60)
Donor	43.5 (16–67)	40.0 (20–62)
Number of patients with panel reactive antibodies > 80%	11	3
Number of patients having graft survival of < 1 year	16	8
Number of patients having both risk factors	5	0
HLA matching		
Mismatch HLA-A	0.8	0.7
Mismatch HLA-B	1	0.4
Mismatch HLA-DR	0.5	0.3

Patients were randomised at a 2 : 1 ratio to receive treatment with tacrolimus- or cyclosporine-based therapy. Patients were stratified into the high risk group if they had a PRA grade of greater than 80% and/or a previous transplant functional for less than 12 months. Other patients were considered to be at a standard risk of allograft rejection.

Patient population

Of the total 448 patients included in the European multicentre study, 33 patients were considered immunologically high risk patients. Twenty-two of these patients received tacrolimus, and 11 patients received cyclosporine. (The standard risk patient population included a total of 415 patients, 281 randomised to tacrolimus treatment and 134 to cyclosporine treatment.) All patients were enrolled into the study between August 1993 and May 1994.

Demographics and baseline characteristics

The two high risk treatment groups were well matched in terms of baseline demographics characteristics, except with regard to high risk criteria (Table 1). A larger proportion of patients with PRA grades greater than 80%, who had a previous graft failure with graft survival of less than 1 year, was present in the tacrolimus treatment group.

Statistical analysis

Although the European multicentre trial ($n = 448$) was enpowered to detect statistical differences, the analysis of the high risk subgroup was based on descriptive comparisons rather than statistical tests because of the limited number of patients.

Table 2 Patient and graft survivals (percentages) and incidence of biopsy-proven and steroid-resistant acute rejections

	Tacrolimus		Cyclosporine	
	High risk ($n = 22$)	Standard risk ($n = 281$)	High risk ($n = 11$)	Standard risk ($n = 134$)
Patient survival	100.0	92.5	90.9	97.0
Graft survival	86.0	82.0	72.0	87.0
Acute rejection (biopsy proven)	31.8	23.5	54.5	42.5
Acute rejection (steroid resistant)	9.1	7.1	36.4	14.8

Results

Efficacy analysis

Patient and graft survival

There was one death in the cyclosporine-treated high risk group (9.1%), versus no deaths in the tacrolimus-treated high risk group (Table 2).

During the 12-month study period, 3 of the 22 patients in the tacrolimus group (13.6%) and 3 of the 11 patients in the cyclosporine group (27.3%) experienced graft failure. In the tacrolimus group, the reasons for graft loss were two thrombotic events and one refractory rejection. In the cyclosporine group, two rejections and one death were the causes of graft loss.

Acute rejection

The incidences of acute and corticosteroid-resistant rejection were lower in the tacrolimus-treated high risk patients than in cyclosporine-treated patients (Table 2). Acute rejections occurred in 7 of the 22 tacrolimus high risk patients (31.8%) versus six of the 11 cyclosporine high risk patients (54.5%).

The clinical severity of the biopsy-proven acute rejections, as judged by the clinical investigators with regard to steroid resistance, was less in tacrolimus-treated high risk patients. The same trend is seen in the grading of the histopathological severity of the biopsy-proven acute rejections in the two high risk treatment groups. The biopsy-proven acute rejections were less severe in the tacrolimus-treated group (moderate, one patient; mild, two patients; borderline, three patients; and a biopsy for one patient was not confirmed) than in the cyclosporine-treated group (severe, one patient; moderate, two patients; mild, one patient; borderline, one patient; and a biopsy sample was not reviewed for one patient).

Tacrolimus dosages and blood concentrations

The peak tacrolimus mean daily oral dosage increased throughout the first month of therapy, and gradually decreased over the rest of the study period. The peak cyclosporine mean daily dosage increased until day 7, and then progressively decreased until month 12 (Figs. 1, 2).

The mean tacrolimus whole blood trough level gradually decreased from month 3 to month 12 in both the high risk and standard risk groups (Fig. 1). The same trend was observed for the mean cyclosporine whole blood trough levels from month 3 to month 12 in the high risk and standard risk groups (Fig. 2).

Steroid usage

The maintenance steroid administration was defined in the clinical study protocol, therefore, the frequency of oral maintenance steroid usage was similar between tacrolimus and cyclosporine high risk groups. The mean daily steroid dosage decreased from 8.6 mg/day at month 3 to 7 mg/day at month 12 in the tacrolimus treatment group, and from 11.1 mg/day to 5.6 mg/day in the cyclosporine treatment group.

The number of patients receiving azathioprine decreased from month 3 to month 12 in both treatment groups. At month 12, 43.75% (7/16) of the tacrolimus-treated patients received azathioprine versus 37.5% (3/8) of the cyclosporine-treated patients.

Serum creatinine levels

Similar levels of mean serum creatinine during the 12-month observation period were seen in both of the high risk treatment groups (Fig. 3).

Safety analysis

During the 12-month treatment period, the overall incidence of adverse events reported was similar between

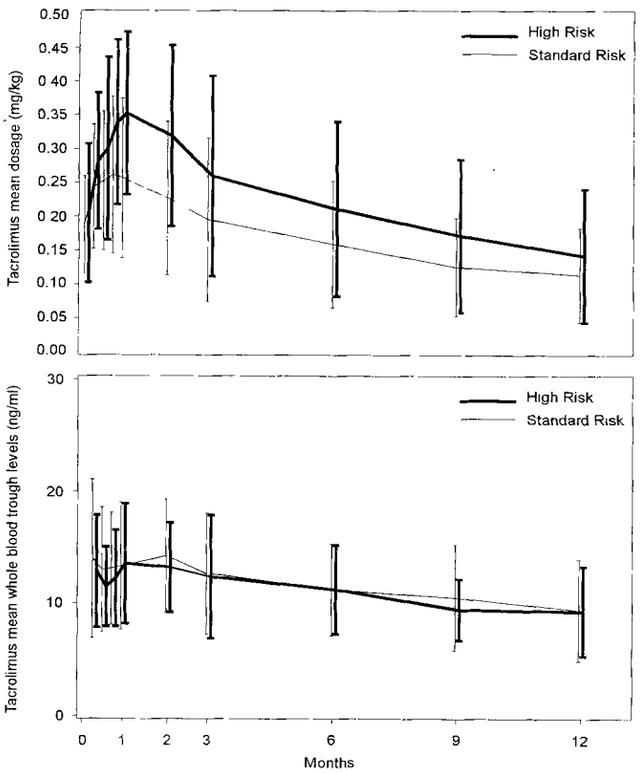

Fig. 1 Mean whole blood trough levels of tacrolimus (± SD) and mean tacrolimus dosage (± SD) in patients with a high risk of acute rejection (n = 22) and patients with a standard risk of acute rejection (n = 281)

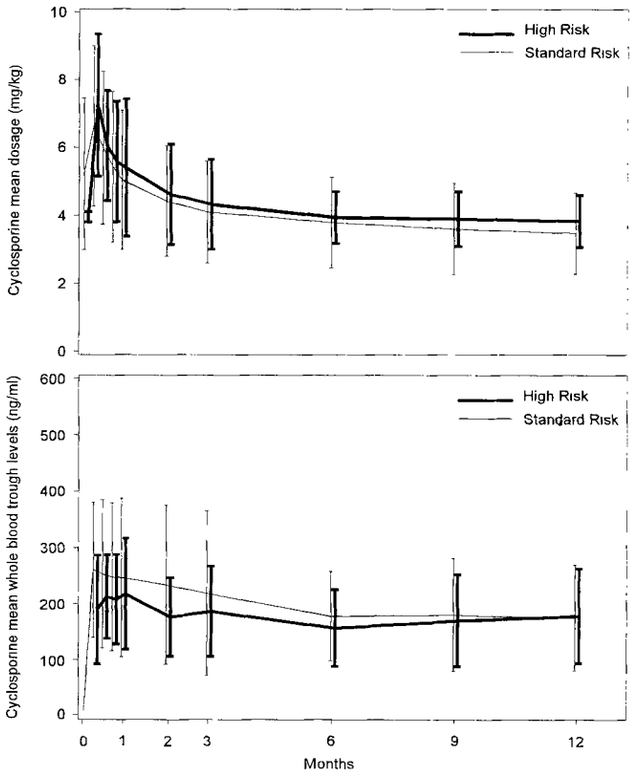

Fig. 2 Mean whole blood trough levels of cyclosporine (± SD) and mean cyclosporine dosages (± SD) in patients with a high risk of acute rejection (n = 11) and patients with a standard risk of acute rejection (n = 134)

the two high risk groups. However, the pattern of adverse events was different between the two treatment groups. The most frequently occurring adverse events (COSTART terms) in both high risk treatment groups were infection, constipation, hyperkalaemia, abdominal pain, kidney tubular necrosis and pain. Increased creatinine, hypertension, dyspepsia and tremor were reported only in the tacrolimus-treated group, whereas oedema, vomiting, peripheral oedema, and nausea occurred only in the cyclosporine-treated group.

Discussion

In the randomised European multicentre trial comparing tacrolimus- with cyclosporine-based therapy, immunologically high risk patients with PRA ≥ 80% and/or previous graft loss during the first year after transplantation were stratified prospectively to the two treatment arms. We demonstrated a reduced incidence of acute severe rejection in patients treated with tacrolimus therapy. Due to the limited number of patients enrolled, statistical evaluation was not possible, but numerical com-

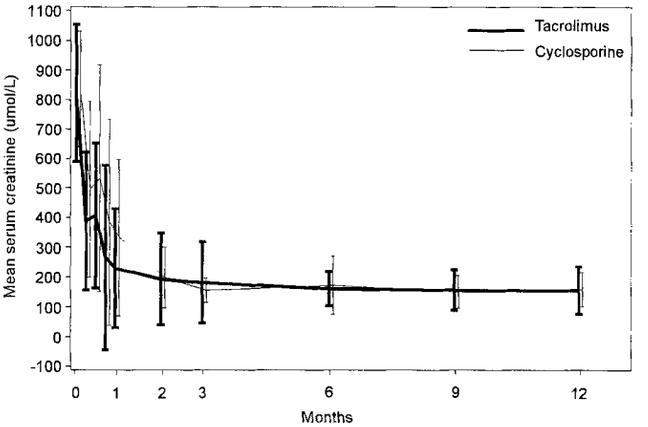

Fig. 3 Mean serum creatinine levels (± SD) of high risk patients in the tacrolimus treatment group (n = 22) and cyclosporine treatment group (n = 11)

parisons suggested a beneficial effect of tacrolimus, particularly for this subgroup of transplant recipients.

The use of tacrolimus in renal transplantation has been associated with patient and graft survival rates equivalent to those observed with cyclosporine-based immunosuppression and, as shown in some studies, the additional advantage of steroid withdrawal [11, 12, 14]. Moreover, rejection episodes refractory to conventional anti-rejection therapy were reversible in > 70% by conversion to tacrolimus, suggesting additional and potent immunosuppressive properties of tacrolimus compared with cyclosporine [3, 7, 15]. For the above reasons, a special benefit of tacrolimus for patients at a high risk for acute rejection in conceivable and could be supported by the results of our study.

As long-term renal allograft survivals is influenced by the incidence, severity and reversibility of acute rejection episodes during the first post-transplant year, prevention of acute allograft rejection is a major goal of primary induction therapy after renal transplantation [1, 8]. In our high risk subgroup, the incidence of acute rejection was lower in the tacrolimus-treated patients than in the cyclosporine-treated patients. This observation is consistent with the findings of the multicentre trial [10], and suggests that primary tacrolimus therapy might be of particular advantage for high risk patients, as well as for the overall study population.

Patients receiving their second or third transplant and/or belonging to the highly immunised population have a high risk of early graft failure and are often waiting for a long time before an appropriate organ with negative crossmatch is available [5]. Patient sensitisation and the population of patients undergoing renal transplantation are not expected to decrease in the near future. Therefore, our promising results demonstrating successful long-term transplant survival in immunologically high risk patients under tacrolimus-based therapy should be statistically proven by a larger randomised trial conducted in this high risk subgroup of transplant recipients.

References

1. Cosio FG, Pelletier RP, Falkenheim ME, Henry ML, Elkhammas EA, Davies EA, et al (1997) Impact of acute rejection and early allograft function on renal allograft survival. Transplantation 63: 1611
2. COSTART (1989) Coding symbols for thesaurus of adverse reaction terms, 3rd edn. Department of Health and Human Services (FDA), Rockville
3. Eberhard OK, Kliem V, Oldhafer K, et al (1996) How to best use tacrolimus (FK506) for treatment of steroid- and OKT3-resistant rejection after renal transplantation. Transplantation 61: 1345
4. Gaber AO, Thistlethwaite JR Jr, Haag BW, Stuart JK, Mayes JT, Lloyd DM, Fellner S, Stuart FP (1987) Potent immunosuppression overcomes immunologic high-risk factors in recipients of cadaveric renal allografts. Am Surg 53: 407–409
5. Groth J, Leverent S, Shonemann C, Kaden J, Moy G, Strobelt V, Schirmer R (1995) Donor-reactive and panel-reactive antibodies in kidney graft recipients. Transplant Med 5: 80
6. Indudhara R, Khauli RB, Menon M, Stoff JS (1994) Simultaneous quadruple immunosuppression. J Urol 152: 307–311
7. Jordan ML, Shapiro R, Vivas CA, et al (1994) FK506 'rescue' for resistant rejection of renal allografts under primary cyclosporine immunosuppression. Transplantation 57: 860
8. Lindholm A, Ohlman S, Albrechtsen D, Tufveson G, Persson H, Persson NH (1993) The impact of acute rejection episodes on long-term graft function and outcome in 1347 primary renal transplants treated by 3 cyclosporine regimens. Transplantation 56: 307–315
9. Lyne JC, Vivas CA, Shapiro R, Scantlebury VP, Hakala TR, Starzl TE, Jordan ML (1997) Cadaveric renal transplantation against a positive historic crossmatch under tacrolimus immunosuppression: long-term follow-up. Transplant Proc 29: 312
10. Mayer AD, Dmitrewski J, Squifflet JP, Besse T, Grabensee B, Klein B, et al (1997) Multicenter randomized trial comparing tacrolimus (FK506) and cyclosporine in the prevention of renal allograft rejection. Transplantation 64: 436–443
11. Pirsch JD, Miller J, Deierhoi MH, Vincenti F, Filo RS (1997) A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression after cadaveric renal transplantation. Transplantation 63: 977
12. Shapiro R, Jordan ML, Scantlebury VP, et al (1995) A prospective randomized trial of FK506-basedimmunosuppression after renal transplantation. Transplantation 59: 485
13. Takemoto S (1995) Sensitization and crossmatch. In: Cecka JM, Terasaki PI (eds) Clinical transplants. UCLA Tissue Typing Laboratory, Los Angeles, pp 417–432
14. Vincenti F, Laskow DA, Neylan JF, Mendez R, Matas AJ (1996) One year follow-up of an open-label trial of FK506 for primary kidney transplantation. Transplantation 61: 1576
15. Woodle ES, Thistlethwaite JR, Gordon JH, et al (1996) A multicenter trial on FK506 (tacrolimus) therapy in refractory acute renal allograft rejection: a report of the tacrolimus kidney transplantation rescue study group. Transplantation 62: 594