Tacrolimus versus cyclosporin for immunosuppression in renal transplantation: meta-analysis of randomised trials

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Abstract

Objective To compare tacrolimus with cyclosporin for immunosuppression in renal transplantation.

Design Meta-analysis of randomised trials of two treatments after kidney transplantation.

Identification Four studies involving 1037 patients. Trials were included if they were randomised, the intervention group received tacrolimus, the control group received cyclosporin, the patients were followed for a minimum of 12 months, and patient survival, graft survival, incidence of acute rejection, need for antilymphocyte treatment, or the prevalence of diabetes mellitus after transplant was reported.

Main outcome measures Pooled estimates of patient mortality, allograft loss, and episodes of acute rejection 1 year after transplantation.

Results The odds ratio for loss of allograft with tacrolimus compared with cyclosporin was 0.95 (95% confidence interval 0.65 to 1.40). The odds ratio for mortality with tacrolimus was 1.07 (0.47 to 2.48). Treatment with tacrolimus was associated with a reduction in episodes of acute rejection (0.52; 0.36 to 0.75), a reduction in the use of antilymphocyte antibodies to treat rejection (0.37; 0.25 to 0.56), and an increased prevalence of diabetes mellitus after transplantation (5.03; 2.04 to 12.36) compared with treatment with cyclosporin.

Conclusions After renal transplantation, immunosuppression with tacrolimus results in a significant reduction in acute rejection compared with cyclosporin. Follow up studies of high methodological quality are needed to determine whether tacrolimus improves long term renal graft survival.

Introduction

The number of new patients requiring dialysis or renal transplantation for permanent kidney failure is increasing worldwide. In the United Kingdom 46% of patients with permanent renal failure have a functioning kidney transplant.[1] Much of the success in organ transplantation has been credited to the use of cyclosporin; after its introduction renal graft survival at 1 year increased from 64% to 78%.[2] Despite the improvement in early graft function, long term kidney graft survival has not changed dramatically since the introduction of cyclosporin.[2] The chronic loss of transplanted kidneys and the potential toxicity of cyclosporin has prompted the development of other immunosuppressant drugs. Tacrolimus (FK506), a drug which has a similar mode of action to cyclosporin, was first used in clinical transplantation in 1989.[3] Benefits of treatment with tacrolimus have included a reduction in steroid dose,[4 5] a decreased need for antihypertensive drugs,[4] and a lower serum cholesterol concentration.[4]

In 1995 Gjertson et al reported a significant improvement in long term renal graft survival for recipients of tacrolimus based immunosuppression.[2] Patients who received tacrolimus had a renal allograft half life of 13.8 years compared with 8.8 years for recipients of cyclosporin based treatment.[2] A recent analysis of this database, however, has failed to confirm these early findings.[6] In addition, no randomised trial has shown an improvement in renal graft survival at 1 year for patients receiving tacrolimus.[4 7–9] Despite the conflicting data concerning allograft survival, the use of tacrolimus in kidney transplantation has increased considerably.[6] To help clarify the role of tacrolimus in renal transplantation we conducted a systematic review of randomised trials that compared tacrolimus with cyclosporin for immunosuppression.

Methods

Literature search

The Medline database was searched for relevant studies published between 1985 and September 1998. The following terms were used: tacrolimus, FK506, Prograf, and kidney transplantation. A similar search strategy was carried out on the Embase database for studies published from 1989 to January 1998 as well as on the Cochrane Library (issue 3, 1998) database. Issues of *Transplantation* (1987 to September 1998) and *Transplantation Proceedings* (1987 to September 1998) were hand searched for relevant publications. The reference lists from all identified studies and review articles were examined for any relevant articles. To locate any unpublished studies the medical editors' trial amnesty (Cochrane Library) was searched and the manufacturer of tacrolimus (Fujisawa USA, Deerfield, Illinois) was contacted.

Study selection

One investigator assessed all the titles and abstracts identified in the literature review. A hard copy was obtained for every study considered to be potentially relevant. Studies published in any language were eligible for inclusion. Both investigators assessed every potentially relevant article. To be included in the analysis the following criteria had to be met: the study was a randomised controlled trial; the study population consisted of recipients of primary or repeat renal transplants (cadaveric or living donor); the intervention group received tacrolimus as prophylaxis against acute rejection in the early period after transplantation; the control group received cyclosporin as prophylaxis against acute rejection in the early period after transplantation; the study reported one of the following outcomes: patient or graft survival, incidence of acute rejection, need for antilymphocyte treatment, or the prevalence of post-transplant diabetes mellitus; and the study had a minimum of 12 months' follow up. Agreement between observers for study selection was

assessed with the κ statistic. Any disagreement on study inclusion was resolved by discussion.

Quality assessment

The methodological quality of all included studies was assessed with the Jadad scale.[10] This validated scale measures blinding, randomisation, withdrawals, and drop outs. A maximum score of 5 represents the highest quality. All included studies were assessed independently by both investigators. Any disagreement on quality score was resolved by discussion.

Data analysis

Data were abstracted by one investigator and verified by the other. From each report we determined year of publication, number, age, and sex of participants, donor source, number of previous transplants, original renal disease, and dose and duration of immunosuppressive medications. The main outcome measures were graft loss at 1 year (defined as death with a functioning allograft or return to dialysis) and patient mortality at 1 year. Secondary outcome measures included the incidence of acute rejection in the 1st year after transplantation, the need for antilymphocyte treatment for acute rejection, and the prevalence of post-transplant diabetes mellitus 1 year after transplantation (defined as the need for insulin at 1 year in patients without a history of diabetes).

For every outcome measure we calculated a summary odds ratio and 95% confidence interval with the random effects model of DerSimonian and Laird.[11] We assessed heterogeneity across studies with the Q statistic with $P \leq 0.1$ considered significant.

Sensitivity analysis

To assess the robustness of the analysis we calculated the summary odds ratio, firstly, for studies that had a methodological quality score >2 and, secondly, for studies that used antilymphocyte antibodies immediately after transplantation (induction immunosuppression).

Results

The search strategy identified 499 articles, of which 129 were considered potentially relevant and were reviewed as full articles. Eight articles fulfilled the inclusion criteria[4 7–9 12–15] and 121 were excluded. The κ for interobserver agreement on study inclusion was 0.91. The 121 studies were excluded for the following reasons: 45 were not randomised controlled trials, 48 had no comparison with cyclosporin, 15 were editorial or review articles, six had inadequate follow up or outcome measures, three were laboratory studies, and four focused on an unrelated topic. Five studies reported different aspects from the same group of patients.[7 12–15] Only the original publication that thoroughly outlined the study methods was selected for inclusion in this meta-analysis.[7] Analysis of data from the same patient more than once would have resulted in a biased estimate of treatment effect.[16] Thus the final analysis was based on four studies involving 1037 patients.[4 7–9]

Table 1 Baseline characteristics of studies included in analysis. Figures are given for tacrolimus/cyclosporin where appropriate

Characteristics	Shapiro[4]	Vincenti[9]	Pirsch[7]	Mayer[8]
Year	1991	1996	1997	1997
No of patients	28/29	92/28	205/207	303/145
Mean age (years)	37/39	44/47	43/44	47/46
Proportion male (%)	NS	65/79	60/62	65/63
Donor	Cadaveric/living	Cadaveric	Cadaveric	Cadaveric
First transplant (%)	100/100	100/100	87/87	90/90
Diagnosis (%):				
Hypertension	NS	19/25	21/19	8/8
Diabetes	NS	26/25	19/19	5/4
Glomerulonephritis	NS	16/25	18/14	40/43
Hereditary	NS	15/14	11/8	15/14
Other	NS	24/11	31/40	32/31
Quality score	1	2	2	2

NS=not specified.

Table 1 summarises the baseline characteristics of the studies included in the analysis. Three studies used cadaveric donors only,[7–9] and one study included both cadaveric and living donors.[4] Most participants were receiving their first renal transplant. The proportion of patients who received tacrolimus was significantly higher in two studies.[8 9] One study randomised patients in a 2:1 ratio of tacrolimus or cyclosporin to gain experience with tacrolimus.[8] One study was designed to test a range of concentrations so patients were randomised to one of three tacrolimus regimens or to a cyclosporin based regimen.[9] The methodological quality scores were low. All four studies were randomised, and three reported complete follow up information.[7–9] None of the studies used a double blind method or described the method of randomisation.

Table 2 summarises the immunosuppressive protocols of the included studies. Two studies used induction immunosuppression with antilymphocyte antibodies,[7 9] one study did not use induction,[8] and the remaining study did not specify if the randomised patients received induction treatment or not.[4]

Table 2 Immunosuppressive protocols of studies included in analysis

Characteristic	Shapiro[4]	Vincenti[9]	Pirsch[7]	Mayer[8]
Induction	NS	Antilymphocyte globulin	Antithymocyte globulin or muromonab-CD3 monoclonal antibody	None
Tacrolimus (mg/kg/day)	0.1 IV to 0.3 oral	0.2, 0.3, or 0.4 oral	0.2 oral	0.3 oral
Azathioprine (mg/kg/day)	NS	1-4 IV then 1-1.5 oral	2-4 IV then 1.5 oral	2 IV then 1-2 oral
Prednisone	NS	2 mg/kg IV/oral; down to 0.5 mg/kg/day; then local protocol	500 mg IV pre-op; then 5-0.5 mg/kg/day; taper to 10 mg/d	500 mg IV; taper 20-5 mg/day
Cyclosporin (mg/kg/day)	NS	6-14 oral	10 oral	8 oral
Trough concentrations (ng/ml) at 1 week:				
Tacrolimus	NS	NS	Median 11.3	Mean 13.9
Cyclosporin	NS	NS	Median 269	Mean 254

NS=not specified.

Table 3 Pooled analysis for graft loss and patient mortality. Figures are odds ratios (95% confidence interval)

Study	Graft loss	Mortality
Shapiro[4]	0.83 (0.22 to 3.12)	0.32 (0.03 to 3.29)
Vincenti[9]	0.58 (0.14 to 2.49)	0.29 (0.04 to 2.15)
Pirsch[7]	0.70 (0.37 to 1.33)	1.31 (0.48 to 3.59)
Mayer[8]	1.33 (0.76 to 2.31)	2.09 (0.77 to 5.65)
Test for heterogeneity	P>0.40	P>0.20
Summary result	0.95 (0.65 to 1.40)	1.07 (0.47 to 2.48)

Although one study did not specify the initial prednisone dose,[4] by the end of the study 55% of the tacrolimus patients were not taking prednisone while most of the cyclosporin group were taking 7.5 mg to 15 mg daily.

All four studies reported on graft loss and patient mortality at 1 year (table 3). There was no significant heterogeneity across the studies for these two outcome measures. There was no significant effect of tacrolimus on graft loss at 1 year (odds ratio 0.95; 95% confidence interval 0.65 to 1.40). Similarly, there was no significant effect of tacrolimus on patient mortality at 1 year (1.07; 0.47 to 2.48).

Three studies reported on the incidence of acute rejection in the 1st year after transplantation (see table 4). Treatment with tacrolimus was associated with a significant reduction in episodes of acute rejection (0.52; 0.36 to 0.75). Also, the use of antilymphocyte antibodies to treat rejection was significantly reduced in patients receiving tacrolimus (0.37; 0.25 to 0.56). Three studies reported on the prevalence of post-transplant diabetes mellitus at 1 year.[7–9] All three showed that a higher proportion of patients treated with tacrolimus had post-transplant diabetes mellitus. The data from one study, however, were not presented in a manner that permitted inclusion in a summary odds ratio.[8] In the combined studies treatment with tacrolimus was associated with a significant increase in the prevalence of post-transplant diabetes mellitus at 1 year (5.03; 2.04 to 12.36).

As none of the studies had a methodological quality score >2 the sensitivity analysis based on study quality was not performed. A sensitivity analysis of studies that used antilymphocyte induction treatment produced results similar to those from the original analysis—that is, treatment with tacrolimus did not have a significant effect on graft loss (0.68; 0.38 to 1.22) or patient mortality (0.80; 0.20 to 3.21).

Discussion

This meta-analysis shows that immunosuppression with tacrolimus results in a significant decrease in episodes of acute rejection and use of antilymphocyte antibody when compared with cyclosporin based treatment. This review, however, did not show any effect of tacrolimus on survival of patients or grafts 1 year after transplantation.

Table 4 Pooled analysis of acute rejection, use of antilymphocyte antibodies, and post-transplant diabetes mellitus. Figures are odds ratios (95% confidence interval)

Study	Acute rejection	Antilymphocyte treatment for rejection	Post-transplant diabetes mellitus
Vincenti[9]	1.02 (0.41 to 2.53)	NS	4.15 (0.5 to 34.04)
Pirsch[7]	0.51 (0.34 to 0.77)	0.36 (0.21 to 0.62)	5.25 (1.94 to 14.20)
Mayer[8]	0.41 (0.27 to 0.63)	0.39 (0.22 to 0.71)	NS
Test for heterogeneity	P>0.20	P>0.80	P>0.80
Summary result	0.52 (0.36 to 0.75)	0.37 (0.25 to 0.56)	5.03 (2.04 to 12.36)

NS=not specified.

Clinical implications of results

Although there was no difference in patient or graft survival, a 48% reduction in acute rejection is a clinically significant finding. This means that seven patients would need to be treated with tacrolimus, rather than cyclosporin, to prevent one episode of acute rejection.[17] Acute rejection often leads to readmission to hospital, increased diagnostic testing (including allograft biopsy), and increased immunosuppression with concomitant increased risk of infection and malignancy, as well as increased costs. More importantly, acute rejection has been shown to be a major determinant of long term graft survival.[18 19] Lindholm et al found that the graft half life was 6.6 years for patients with a history of acute rejection compared with 12.5 years for recipients without rejection.[18] The impact of a reduction in acute rejection on graft survival may require a longer follow up period than the 1 year period used in this study.

The patients treated with tacrolimus had a 63% reduction in the use of antilymphocyte antibodies to treat acute rejection. As this treatment is usually reserved for steroid resistant or vascular rejection the tacrolimus patients probably had fewer episodes of severe rejection. This is an important finding as antilymphocyte treatment has been associated with an increased risk of malignancy[20] and infection[21] in organ transplantation.

A major side effect of tacrolimus has been the development of post-transplant diabetes mellitus.[22] This complication usually occurs early after transplantation and has been linked with both prednisone dose and tacrolimus blood concentrations.[7] We chose to examine the prevalence of post-transplant diabetes mellitus at 1 year as a significant proportion of patients are able to discontinue insulin over time. At 1 year the patients treated with tacrolimus still had about five times the risk of post-transplant diabetes mellitus compared with patients treated with cyclosporin. This clearly represents a major risk that must be balanced with the potential benefits of tacrolimus. Patients with post-transplant diabetes mellitus may benefit from reduced doses of prednisone and tacrolimus.[23]

Limitations of study

A major limitation of this study is the small number of trials that were available for analysis. Although there are many publications on tacrolimus, most have not involved randomised trials. We could have included non-randomised studies to increase the sample size of our analysis, but such studies have been shown to produce an exaggerated treatment effect that is probably biased.[24]

As with all systematic reviews this study is limited by the quality of the available trials. The four trials in this meta-analysis had low scores for methodological quality as they were not double blind and the methods of randomisation were not described. Trials of low methodological quality have been shown to produce a greater treatment effect.[25 26] Thus without high quality

Key messages

- Cyclosporin is currently the most widely used and important immunosuppressive agent in renal transplantation
- The use of tacrolimus, an alternative immunosuppressant to cyclosporin, has increased in recent years
- Treatment with tacrolimus resulted in a significant reduction in episodes of acute rejection compared with cyclosporin
- Follow up studies are required to see if tacrolimus improves long term survival of kidney grafts

trials available for analysis the reduction in acute rejection shown in our study may be an overestimate of the true treatment effect of tacrolimus.

Another limitation of this analysis was the exclusion of newer immunosuppressive agents. In the four included studies, Sandimmun (original cyclosporin formulation) rather than Neoral (new microemulsion formulation of cyclosporin) was used. Because of its improved bioavailability, Neoral has now replaced Sandimmun at most transplant centres. Also, mycophenolate mofetil in combination with cyclosporin has been shown significantly to decrease episodes of acute rejection.[27] Accordingly, our meta-analysis cannot provide recommendations concerning the concomitant use of these novel drugs in renal transplantation.

Conclusions

This meta-analysis of randomised trials has shown that after renal transplantation tacrolimus based immunosuppression is associated with a significant reduction in acute rejection, a significant reduction in use of antilymphocyte antibodies, and a significant increase in the prevalence of post-transplant diabetes mellitus at 1 year compared with cyclosporin.

Future studies should evaluate the use of tacrolimus along with newer immunosuppressive drugs as well as its use in high risk groups that could not be assessed in this analysis. These might include patients who are highly sensitised, African-Americans, or recipients of repeat transplants. In addition, future trials should strive to improve methodological quality—for example, double blinding and adequate randomisation—to produce more reliable estimates of treatment effect. Finally, outcome studies with longer follow up are needed to see if the early reduction in acute rejection translates into improved long term graft survival.

Contributors: GK coordinated the study, participated in database and hand searching, study identification, study selection, quality assessment, data extraction, data analysis, data interpretation, and writing of the paper. RB participated in hand searching, study selection, quality assessment, data verification, data interpretation, and writing of the paper. GK is guarantor.

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Endpiece

A man's best friend

Outside of a dog, a book is man's best friend. Inside of a dog it's too dark to read.

Attributed to Groucho Marx