WORKING GROUP ON ACUTE PURCHASING

Tacrolimus and Mycophenolate Mofetil as Maintenance Immunosuppressants following Renal Transplantation

August 1999

GUIDANCE NOTE FOR PURCHASERS 99/07

Series Editor: Nick Payne

InterDEC Report No. 16/1999

Trent Development and Evaluation Committee

The purpose of the Trent Development and Evaluation Committee is to help health authorities and other purchasers within the Trent Region by commenting on expert reports which evaluate changes in health service provision. The Committee is comprised of members appointed on the basis of their individual knowledge and expertise. It is chaired by Professor Sir David Hull.

The Committee recommends, on the basis of evidence provided, priorities for:

- the direct development of innovative services on a pilot basis;
- service developments to be secured by health authorities.

The statement that follows was produced by the Development and Evaluation Committee at its meetings on 28 October 1998 and 13 April 1999 at which this Guidance Note for Purchasers (in a draft form) was considered.

TACROLIMUS AND MYCOPHENOLATE MOFETIL AS MAINTENANCE IMMUNOSUPPRESSANTS FOLLOWING RENAL TRANSPLANTATION

AUTHORS: Chilcott J, Corcoran M, Rigg KM, Burden RP. Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield 1999. Guidance Note for Purchasers: 99/07.

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(The recommendations made by the Committee may not necessarily match the personal opinions expressed by the experts)

DECISION: In the light of limited benefits and high costs, the Committee considered that if tacrolimus and MMF were used as maintenance immunosuppressants following renal transplantation, they should be used for high risk patients only. This sub-group of patients accounts for about 30% of the total number of renal transplant patients.

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Conflict of Interest

None of the authors of this document has any financial interests in the drugs or products being evaluated here. ScHARR is in receipt of funding for unrelated work in the field of transplantation from Novartis AG. In view of this, however, the report has been reviewed by the Wessex Institute for Health Research and Development.

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ABOUT THE TRENT INSTITUTE FOR HEALTH SERVICES RESEARCH

The Trent Institute for Health Services Research is a collaborative venture between the Universities of Leicester, Nottingham and Sheffield with support from NHS Executive Trent.

The Trent Institute:

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- provides advice and support to NHS staff on undertaking Health Services Research (HSR);
- provides training in HSR for career researchers and for health service professionals;
- provides educational support to NHS staff in the application of the results of research;
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Professor Clarke currently undertakes the role of Institute Co-ordinator.

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FOREWORD

The Trent Working Group on Acute Purchasing was set up to enable purchasers to share research knowledge about the effectiveness and cost-effectiveness of acute service interventions and determine collectively their purchasing policy. The Group is facilitated by The School of Health and Related Research (ScHARR), part of the Trent Institute for Health Services Research, the ScHARR Support Team being led by Professor Ron Akehurst and Dr Nick Payne, Consultant Senior Lecturer in Public Health Medicine.

The process employed operates as follows. A list of topics for consideration by the Group is recommended by the purchasing authorities in Trent and approved by the Purchasing Authorities Chief Executives (PACE) and the Trent Development and Evaluation Committee (DEC). A public health consultant from a purchasing authority leads on each topic assisted by a support team from ScHARR, which provides help including literature searching, health economics and modelling. A seminar is led by the public health consultant on the particular intervention where purchasers and provider clinicians consider research evidence and agree provisional recommendations on purchasing policy. The guidance emanating from the seminars is reflected in this series of Guidance Notes which have been reviewed by the Trent DEC, chaired by Professor Sir David Hull.

In order to share this work on reviewing the effectiveness and cost-effectiveness of clinical interventions, The Trent Institute's Working Group on Acute Purchasing has joined a wider collaboration, InterDEC, with units in other regions. These are: The Wessex Institute for Health Research and Development and The University of Birmingham Department of Public Health and Epidemiology.

Professor R L Akehurst,
Chairman, Trent Working Group on Acute Purchasing.

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EXECUTIVE SUMMARY

Transplantation with either a cadaveric or living donor kidney is the preferred treatment of end stage renal failure. There is, however, a steadily increasing waiting list of people eligible for transplantation due to the lack of suitable donor organs. This is exacerbated by the fact that about 10% of transplants will fail within one year, despite matching, as closely as possible, the donor and recipient for tissue compatibility.

Until recently, post-operative management to reduce the risk of rejection has been based on cyclosporin, azathioprine and corticosteroids. Two new drugs are now available: tacrolimus and mycophenolate mofetil.

The primary focus of this paper is on the use of these drugs in maintenance therapy for adults. There is also evidence of their efficacy in rescue therapy in response to episodes of acute rejection. The Wessex Institute Development and Evaluation Committee Report No.74 “Tacrolimus after kidney transplantation” recommends tacrolimus as a rescue therapy agent.

The clinical effectiveness of these drugs in primary maintenance therapy, in the short to medium-term, has been determined in five randomised controlled trials. Trials of tacrolimus, which replaces cyclosporin, showed a significant reduction of 15% to 20% in the number of episodes of acute rejection, and of between 10% and 15% in steroid resistant rejection after 12 months of treatment.

Trials of mycophenolate mofetil, which is used in addition to cyclosporin, showed a significant reduction of between 20% and 25% in episodes of acute rejection and reduction in steroid resistant rejection, similar to tacrolimus at six months. A pooled analysis of these trials confirmed this reduction at 12 months.

A new preparation of cyclosporin has been made available since the published trials of tacrolimus and mycophenolate mofetil were commissioned. Studies investigating the efficacy, in terms of acute rejection avoided, of the new formulation (Neoral) in comparison to the older formulation (Sandimmun) claim reductions ranging from 8% to 16%. Synthetic comparisons constructed between the new cyclosporin formulation and both tacrolimus or mycophenolate mofetil indicate that the marginal benefit of both newer drugs may potentially be reduced compared with the older formulation.

Follow-up results at three years of two of the mycophenolate mofetil trials showed a marginal, but not statistically significant, difference in the rate of graft failure or death, although the trials were not designed or powered to detect such differences initially. All five trials had a relatively large proportion of withdrawals, ranging from 16.5% for tacrolimus up to 35% in one trial for the 3mg dose of mycophenolate. These were mainly due to adverse side effects which were dose dependent. Lower maintenance doses for tacrolimus have been recommended as a result of these trials.

Both tacrolimus and mycophenolate are more expensive than conventional therapy, but their additional cost needs to be balanced against the reduced costs of treating episodes of acute rejection and the potential averted costs of transplant failure, dialysis and retransplantation. Some of the costs saved, such as the drugs used for steroid resistant rejection, are realisable, but others, such as the number of bed days saved, may not be. There are also advantages to the patient which have not been quantified. Hospital based cost savings arising from tacrolimus treatment mean that this therapy is estimated to be approximately cost neutral compared to conventional (Sandimmun) therapy. Against Neoral cyclosporin, however, tacrolimus is estimated to cost an extra £1,000 per patient per year. Mycophenolate mofetil is estimated to cost approximately £2,000 more per patient than cyclosporin (Sandimmun) for the same period, similarly, against Neoral cyclosporin, the estimate is £3,000 per patient per year.

There is insufficient direct evidence as yet to make firm conclusions about the value of these drugs as maintenance therapy in the longer-term, although initial evidence indicates that a modest increase in patient and graft survival may be achieved. The comparative cost with conventional therapy depends on the actual steady state dosages achieved.

Children justify special consideration because one of the major benefits of transplantation in children is to enable them to grow satisfactorily and for them to achieve their school and developmental potential. It is essential that the best graft function possible is achieved and the use of these newer agents would enable a reduction of acute rejection. This may, in turn, reduce the incidence of chronic rejection and the need for the child to undergo further transplants either in late childhood or early adulthood. A lot of focus in the document is on saving kidneys in the long-term from rejection and this is of major importance in children.

Given the lack of information on risks of infectious complications and malignancy associated with the long-term use of the two new agents, it may be appropriate initially to implement the new agents as primary maintenance in immunologically high risk patients, whilst using conventional primary maintenance therapy for immunologically low risk patients.

1. INTRODUCTION

1.1 Incidence and Pathology

Transplantation is the preferred therapy for end stage renal failure as it improves a patient's quality of life, encourages occupational rehabilitation and is more cost-effective compared with the alternative of dialysis. However, a shortage of organs restricts the number of patients who can receive transplantations.

More than 11,000 people are receiving renal dialysis in the UK, costing some £220 million each year and these figures are expected to double in the next five to ten years. Based on estimates of incidence, the acceptance rate for transplantation or dialysis needs to be 80-100 per million population per annum for patients aged under 80 years, from a white population, and excluding patients with a malignancy or major stroke. This acceptance rate, however, needs to be higher in the Afro-Caribbean and Asian groups where incidence is as high as 240-300 per million population per annum. The commonest causes of renal failure are glomerulonephritis, diabetes and hypertension.[1]

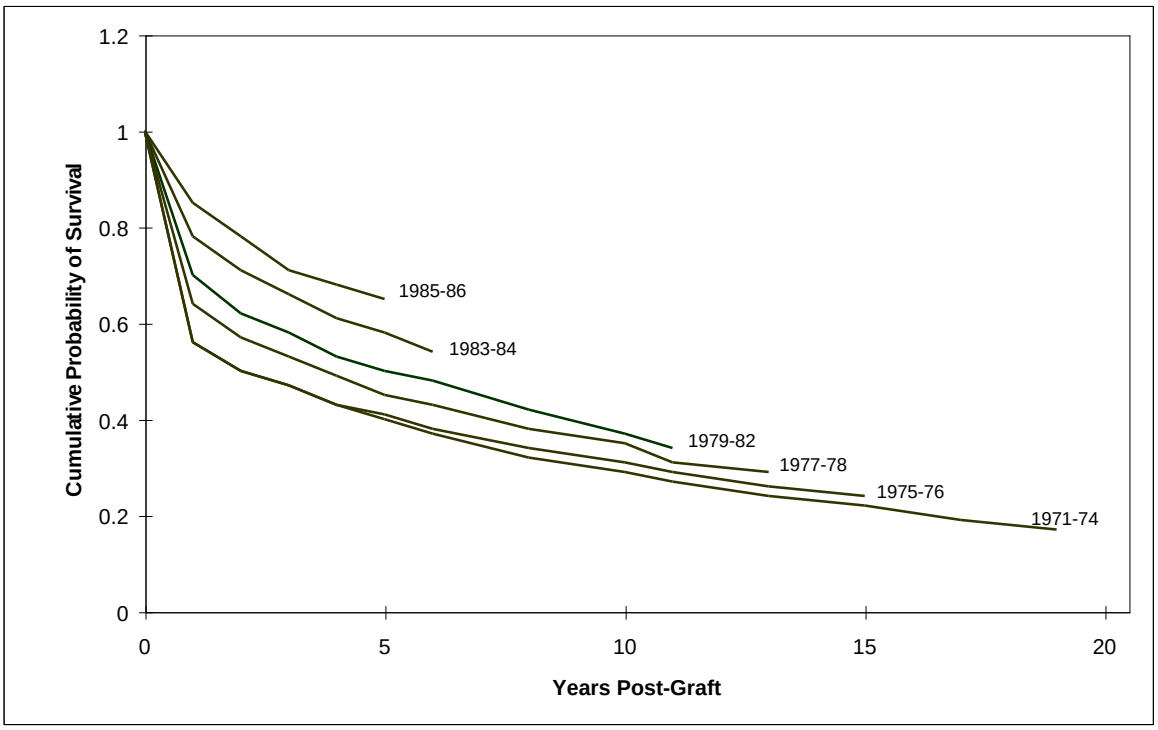
1.2 Prognosis and Mortality

One year graft survival has steadily improved over the last two decades and is now around 90% for low risk patients. However, for transplant patients who survive beyond the first year, there has been no corresponding improvement in the rate of graft failure. The improvement in graft failure rates over the last two decades is illustrated in Figure 1.

In the long-term, approximately 50% of grafts are still functioning at the death of transplant patients, the most common cause of death in these patients being cardiovascular complications. Chronic rejection, which is a slow progressive process, is responsible for 25% to 35% of graft losses after one year. The major risk factor for the development of chronic rejection is acute rejection. Acute rejection occurs in 30-50% of all transplants, usually in the first three months, and can be treated successfully in over 90% of cases. The development of chronic rejection is usually associated with episodes of acute rejection that are severe, recurrent or late. Therefore, there is evidence to suggest that therapeutic manoeuvres to reduce the incidence or severity of acute rejection episodes could lead to a lower incidence of chronic rejection with an associated improvement in long-term graft survival.

Two new immunosuppressant agents, tacrolimus (Prograf) and mycophenolate mofetil (MMF)(Cellcept) have been claimed to be effective in reducing the incidence and severity of acute rejection when administered as a daily maintenance regimen, and in treating acute rejection when administered as 'rescue' therapy. There is currently no fully published randomised controlled trial (RCT) evidence which addresses the effect of either drug on long-term graft survival.

Figure 1 Observed Graft Survival Curves in First Cadaveric Grafts Performed Between 1971 and 1986 (After Landais[2]).



1.3 Prevention of Acute Rejection

Cyclosporin, azathioprine (AZA) and prednisolone are used for maintenance therapy in a number of different regimens; even so, acute rejection will still occur in 30-50% of patients and particularly in those who are at high risk immunologically. The newer agents, tacrolimus and mycophenolate mofetil, have been shown, in multicentre studies, to reduce the incidence of acute rejection in the first year post transplant. Tacrolimus is used in place of cyclosporin and mycophenolate mofetil in place of azathioprine. This paper evaluates their use in comparison with conventional immunosuppression. The management strategies evaluated are:

- Tacrolimus — Maintenance immunosuppression with tacrolimus, azathioprine and prednisolone;
- Mycophenolate mofetil — Maintenance immunosuppression with cyclosporin, mycophenolate mofetil and prednisolone;
- Conventional — Maintenance immunosuppression with cyclosporin, azathioprine and prednisolone.

1.4 Treatment of Acute Rejection

The first line treatment for acute rejection is high dose methylprednisolone, but up to 20% of rejection episodes may be steroid resistant. Conventionally, polyclonal antibodies (anti-thymocyte globulin or anti-lymphocyte globulin) or monoclonal antibodies have been given for steroid resistant or refractory rejection. However, tacrolimus is being used increasingly, as clinical experience and case studies suggest that it is better tolerated by the patient and more effective.[3,4,5]

A review of the evidence for tacrolimus in transplant rescue is contained in the Wessex Institute Development and Evaluation Committee (DEC) Report No.74 "Tacrolimus after kidney transplantation".[6] This report identifies that the evidence for tacrolimus in rescue therapy comes from non-controlled case series and, as such, the evidence is of poorer quality than the RCT evidence available for primary immunosuppression. It should be noted, however, that ethical and practical difficulties preclude randomisation and control for novel rescue therapies. The Wessex report notes that the studies reviewed have quite large sample sizes and adequate follow-up and show a good response to tacrolimus treatment. The Wessex DEC report, therefore, recommends tacrolimus as rescue therapy.

The evidence for mycophenolate mofetil in transplant rescue consists of randomised and non-randomised studies and case series. A search for studies has been undertaken, though it should be noted that these have not been subjected to a full systematic review, this being outside the scope of this report.

A six month open label, randomised, multicentre trial[7] compared the efficacy and safety of mycophenolate mofetil with high dose intravenous steroids for the treatment of refractory

acute rejection. A total of 150 patients were randomised in a 1-to-1 ratio. Graft loss and death at six months, the primary efficacy variable, was reduced from 26% in the steroid group to 14% in the mycophenolate mofetil treatment group. The 45% reduction at six months was not statistically significant; however, at 12 months the reduction was significant (p=0.042). Furthermore, the number of patients who received a full course of anti-lymphocyte therapy was more than double in the steroid group (18 patients) than in the mycophenolate mofetil group (eight patients). Adverse events were recorded in 74.6% of the steroid group and 93.5% of the mycophenolate mofetil group.

In a further study, Sollinger[8] investigated the use of mycophenolate mofetil in a series of 75 patients who had previously undergone anti-rejection therapy with high dose steroids, OKT3 or both treatments. Successful rescue was achieved in 52 of 75 (69%) of patients, with an overall infection rate of 40%; no significant nephrotoxicity, hepatotoxicity or myelosuppression was found.

These studies indicate that mycophenolate mofetil may be effective in the treatment of refractory rejection.

1.5 Scale of Problem in a 'Typical' District

In the UK and Republic of Ireland there are currently 6,000 patients awaiting transplantation but only 1,800 transplants are performed each year. In the Trent Region there are over 450 patients on the waiting list, but only 130 transplants are carried out each year. Therefore, strategies to improve both organ supply and graft survival are imperative if this deficit is to be addressed.

There are three renal units which undertake transplantation within the Trent Region; the Northern General Hospital in Sheffield, Nottingham City Hospital and Leicester General Hospital, each centre serving a population of approximately 1.5 - 2 million people. For a population of two million people there would be approximately 180 patients waiting for a transplant and approximately 52 transplants undertaken annually. For a 'typical' district population of 500,000 the corresponding figures are 45 patients on the waiting list and 13 renal transplants carried out each year.

2. THE USE OF TACROLIMUS AND MYCOPHENOLATE MOFETIL AS MAINTENANCE IMMUNOSUPPRESSANTS: SUMMARY OF EVIDENCE OF EFFECTIVENESS

2.1 Summary of Literature Search for Evidence

Searches of EMBASE, the Cochrane Clinical Trials Library, and MEDLINE were undertaken. The searches identified papers in the intersection of three domains: kidney transplantation; randomised controlled trials (as defined by the Cochrane comprehensive strategy) and the drug of interest. The tacrolimus search included Prograf, FK506 and the CAS registry number, the mycophenolate mofetil search included in the terms Cellcept, and the CAS registry number. These searches covered the period 1985 to 1998, though a subsequently published meta-analysis of tacrolimus has been identified and the implications of the results reviewed. The searches were assessed by title and abstract, where available, by one clinical and one analytical support member of the project team. The following inclusion criteria were used in selecting papers; reports of randomised controlled trials of either tacrolimus or mycophenolate mofetil used as primary maintenance agents following kidney transplantation; comparisons of either drug against placebo or against each other (non-randomised) were identified; small pre-clinical and Phase II studies were excluded.

Ideally, clinical outcome measures would address either graft loss over a sufficiently long follow-up period to identify clinically significant differences or quality and duration of life during the transplant period. The occurrence of acute rejection is used as a proxy or surrogate outcome measure for these final endpoints, firstly on the basis of its relation to long-term chronic rejection and graft loss, and secondly in its own right as being associated with significant morbidity. The large majority of episodes of acute rejection occur in the first three months post transplant, this was, therefore, considered a minimum period for follow-up. The potential implications of the reported short-term acute rejection results on long-term graft survival have been addressed through a simple modelling study reported in Section 3.4.

The search has identified two trials of tacrolimus[9,10] and three trials involving mycophenolate mofetil[11,12,13] as part of primary maintenance regimens. Details of these trials are summarised in Tables 1 and 2.

The evidence for Tacrolimus in rescue therapy is reviewed in the Wessex Institute DEC Report No 74 “Tacrolimus after kidney transplantation”.[6] A topic search of the above health databases was undertaken to identify evidence on the use of mycophenolate mofetil in rescue therapy.

2.2 Tacrolimus

2.2.1 Evidence of Effectiveness of Tacrolimus

The major multi-centre clinical trials of tacrolimus as a maintenance immunosuppressant had similar entry criteria, including male and female patients undergoing renal transplantation. The European Tacrolimus Multicentre Renal Study Group trial[9] (European Tacrolimus trial) included people over 18 years of age, whilst the FK506 Kidney Transplant Study Group trial[10] (US Tacrolimus trial) included those over six years of age who were receiving their first or second transplant.

Exclusion criteria common to the trials were: serological evidence of Human Immunodeficiency Virus; ABO-incompatible grafts; and patients undergoing multiple organ transplants. Women who were pregnant, lactating or who were using inadequate contraception were also excluded, as were patients with significant hepatic disease.

The trials both consisted of two arms:

- conventional treatment, consisting of cyclosporin maintenance therapy in the European study and cyclosporin with azathioprine in the US study;
- daily tacrolimus as a replacement for cyclosporin therapy.

The drug dosages recorded in the trials are consistent. The cyclosporin dosages were reduced during the course of both trials; the European Tacrolimus trial recorded initial dosages of 6.9 mg/kg reducing to an average of 3.5 mg/kg over months 10-12, this being consistent with the overall mean dosage recorded within the US Tacrolimus trial of 5.5 mg/kg. Similarly, the tacrolimus dosages compare well, with a reduction from 0.26 mg/kg to 0.12 mg/kg over the European Tacrolimus trial period, compared with an overall mean dosage of 0.18 mg/kg in the US Tacrolimus trial.

The more recent European Tacrolimus trial focused on first biopsy proven acute rejection as the primary outcome measure, whereas the earlier US Tacrolimus trial had patient survival

and graft survival as the primary outcome measures, with first biopsy proven acute rejection as a secondary outcome measure. However, the results are remarkably consistent and are detailed in Tables 1 and 3. No statistical test for homogeneity has been undertaken, the low power of available tests, the small number of trials and the visually assessed consistency in the results make such a statistical test obsolete. A meta-analysis of the randomised controlled trial evidence for tacrolimus versus cyclosporin confirms this high level consistency.[14] The one year patient and graft survival rates show no significant difference between cyclosporin and tacrolimus treatment. There was, however, a significant reduction in the acute rejection rates for tacrolimus treatment over cyclosporin treatment.

Table 3 summarises the acute rejection rates observed in the reviewed trials, the biopsy proven acute rejection rate for cyclosporin was between 43.4% and 46.4%, whilst the same figure for tacrolimus was between 24.1% and 30.7%.

The absolute decrease in first biopsy proven acute rejection rate, obtained through the use of tacrolimus over the 12 months following transplantation, was approximately 15-20%. This implies that the number needed to treat (NNT) to avoid acute rejection in one patient is between five and seven.

The severity of episodes of acute rejection was also reported as another secondary outcome measure in both trials. Tacrolimus was found to decrease significantly the incidence of corticosteroid resistant acute rejection in both trials. The European Tacrolimus trial reported a statistically significant decrease from 20.7% of the cyclosporin treated patients experiencing corticosteroid resistant acute rejection compared with 10.2% of the tacrolimus treated patients. The equivalent figures in the US Tacrolimus trial were 25.1% and 10.7%. This implies an NNT of between seven and ten to avoid corticosteroid resistant rejection in one patient.

2.2.2 Adverse Events and Contraindications Associated with Tacrolimus

Adverse events were common throughout all treatment arms of all trials. Tacrolimus was associated with the following adverse events profile compared to conventional therapy in both trials:

- increased incidence of tremor;
- increased diabetes mellitus;
- increased incidence of alopecia and decreased incidence of hirsutism;

- decreased incidence of gingival hyperplasia.

Other adverse events associated with tacrolimus, but, either not recorded in both trials, or found not to be significantly different from cyclosporin treatment in both trials were:

- elevated serum creatinine found in the European Tacrolimus trial but not found in the US Tacrolimus trial;
- a higher incidence of deep vein thrombosis identified in the US Tacrolimus trial, but not in the European Tacrolimus trial;
- a higher incidence of diarrhoea identified in the European Tacrolimus trial, but not found in the US Tacrolimus trial.

There is evidence that a higher withdrawal rate occurred with tacrolimus treatment than with cyclosporin treatment. The withdrawal rate in the European Tacrolimus study was 16.5% in the tacrolimus arm and 2.8% in the cyclosporin arm, a statistically significant difference. The main reasons for withdrawal in the tacrolimus treated patients were renal disorders, neurological and cardiovascular complications and opportunistic infections.

2.2.3 Dose Response of Tacrolimus

A systematic search of the usual databases was undertaken for published evidence on the effectiveness of tacrolimus when given in doses lower than those studied in the Phase III trials. In addition, a request for grey literature was made to the Medicines Control Agency. The systematic search uncovered no published evidence on efficacy of maintenance with doses lower than those used in the Phase III trials. Therefore, the search was expanded to cover evidence on the dose response relationship from early studies; two papers[15,16] based upon the same Phase II study were identified. The results in this study relate to the first 42 days after transplantation, therefore, whilst they address the effect of lowering the initial dose, efficacy of long-term low dose maintenance is not addressed.

The occurrence of episodes of acute rejection and of adverse events necessitating a reduction in dose at the three tacrolimus dosage levels in the Phase II study are given in Figures 2 and 3. The low dose Phase II results were corroborated by the European and US Phase III trials, which were undertaken at a similar dose and gave similar results both in terms of acute rejections and study withdrawal. The evidence on dose response supplied by this Phase II study indicates that the effectiveness is likely to be reduced if lower initial

doses are used, however there is insufficient evidence to quantify this reduction and, furthermore, this does not necessarily imply that lowering long-term maintenance doses will lead to significant increases in acute rejection.

Table 1 Randomised Controlled Trials Involving Tacrolimus

TRIAL	**EUROPEAN TACROLIMUS TRIAL [9]**		**US TACROLIMUS TRIAL[10]**	
DESIGN	Randomised, open-label placebo controlled		Randomised, open-label, placebo controlled	
PATIENT NUMBERS	448 (303 tacrolimus, 145 cyclosporin)		412 (205 tacrolimus, 207 cyclosporin)	
INCLUSION CRITERIA	age ≥ 18 undergoing renal transplantation		age ≥ 6 undergoing first or second renal transplantation	
EXCLUSION CRITERIA	HIV+ive, ABO-incompatible grafts, multiple organ transplants, pregnant women, women using inadequate contraception, significant hepatic disease		ABO-incompatible grafts, multiple organ transplants, pregnant or nursing women, HIV+ive	
STUDY PERIOD	12 months		12 months	
MEAN DAILY DOSE	**Tacrolimus**	**Cyclosporin**	**Tacrolimus**	**Cyclosporin**
Initial	0.26 mg/kg	6.90 mg/kg	0.18 mg/kg*	5.5 mg/kg*
Month 10-12 mean	0.12 mg/kg	3.50 mg/kg		
			*12 month mean	
EFFICACY	**Tacrolimus**	**Cyclosporin**	**Tacrolimus**	**Cyclosporin**
Patient survival	282/302 (93.0%)	140/145 (96.5%) [p=0.140]	196/205 (95.6%)	200/207(96.6%) [p=0.576]
Graft survival	245/303 (82.5%)	125/145 (86.2%) [p=0.380]	187/205 (91.2%)	182/207(87.9%) [p=0.289]
Acute rejection	73/303 (24.1%)	63/145 (43.4%) [p<0.001]	63/205 (30.7%)	96/207 (46.4%) [p=0.001]
Steroid resistant	31/303 (10.2%)	30/145 (20.7%) [p=0.004]	22/205 (10.7%)	52/207 (25.1%) [p<0.001]
WITHDRAWAL DUE TO ADVERSE EVENTS	50/303 (16.5%)	4/145 (2.8%) [p<0.001]	[?]	

The manufacturers recommend an initial dose of 0.15-0.30mg/kg/day which is in line with clinical trials. Most UK units tend to commence patients at the lower level and titrate that according to clinical response and blood levels. The manufacturers also state that the dose can frequently be reduced during maintenance therapy, although a target dose is not specified. Current clinical practice has shown that it is safe to reduce the dose to 0.08-0.1mg/kg/day in the maintenance phase, with careful monitoring of the clinical response.

Figure 2 Dose Response of Acute Rejection

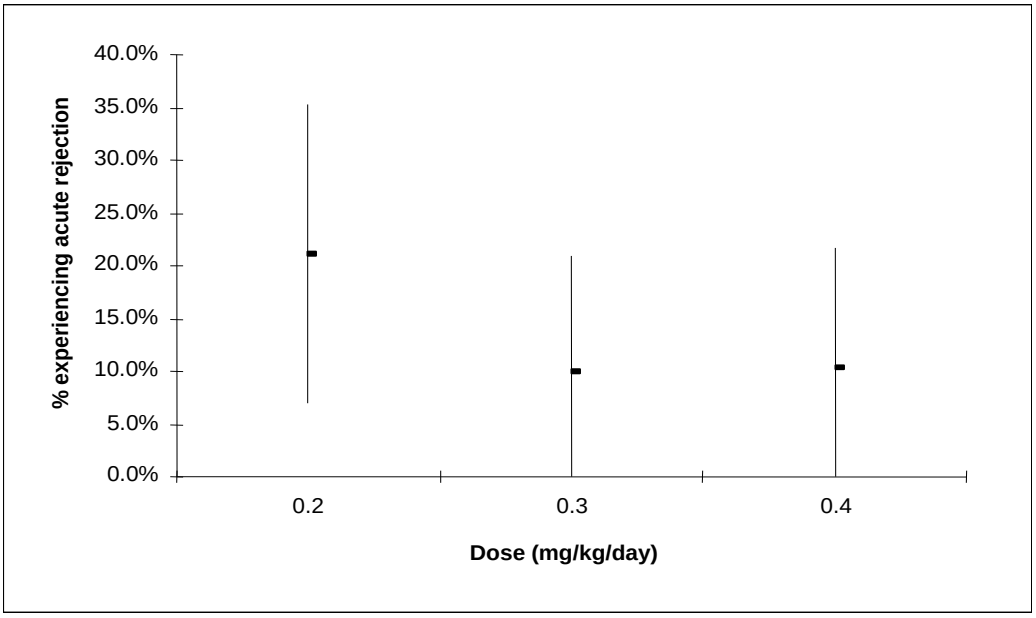
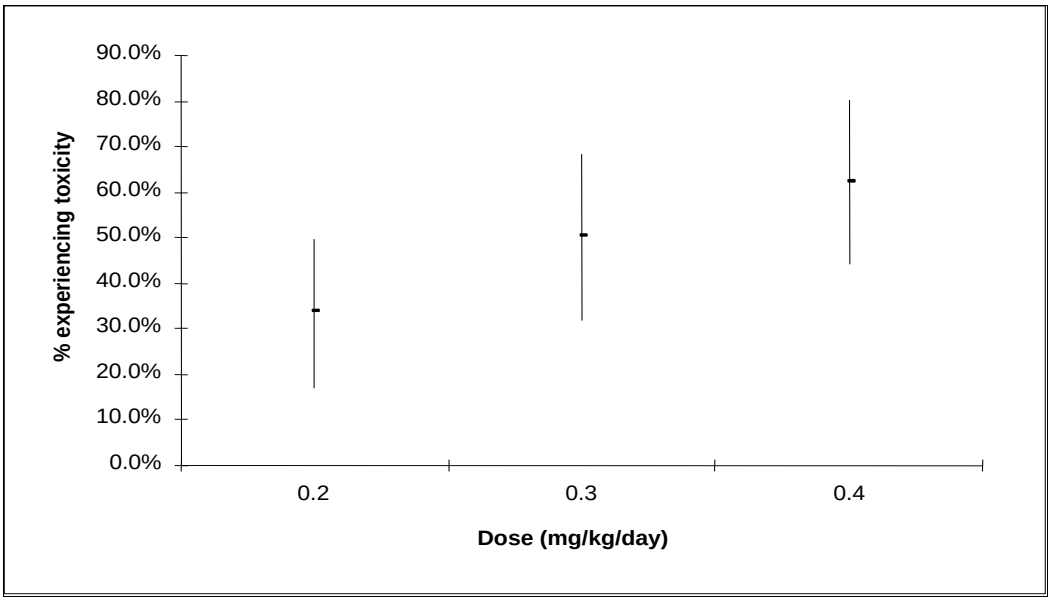


Figure 3 Dose Response of Toxicity (i.e. Adverse Events Necessitating a Reduction in Dose)



2.3 Mycophenolate Mofetil

2.3.1 Evidence of Effectiveness of Mycophenolate Mofetil

Three phase III, randomised, double-blind, multi-centre clinical trials have been undertaken by three groups, each supported by F. Hoffmann-La Roche:

- European Mycophenolate Mofetil Cooperative Study Group;[11]
- US Renal Transplant Mycophenolate Mofetil Study Group;[12]
- The Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group.[13]

The primary efficacy endpoint in each of the individual trials was biopsy proven rejection or treatment failure at six months. The results of the three trials have all been published separately. Furthermore, a pooled analysis of the results of all three trials after 12 months has been reported.[17] This pooling is justified since the analysis was intended from the outset, thus, the trial designs, including endpoints and inclusion/exclusion criteria, were similar for all trials.

The trials had similar entry criteria to the tacrolimus studies, including male and female patients over 18 years of age undergoing renal transplantation. The European and Tricontinental studies included patients receiving their first or second transplant, whilst the US study was restricted to first transplants.

Exclusion criteria were also similar to the tacrolimus studies. More specifically, the exclusion criteria were: serological evidence of human immunodeficiency virus; ABO-incompatible grafts; patients with a history of malignant disorders; patients with severe diarrhoea, gastrointestinal disorders including active peptic ulcer disease and women who were pregnant, lactating or who were using inadequate contraception. Patients were also excluded if they had a white blood cell count of $<2.5x10^3/\mu l$, a platelet count of $<100x10^3/\mu l$ or a haemoglobin concentration of <6g/dl at the time of randomisation.

The trials all consisted of three arms:

- conventional treatment, consisting of cyclosporin maintenance therapy in the European study and cyclosporin with azathioprine in the Tricontinental and US studies;
- daily 2mg mycophenolate mofetil as an adjunct to cyclosporin therapy, but without the use of azathioprine;

- daily 3mg mycophenolate mofetil as an adjunct to cyclosporin therapy, but without the use of azathioprine.

The primary outcome measure in all trials was the incidence of first biopsy proven acute rejection or treatment failure. Patient survival and graft loss were reported along with severity of acute rejection as secondary outcome measures. These primary outcome measures were all defined to be measured at the six month point in the individual trial designs, although the twelve month results are reported in the pooled analysis.

The six month results for the individual trials are summarised in Table 2. The pooled analysis results at 12 months indicated that patient survival and graft survival were not statistically different from placebo or azathioprine treatment for either of the mycophenolate mofetil treatment arms. Strictly speaking, the pooled analysis should have undertaken a formal meta-analysis of the trials rather than simply pooling the results. The trials should have been tested for homogeneity and, only if this were proven, used a fixed or random effects model to combine the results. The biopsy proven acute rejection rates at 12 months were 40.8% for conventional treatment and 19.8% and 16.5% for the 2mg and 3mg mycophenolate mofetil treatment arms respectively.

The absolute decrease in biopsy proven acute rejection was, therefore, in the range 20-25%. This implies a NNT to avoid acute rejection in one patient of between four and five.

As with tacrolimus, the severity of acute rejection episodes, in terms of both histological severity rating and resistance to corticosteroids, was reduced. The proportion of patients requiring anti-lymphocyte or monoclonal antibody therapy for steroid resistant rejection was 19.7% in the conventional therapy population compared to 8.8% and 4.9% in the 2mg and 3mg mycophenolate mofetil treated patients.

The absolute decrease in steroid resistant rejection was, therefore, in the range 10-15%. This implies a NNT to avoid resistant rejection in one patient of between seven and ten.

Three year follow-up studies of the Tricontinental and US mycophenolate mofetil trials have recently reported results (currently in abstract form):

- The Tricontinental study[18] reports that at three years mortality was comparable between all arms (mycophenolate mofetil 3g: 9.8%, mycophenolate mofetil 2g: 4.7%, azathioprine

: 8.6%). A marginal advantage in terms of graft and patient survival was found from mycophenolate mofetil treatment compared to conventional treatment (mycophenolate mofetil 3g: 84.8%, mycophenolate mofetil 2g: 81.9%, azathioprine : 80.2%). This marginal improvement was not statistically significant, though the study was neither designed nor powered to detect significant difference on graft survival at the three year time point.

- Similarly, an intention to treat analysis of the US study[19] data found no significant difference in: graft loss or death; graft loss only; graft loss due to rejection; or death, at either one year or three years, although it did find a marginal advantage in favour of mycophenolate mofetil. However, the study did not provide adequate statistical power to address these survival endpoints.

2.3.2 Adverse Events and Contraindications Associated with Mycophenolate Mofetil

Withdrawal due to adverse events and treatment failure was common throughout all treatment arms. It should also be noted that the high level of withdrawal was reported in all trials. A pooled analysis of study withdrawal at 12 months showed that the withdrawal rates without prior biopsy proven rejection were 13.0%, 17.0% and 23.1% in the conventional, 2mg and 3mg mycophenolate mofetil arms respectively. The proportion of patients withdrawing due to adverse events was higher in the two treatment arms than the conventionally treated arm and appeared to be dose related (5.2%, 8.7% and 14.7% respectively). However, the proportion of patients withdrawing due to graft loss/death was marginally higher in the conventionally treated group than in the two treatment arms (3.4%, 2.8% and 2.9%).

Adverse events associated with mycophenolate mofetil treatment in the trial were:

- increased gastrointestinal events, specifically vomiting, abdominal pain and diarrhoea;
- increased leucopoenia and anaemia;
- increased incidence of opportunistic infections.

Table 2 Randomised Controlled Trials Involving Mycophenolate Mofetil

TRIAL	EUROPEAN MMF TRIAL[11]			US MMF TRIAL[12]			TRICONTINENTAL MMF TRIAL[13]		
DESIGN	Multi-centre, randomised, double-blind, placebo controlled			Multi-centre, randomised, double-blind, controlled			Multi-centre, randomised, double-blind, controlled		
PATIENT NUMBERS	491 (160 MMF3g,165 MMF2g, 166 placebo)			499 (166 MMF3g, 167 MMF2mg, 166 Azath.)			503 (164 MMF3g, 171 MMF2mg, 162 Azath.)		
INCLUSION CRITERIA	age ≥ 18 1st/2nd renal allograft			age ≥ 18 1st renal allograft			age ≥ 18 1st/2nd renal allograft		
EXCLUSION CRITERIA	History of malignant disorders, HIV+ive, HBsAG infection, gastrointestinal disorders, pregnant and lactating women, inadequate contraceptive methods			Contraindication to cyclosporin, prednisone, azathioprine, ALG, unable to take oral medication, positive Tcell crossmatch. Pregnant women and men and women taking inadequate contraception methods. White blood cell count $<2.5x10^3/\mu l$, platelet count $<100x10^3/\mu l$, haemoglobin concentration <6g/dl,HIV-I or HTLV-I +ive, presence of HB_sAg, active peptic ulcer disease, severe diarrhoea, current or historical malignancy.			Unable to take oral medication, pregnant women and men and women taking inadequate contraception methods. Serological evidence of HIV+ive, HBsAG infection, active peptic ulcer disease, severe diarrhoea, gastrointestinal disorders, current or historical malignancy.		
STUDY PERIOD	6 months			3 years, interim results published at 6 months			3 years, interim results published at 6 months		
MEAN DAILY DOSE	Cyclosporin dose ranged between 5 - 15 mg/kg			n/a			Initially 8-10mg/kg, 6 months 3.7-4.0 mg/kg		
EFFICACY	MMF3mg	MMF2mg	Placebo	MMF3mg	MMF2mg	Azathioprine	MMF3mg	MMF2mg	Azathioprine
n	160	165	166	166	165	164	164	171	164
Patient survival	156 (97.5%)	161 (97.6%)	164 (98.8%)	157 (94.5%)	159(96.4%)	159 (97.0%)	157 (95.7%)	165 (96.5%)	155 (95.7%)
Graft survival	146 (91.3%)	154 (93.3%)	149 (89.8%)	152 (91.5%)	156(94.5%)	147 (89.4%)	146 (89.0%)	151 (88.3%)	140 (86.4%)
Acute rejection	22 (13.8%) *	28 (17.0%) *	77 (46.4%)	29 (17.5%)	33† (19.8%)	63 (38.0%)	26 (15.9%)	34† (19.7%)	59† (35.5%)
Steroid resistance	4 (2.5%)	5 (3.0%)	31 (18.7%)	6 (3.6%)	13 (7.9%)	29 (17.7%)	5 (3.0%)	12 (6.9%)	17 (10.2%)
	* [p<0.001]				† n=167			†n=173	†n=166
WITHDRAWAL DUE TO ADVERSE EVENTS AND TREATMENT FAILURE	56/160 (35.0%)	37/165 (22.4%)	58/166 (34.9%)	43/166 (25.9%)	35/165 (21.2%)	37/164 (22.6%)	42/164 (26%)	46/173 (27%)	50/166 (30%)

Table 3 Summary of Acute Rejection Rates

ACUTE REJECTION RATES (12 MONTHS)		SYMPTOMATIC	BIOPSY PROVEN	BLINDED REVIEW	CORTICOSTEROID RESISTANT	HISTOLOGICALLY SEVERE
CYCLOSPORIN	European Tacrolimus	54.4%	43.4%	35.9%	21.6%	6.2%
	US Tacrolimus	n/a	46.4%	44.4%	25.1%	4.3%
	Pooled MMF trials	49.0%	40.8%	n/a	19.7%	n/a
TACROLIMUS	European Tacrolimus	32.3%	24.1%	17.5%	11.3%	2.6%
	US Tacrolimus	n/a	30.7%	27.8%	10.7%	2.0%
MYCOPHENOLATE MOFETIL	2mg MMF pooled	29.7%	19.8%	n/a	8.8%	n/a
	3mg MMF pooled	25.1%	16.5%	n/a	4.9%	n/a

2.4 Neoral versus Sandimmun Formulations of Cyclosporin

As highlighted by Moore,[20] the control arms of the trials of tacrolimus and mycophenolate mofetil (MMF) in primary maintenance therapy all used the Sandimmun formulation of cyclosporin. This has recently been replaced by a new microemulsion cyclosporin formulation, Neoral. Improved effectiveness in preventing episodes of acute rejection is claimed for Neoral over Sandimmun, which will potentially affect the marginal effectiveness and cost-effectiveness of the other new drugs.

A topic search for published trials of the Neoral formulation of cyclosporin versus the Sandimmun formulation, comparing the efficacy in preventing episodes of acute rejection, has identified three studies[21,22,23] which compare primary maintenance for new transplant patients. The characteristics of these studies are detailed in Table 4. There exists further considerable literature on the conversion of existing transplant patients from Sandimmun to Neoral based maintenance therapy.

Table 4 Trials of Neoral versus Sandimmun Formulations of Cyclosporin

Trial	Lodge JPA.[21]	Senel FM.[22]	Keown P.[23]
Year (Publication)	1997	1997	1998
Design	Prospective, randomised, controlled, open label, multi-centre trial	Non-randomised, consecutive case series comparison.	Prospective, randomised, controlled, double blind, multi-centre trial
Population	1st/2nd cadaveric transplant recipients	Consecutive renal transplant recipients	1st/2nd cadaveric transplant recipients
Patient Numbers	288	143	167
Duration	12 weeks interim, 1 year	1 year	3 months
Efficacy outcomes	Acute rejection, patient and graft survival.	Acute rejection, patient and graft survival.	Acute rejection, graft survival.

Table 5 below, summarises the results of the Neoral versus Sandimmun trials and summarises the comparative Sandimmun results from the cyclosporin arms of the

tacrolimus and mycophenolate trials. Note that in all the trials considered, over 90% of acute rejection episodes in the first year occur in the first three month period, the different durations of the trials are, therefore, unlikely to be critical.

Neoral is a microemulsion formulation of cyclosporin which gives improved absorption in comparison to the traditional oil-based oral Sandimmun formulation. Sandimmun, which has recently come out of patent, is no longer actively marketed by Novartis AG and is only available on request. This makes its use as a conventional treatment comparator in the evaluation prone to criticism.

Trials have shown that it is possible to obtain higher trough blood levels at lower doses with Neoral and that these trough blood levels are obtained sooner than with Sandimmun. In the above trials, these benefits in cyclosporin absorption are claimed to give rise to the improvements in acute rejection rates. All trials monitored adverse events and particularly those known to be associated with cyclosporin; none of the above trials found an increase.

Table 5 Suspected Acute Rejection Rates Associated with Neoral or Sandimmun Primary Maintenance Therapy

Source	n (Neoral: Sandimmun)	Period	Sandimmun	Neoral	% Relative reduction in acute rejection rate
Lodge[21]	288 (2:1)	12 weeks	54.6%	41.4%	24%
Senel[22]	143 (40:103)	12 months	57%	49%	14%
Keown[23]	167 (1:1)	3 months	60.5%	44.2%	27%
Tacrolimus trials		12 months	54.4%	--	
MMF trials		12 months	49.0%	--	

These results imply that the clinical benefit of both tacrolimus and mycophenolate mofetil over Sandimmun may be less than any clinical benefit over Neoral. The cost of Neoral is similar to the cost of Sandimmun and, therefore, the marginal cost-effectiveness of tacrolimus and mycophenolate mofetil is likely to be adversely affected. In order to estimate this marginal effectivenes (and marginal cost-effectiveness), it is necessary to construct synthetic comparisons between tacrolimus and Neoral, and between mycophenolate mofetil and Neoral.

In order to generate the required synthetic comparisons an adjustment in acute rejection rates obtained by replacing Neoral for Sandimmun in the appropriate trials is required. The problem is to obtain a justifiable adjustment factor.

It should be noted that the acute rejection rates achieved in any of the trials are related to doses used and to the prognostic characteristics of the trial populations. This makes the comparison between trials very difficult. The suspected acute rejection rates for the Sandimmun arms of the Sandimmun versus Neoral trials ranged from 55% to 61%, whilst the Sandimmun arms of the tacrolimus and mycophenolate mofetil trials ranged from 49% to 55%, that is consistently lower. Thus, assuming that the use of Neoral would have given rise to even lower rates of suspected acute rejection may give misleading results.

2.5 Conclusion on Direction of Evidence and its Quality

The published trials provide strong evidence that either replacing cyclosporin with tacrolimus in the maintenance immunosuppression regimen or prescribing mycophenolate mofetil as an adjunct to cyclosporin, decreases the incidence of episodes of acute rejection in the first year after transplantation in comparison to the Sandimmun formulation of cyclosporin.

There is also strong evidence that the severity of episodes of acute rejection is significantly reduced under both the tacrolimus and mycophenolate mofetil regimens. This improvement is apparent both in terms of episodes classified as histologically severe and in terms of patients requiring anti-lymphocyte antibody or monoclonal antibody treatment for corticosteroid resistant acute rejection.

Patient death and graft loss in the first year after transplantation under conventional immunosuppressant maintenance and rescue therapy is rare. The evidence from the published trials is that patient survival and graft survival for the new tacrolimus and

mycophenolate mofetil treatments are comparable to conventional therapy. No statistically significant differences in patient death or graft loss were found in any of the analysed trials.

Withdrawal rates were high in all studies. Furthermore, the incidence of withdrawal due to adverse events was higher in the treatment arms for both tacrolimus and mycophenolate mofetil than in the conventional treatment arms. In the case of tacrolimus, treatment was associated with increased renal, neurological and cardiovascular complications. Mycophenolate mofetil was associated with increased levels of gastrointestinal complications and opportunistic infections, and withdrawal due to adverse events appeared to be dose related.

There is some evidence that the microemulsion formulation of cyclosporin, that replaces Sandimmun, improves control of acute rejection. Whilst this may potentially reduce the marginal effectiveness of tacrolimus and mycophenolate mofetil, and it is possible to estimate the potential magnitude of this bias, this inevitably introduces a new layer of uncertainty into the comparisons.

Episodes of acute rejection are one of the most important prognostic indicators for later chronic rejection and consequential graft loss.[24,25,26,27,28] This fact provides a logical basis for the conjecture that a reduction in the incidence of acute rejection, in the period following transplantation, will lead to a corresponding reduction in long-term graft loss. If this conjecture were proven, then it would be an important outcome of any new maintenance strategy. The currently published trials of the new therapies, however, were not designed to address the long-term outcomes related to graft loss. There is, therefore, no significant direct evidence concerning the effects of the new agents on long-term graft survival.

3. COST AND BENEFIT IMPLICATIONS OF NEW IMMUNOSUPPRESSANT MAINTENANCE STRATEGIES FOR RENAL TRANSPLANTATION

3.1 Analytical Overview

Two new immunosuppressant maintenance strategies are evaluated in comparison to a conventional maintenance strategy which reflects most common current practice.

- Tacrolimus — Maintenance immunosuppression with tacrolimus, azathioprine and prednisolone;
- Mycophenolate mofetil — Maintenance immunosuppression with cyclosporin, mycophenolate mofetil and prednisolone;
- Conventional — Maintenance immunosuppression with cyclosporin, azathioprine and prednisolone.

The immunosuppressive agents tacrolimus and mycophenolate mofetil are more expensive than the agents they replace. The annual drug costs associated with the two new maintenance strategies are, therefore, higher than for conventional maintenance therapy.

The potential benefits to be gained from the adoption of the new interventions are:

- avoidance of episodes of acute rejection, leading to improved quality of life;
- reduction in the severity of episodes of acute rejection, again leading to improved quality of life;
- reduced costs associated with treatment of acute rejection including reduced costs of treating severe or corticosteroid resistant rejection;
- possible reduction in later chronic rejection and graft failure related to reduced acute rejection;
- possible reduction in the costs associated with treating chronic rejection and graft failure;
- possible reduction in indirect costs arising from graft failure, for instance, retransplantation and dialysis;
- possible increase in the expected life of renal transplants which would lead to a decrease in the demand for retransplantation and a consequential increase in the availability of transplantation for new and waiting patients.

The large majority of episodes of acute rejection occur within six months of transplantation. The Halloran pooled analysis[17] of mycophenolate mofetil showed that approximately 99% of episodes within the first year occurred within the first six months. The currently available RCTs concerning the new agents provide strong evidence about their health benefits in relation to early episodes of acute rejection. Therefore, the cost and benefits of treatment over the first year of treatment after transplantation based on this trial evidence can be evaluated. The costs of treatment used in the analysis are summarised in Section 3.2 and the short-term marginal costs of treatment are estimated in Section 3.3 .

The published evidence[24-28] concerning prognostic factors for chronic rejection identifies episodes of acute rejection as a major risk factor. This provides a theoretical basis for the proposition that the new agents may provide a long-term benefit in terms of reduction in chronic rejection and graft loss. There is, however, little RCT evidence concerning the possible long-term benefits in terms of avoidance of chronic rejection or graft loss. There is, therefore, a much greater level of uncertainty concerning the potential costs and consequences of long-term usage of the new agents; this is explored in Section 3.4.

The RCTs of the new agents all use a formulation of cyclosporin that has since been superseded. There is some evidence that the new microemulsion formulation of cyclosporin provides greater control of acute rejection than the older formulation. The evidence for this benefit is summarised in Section 3.5 and the potential effect on the marginal costs and benefits of the new agents over the first year post transplant is explored.

3.2 Costs of Treatment

3.2.1 Costs Included in the Evaluation

This evaluation uses a health service perspective in relation to costs. Indirect costs, such as, societal costs and costs to the patient due to episodes of acute rejection have not been included. The new treatments might be expected to reduce indirect costs by reducing the support required by patients during episodes of acute rejection. Not including these costs, therefore, favours conventional therapy in this evaluation.

The available evidence shows no significant difference between the treatments in patient death and graft loss in the first year after transplantation and, moreover, does not address these outcomes in the longer-term. This comparative evaluation, therefore, excludes costs

associated with these events. In the short-term, one year evaluation, these costs are expected to be similar between treatments. In the longer-term, on the assumption that long-term chronic rejection rates are reduced, ignoring costs associated with these events will favour the conventional therapy in this evaluation.

The costs associated with treatment and considered in this model, can be broken down into:

- cost of maintenance immunosuppressant drugs;
- cost of treating corticosteroid responsive acute rejection;
- cost of treating corticosteroid resistant acute rejection.

3.2.2 Cost of Maintenance Immunosuppressant Drugs

For both the cyclosporin and tacrolimus treatments, elevated doses are required in the high risk period following transplantation. The maintenance drug costs are, therefore, broken down into 'Initial 3 Month Period' costs and 'Steady State' costs.

Where drug dosages are specified in terms of mg/kg, an average adult body mass of 77kg has been used to calculate average daily dosages, this average body mass was provided by the Nottingham City Hospital Renal Pharmacy Unit. The cost of drugs has been taken from the charged prices incurred by the Nottingham City Hospital Renal Pharmacy Unit. Table 6 shows the quarterly maintenance drug dosages and costs based upon these assumptions.

Table 6 Maintenance Drug Dosages and Costs

		Daily dose (mg/kg/day)	Daily Cost	Quarterly Cost	Annual Cost
Cyclosporin (Sandimmun)	Initial 3 months Steady state	7 4	£13.37 £7.64	£1,220 £697	£3,313
Tacrolimus (Prograf)	Initial 3 months Steady state	0.15 0.075	£21.85 £10.92	£1,994 £997	£4,984
Cyclosporin & Mycophenolate mofetil (Cellcept)	Cyc. initial MMF initial Total	7 2mg total	£13.37 £10.60	£1,220 £968 £2,188	
	Cyc. steady state MMF steady state Total	4 2mg total	£7.64 £10.60	£697 £968 £1,665	£7,183

Note: The above excludes the costs associated with prednisolone and azathioprine, as both of these drugs are of negligible cost relative to cyclosporin, tacrolimus and mycophenolate mofetil.

3.2.3 Cost of Treating Acute Rejection

Where symptoms of acute rejection occur, a number of diagnostic tests are undertaken. The evaluation only includes diagnostic costs as an element of acute rejection costs; no account is taken of diagnostic costs which do not lead to acute rejection being identified.

The standard treatment for acute rejection is intravenous methylprednisolone given as an out-patient on three consecutive days.

If the acute rejection is resistant to corticosteroid treatment then polyclonal antibodies, anti-thymocyte globulin (ATG) or anti-lymphocyte globulin (ALG), or monoclonal antibodies (OKT3) are given. At Nottingham City Hospital this therapy would usually take place within the hospital and involve an in-patient stay in a high dependency ward of between 10 and 14 days.

The costs associated with acute rejection are:

- cost of diagnosis;
- cost of treating corticosteroid responsive acute rejection;
- cost of treating corticosteroid resistant acute rejection.

These are detailed further below:

Cost of diagnosis:

Renal biopsy	£180.00
Blood tests	£ 50.00
Ultrasound scan	£ 45.00
Total diagnostic costs	£275.00

This does not include costs associated with in-patient or day case admissions or out-patient attendances for diagnostic procedures. It is, therefore, an underestimate of the total cost.

Cost of treating corticosteroid responsive acute rejection:

The cost of an out-patient attendance is available from the routine hospital returns (TFR2). The average cost in 1994/95 of attendance at a renal transplant out-patient clinic at Nottingham City Hospital was £83.36; between three and five out-patient attendances are normally required.

Table 7 Costs of Treating Corticosteroid Responsive Acute Rejection

Drug	Infusion Dose	Infusion Cost	Out-patient Attendance	Infusions	Total Cost
Methylprednisolone	500mg	£2.74	£83.36	3	£258.30

Cost of treating corticosteroid resistant acute rejection:

A 14 day in-patient stay cost is estimated at:
High dependency ward @ £350 per day : £4,900

A number of different treatments are available for the treatment of corticosteroid resistant rejection. These are the polyclonal antibodies, ATG and anti-lymphocyte globulin (ALG) and OKT3. The dosages, treatment regimen and costs are detailed in Table 8. Of these therapies ATG is the most commonly used treatment.

Table 8 Cost of Drugs for Treating Steroid Resistant Acute Rejection

Drug	Infusion Dose	Infusion Cost	Infusions	Total Drug Cost
ATG	154 mg	£347.42	7	£2,432
ALG	770 mg	£380.00	14	£5,320
OKT3	5 ml	£440.45	14	£6,166

3.3 One Year Cost and Consequences Analysis

Table 9 summarises the expected number and severity of episodes of acute rejection in 13 new transplants, being the annual number of transplants undertaken from a 'typical' district population of 500,000 under the maintenance strategies considered. These estimates are based on trial comparisons of tacrolimus and mycophenolate mofetil with a conventional therapy based on the Sandimmun formulation of cyclosporin.

Table 10 summarises the expected costs associated with the treatment strategies on a per patient basis and for 13 new transplant patients.

The published Kaplan-Meier estimates of acute rejection rates relate to the first episode of rejection. For the purposes of this evaluation, it has been assumed that the incidence of further episodes of rejection follow a similar distribution to the first episode. The expected number of episodes of rejection in the first year is greater, therefore, than the base rejection rates quoted in the published trials. For example, for cyclosporin the 12 month biopsy proven rejection rate from the pooling of all trials is approximately 45% (c.f. European Tacrolimus[9] trial at 12 months is 43%), however, based on this assumption, the expected number of rejection episodes for an individual in the first year is 0.78 not 0.45. The numbers of patients with 0,1,2,3 and ≥ 4 episodes of rejection obtained from this model of multiple episodes has been validated against the corresponding numbers of patients at Nottingham City Hospital under cyclosporin maintenance therapy.

The costs of treating corticosteroid resistant acute rejection are based on the use of ATG, which is the preferred antibody regimen at Nottingham City Hospital, and one of the primary resistant rescue regimens used in the trials. A hospital stay of 14 days in a high dependency ward is appropriate with this use of ATG as the more intensive monitoring (specifically of CD3 count) allows lower dosages to be used, thus avoiding over immunosuppression.

Although hospital stays constitute a major resource use in the treatment of acute rejection, the savings associated with a reduction in total bed usage may not be directly realisable unless the reduction is sufficient either to allow a reduction in capacity or to allow capacity to be used in the treatment of other patients.

The average cost of acute rejection per patient given below is calculated from the expected cost per episode multiplied by the expected number of episodes per patient.

Table 9 **Summary of Acute Rejection Episodes in an Annual District Transplant Population**

Maintenance Strategy	Expected Number of Episodes of Acute Rejection Rrange)		
	Responsive	Resistant	Total
Tacrolimus	2.9 (2.4, 3.5)	1.8 (1.5, 2.2)	4.7 (3.9, 5.7)
MMF 2mg	1.8 (1.4, 2.2)	1.4 (1.1, 1.7)	3.3 (2.5, 3.9)
Cyclosporin (Sandimmun)	4.7 (4.2, 5.2)	4.5 (4.0, 5.0)	9.2 (8.1, 10.2)
Tacrolimus vs Cyclosporin (Sandimmun)	-1.8 (-2.9, -0.7)	-2.7 (-3.5, -1.8)	-4.4 (-6.4, -2.5)
MMF vs Cyclopsorin (Sandimmun)	-2.9 (-3.8, -2.0)	-3.1 (-3.9, -2.3)	-5.9 (-7.7, -4.3)

Table 10 **Summary of Patient and Population First Year Costs for Maintenance Strategies**

Maintenance Strategy	Cost of Acute Rejection Per Patient			Cost of Maintenance per Patient	Total Cost per Patient	Total Cost 13 Patients
	Responsive Rejection	Resistant Rejection				
		Drugs and diagnosis	In-patient			
Tacrolimus	£118	£383	£694	£4,890	£6,086	£79,119
MMF 2mg	£75	£298	£540	£7,105	£8,017	£104,226
Cyclosporin (Sandimmun)	£192	£936	£1,694	£3,204	£6,026	£78,332
Tacrolimus vs Cyclosporin (Sandimmun)	-£74 (-£117, -£29)	-£552 (-£730, -£375)	-£1000 (-£1321, -£680)	£1,686 (£1658, £1713)	£61 (-£454, £574)	£787 (-£5902, £7459)
MMF vs Cyclosporin (Sandimmun)	-£117 (-£156, -£83)	-£637 (-£812, -£483)	-£1154 (-£1470, -£875)	£3900 (£3876, £3929)	£1,992 (£1492, £2435)	£25,895 (£19391, £31649)

The trials all show a remarkable consistency in the rates of acute rejection achieved, see Table 3, for each of the maintenance strategies. The above estimates are based upon pooled acute rejection rates for cyclosporin, tacrolimus and mycophenolate mofetil respectively. A sensitivity analysis for the total cost of treatment based upon the maximum

and minimum advantage in terms of acute rejection rates shown in the trials is presented in Table 11. The maximum advantage is derived from the highest rejection rate (that is the upper 95% confidence limit) for cyclosporin treatment and the lowest rate (that is the lower confidence limit) for tacrolimus or mycophenolate mofetil. The minimum advantage is derived from the lowest rejection rate for cyclosporin and the highest rejection rates for the new treatments.

Table 11 Sensitivity of Total Cost Per Patient to Error in Acute Rejection Rates

Maintenance Strategy	Minimum Advantage	Central Estimate	Maximum Advantage
Tacrolimus vs Cyclosporin (Sandimmun)	£574	£61	-£454
MMF vs Cyclosporin (Sandimmun)	£2,435	£1,992	£1,492

3.4 Long-term Cost and Consequences Analysis

The one year post-transplant analysis detailed in Section 3.3 identifies the potential for cost savings arising in the first year. These cost savings arise from a reduction in the number and severity of acute rejection episodes which offset the increase in maintenance therapy costs. If graft survival to one year is achieved, then the risk of further episodes of acute rejection is much reduced. Therefore, the full increase in maintenance costs is likely to be borne for patients after the initial year post transplantation.

Table 10 shows the average cost per year of maintenance therapy once a steady state has been achieved. In conventional therapy, most UK centres would give a mean dose of 4mg/kg/day of cyclosporin to maintain a therapeutic level of 100-200ng/ml. In the tacrolimus clinical trials already analysed, an initial dose of 0.15mg/kg/day was given which resulted in a significant number of withdrawals due to side-effects. These side-effects are dose dependent and it has been recommended subsequently that the dose of tacrolimus should be titrated against response and side-effects. Once a steady state has been achieved, usually within three months, 0.05-0.075mg/kg/day in a divided dose can be given. In practice, an equal dose is given twice daily to fall within that window. Thus an 85kg patient will receive 3mg twice daily (0.071mg/kg/day) rather than 2mg twice daily (0.047mg/kg/day),

whereas a 72kg patient will receive 2mg twice daily (0.055mg/kg/day) rather than 3mg twice daily (0.083mg/kg/day).

There has been some early work, as yet unpublished, showing that mycophenolate mofetil can be given safely with a dose of cyclosporin of 2.5mg/kg/day in stable patients. This likewise would reduce the cost difference when compared to conventional therapy.

The cost per year of maintenance with immunosuppressive drugs after the first year is calculated from the steady state dosages for the three management strategies considered and is very sensitive to the mean dosages achieved. At Nottingham City Hospital the current target steady state dosage for tacrolimus is 0.05 - 0.075 mg/kg; where this is achieved the annual steady state cost for tacrolimus would be £2,660 - £3,390. Note that in the case of child transplant patients the dosages, and hence maintenance costs, are likely to be markedly less than in the adult population.

Table 12 Cost Per Year of Maintenance Therapy at Steady State Dosage

Maintenance Strategy	Mean Daily Dose	Annual Cost per Patient	Difference
Cyclosporin (Sandimmun)	4 mg/kg	£2,790	--
Tacrolimus	0.075 mg/kg	£3,990	£1,200
Cyclosporin (Sandimmun) & Mycophenolate mofetil	4 mg/kg 2 mg	£6,660	£3,870

As highlighted in Section 3.1, the occurrence of severe, multiple and late episodes of acute rejection are all risk factors for the development of chronic rejection and consequent reduced graft survival. It can be hypothesised that, by reducing both the number and severity of acute rejection episodes using tacrolimus and mycophenolate mofetil based regimens, the onset of chronic rejection and subsequent graft loss may be prevented or delayed.

A long-term cyclosporin dose-ranging study involving both cadaveric and living donor transplants[28] identified a five year graft survival rate of 68.7% in patients who had no history of acute rejection compared with 42.9% in patients who had experienced acute rejection. If

these five year survival rates are applied to the trial populations considered in Section 3.3, the reduction in first year biopsy proven acute rejection from approximately 43% for cyclosporin to 28% for tacrolimus treatment would imply a 4% improvement in graft survival at five years. Similarly, the figures for mycophenolate mofetil would imply a 6% improvement in five year graft survival.

It should be noted that these figures are consistent with the three year graft survival improvement reported in the abstract[19] from the US mycophenolate mofetil study. This study reported a 6% improvement in patient/graft survival for mycophenolate mofetil 2mg treatment compared to cyclosporin with azathioprine treatment, although this improvement was not statistically significant, Table 12 refers.

Table 13 Long-term Results from US Mycophenolate Mofetil Trial

Intention to Treat Analysis at 3 Years				
	MMF 2mg	**MMF 3mg**	**Azathioprine**	**p**
Graft loss/death	18.8%	21.7%	25.0%	not significant
Graft loss only	12.7%	15.7%	16.5%	not significant
Graft loss due to rejection	10.3%	10.2%	12.8%	not significant
Death	10.3%	12.0%	11.6%	not significant

Thus, an estimate of the additional cost per graft loss or death avoided can be obtained and is outlined in Table 14. The figures will be over-estimates as they are based on treatment for the full three years for all patients, i.e. treatment failures leading to switching or cessation of drug regimens prior to three years or deaths are not accounted for.

Although long-term use of the new regimens has an increased cost, this would be offset to some extent, by reducing the costs associated with graft failure. These would include avoidance of dialysis, estimated at £17,800 per year and avoidance of the higher treatment costs associated with re-transplantation and treatment during the first year after re-transplantation. The cost of a failed transplant has been estimated at approximately £94,000

per patient per year, including not only the costs associated with the recipient (extra immunosuppressive therapy, resumption of dialysis and continuation of dialysis), but also those from the denial of that kidney for another dialysis dependent patient in whom it may have worked better.[29]

Table 14 Additional Maintenance Drug Costs in Years 2 and 3 per Graft Loss Avoided

	Improvement in Graft/ Patient Survival	Number Needed to Treat	Additional Cost per Patient Year in Years 2 and 3	Cost per Graft Loss/ Patient Death Avoided
Tacrolimus	4%	25	£1,200	£30,000
Cyclosporin & Mycophenolate mofetil 2mg	6%	17	£3,870	£64,500

Since these agents are more potent immunosuppressants their long-term use may allow the cessation of steroids and reduction of the cyclosporin dose. Tacrolimus could be given as monotherapy and mycophenolate mofetil with a reduced cyclosporin dosage (2mg/kg/day). The potential steroid sparing effect of both of these regimens should have a significant effect upon long-term morbidity e.g. cataracts and bone problems. Likewise, lower doses of cyclosporin reduce the risk of chronic cyclosporin nephrotoxicity.

3.5 Potential Impact of Replacing Sandimmun with Neoral on the Marginal Cost and Marginal Effectiveness of Tacrolimus and Mycophenolate Mofetil

The trials of tacrolimus and mycophenolate mofetil in primary maintenance therapy all used the Sandimmun formulation of cyclosporin. This has recently been replaced by a new microemulsion cyclosporin formulation, Neoral. The improved clinical effectiveness of Neoral in comparison to Sandimmun is discussed in Section 2.4. The potential impact on the marginal cost-effectiveness of tacrolimus and mycophenolate mofetil is investigated here.

Table 15 summarises the potential clinical impact of using Neoral in place of Sandimmun. The most favourable assumptions for Neoral (and conversely the most conservative assumptions for tacrolimus and mycophenolate mofetil) are considered, that is that Neoral

imparts a 25% advantage in terms of acute rejections avoided over Sandimmun. If Neoral imparts no benefit over Sandimmun the marginal cost-effectiveness is as previously analysed.

Table 15 Summary of Acute Rejection Episodes in a 'Typical' District Transplant Population of 13 Patients

Maintenance Strategy	Expected Number of Episodes of Acute Rejection (Range)		
	Responsive	Resistant	Total
Tacrolimus	2.9	1.8	4.7
MMF 2mg	1.8	1.4	3.3
Cyclosporin (Sandimmun)	4.7	4.5	9.2
Tacrolimus vs Cyclosporin (Sandimmun)	-1.8	-2.7	-4.4
MMF vs Cyclosporin (Sandimmun)	-2.9	-3.1	-5.9
Cyclosporin (Neoral)	3.1	3.0	6.1
Tacrolimus vs Cyclosporin (Neoral)	-0.2	-1.2	-1.4
MMF vs Cyclosporin (Neoral)	-1.3	-1.6	-2.9

Note: mycophenolate mofetil here indicates a combination therapy using mycophenolate mofetil with cyclosporin as compared with cyclosporin alone.

Under the most extreme assumption in terms of benefit from Neoral therapy, it can be seen that the advantage of tacrolimus over Sandimmun is reduced from 4.4 to 1.4 episodes of acute rejection in an annual district population of 13 new transplant patients in their first year. Similarly, the advantage of mycophenolate mofetil is reduced from 5.9 episodes to 2.9 episodes.

Given the uncertainty concerning the actual benefit achieved from Neoral relative to Sandimmun, and uncertainty as to whether this benefit would be seen in head to head trials

against tacrolimus or mycophenolate mofetil, the other extreme estimate must be that the marginal cost and marginal effectiveness would be as previously estimated.

Furthermore, mycophenolate mofetil is given in addition to cyclosporin and has a very distinct mode of action, therefore, it may be argued that the marginal effectiveness of mycophenolate mofetil plus Sandimmun over Sandimmun alone may be similar to the marginal effectiveness of mycophenolate mofetil plus Neoral over Neoral alone. In this case the marginal cost-effectiveness would be similar to the estimates previously obtained.

Table 16 summarises the first year costs associated with use of Neoral in place in Sandimmun.

Table 16 Summary of Patient and Population First Year Costs for Maintenance Strategies

Strategy	Responsive Rejection	Resistant Rejection		Maintenance per Patient	Total cost per Patient	Total cost 13 Patients
		Drugs and Diagnosis	Inpatient			
Tacrolimus	£118	£383	£694	£4,890	£6,086	£79,119
MMF 2mg	£75	£298	£540	£7,105	£8,017	£104,226
Cyclosporin (Sandimmun)	£192	£936	£1,694	£3,204	£6,026	£78,332
Tacrolimus vs Cyclosporin (Sandimmun)	-£74	-£552	£1000	£1686	£61	£787
MMF vs Cyclosprorin (Sandimmun)	-£117	-£637	-£1154	£3900	£1,992	£25,895
Cyclosporin (Neoral)	£128	£625	£1,131	£3,237	£5,122	£66,582
Tacrolimus vs Cyclosporin (Neoral)	-£10	-£241	-£437	£1,653	£964	£12,537
MMF vs Cyclosporin (Neoral)	-£53	-£327	-£591	£3,867	£2,896	£37,644

Note: mycophenolate mofetil here indicates a combination of therapy using mycophenolate mofetil with cyclosporin as compared with cyclosporin alone.

Under the most extreme assumption in terms of benefit from Neoral therapy, it can be seen that, whereas tacrolimus was estimated to be approximately cost neutral over Sandimmun (difference of £61 per patient) in the first year, over Neoral the cost difference would be approximately £1,000 per patient. Similarly, for mycophenolate mofetil the cost difference has risen from approximately £2,000 to nearly £3,000 per patient in the first year.

4. OPTIONS FOR PURCHASERS AND PROVIDERS

The options available depend on whether purchasers wish to specify the use of a particular drug in their service agreements. Service agreements often specify the number of patients on dialysis, by type of dialysis, and the number of 'new', that is within one year of a transplant, and 'old' transplant patients. An agreement of this type enables any drug to be introduced at the discretion of the clinician, if there is no resulting change in the overall cost of treating patients in that particular category. This can be achieved either if the drug is the same price as the previous treatment or if the hospital can make compensatory savings in another part of the service. The impact of the new drugs available for reducing the risk of rejection is, however, likely to raise the costs per case within the hospital budget, not only due to the cost of the individual drugs, but also because these drugs will be perceived as less suitable for prescription in general practice.

Purchasers could insist that, if the drugs are seen to be effective, their use should be prioritised within the unit, at the expense of other, possibly less well researched, treatments or procedures.

Within a renal unit the options are:

- to continue to use conventional treatment as previously;
- to use tacrolimus, for either all or selected patients;
- to use mycophenolate mofetil, for either all or selected patients; or
- to use both mycophenolate mofetil and tacrolimus for appropriate patients.

Given the lack of information on risks of infectious complications and malignancy associated with the long-term use of the two new agents, it may be appropriate to implement initially the new agents as primary maintenance in immunologically high risk patients whilst using conventional primary maintenance therapy for immunologically low risk patients.

The definition of high risk used at the Nottingham Renal Unit is:

- loss of previous transplant to acute rejection;
- the presence of >50% cytotoxic antibodies in current or historic serum;
- third or subsequent transplant;
- 1 or 2 DR mismatch.

On this basis, for the calendar years 1997 and 1998, the Nottingham unit performed 81 adult renal transplants. Using the above criteria 30% of transplants were on immunologically high risk patients.

Over the same period, 34% of newly transplanted patients had at least one episode of rejection in the first three months post-transplant. 40% of these patients experiencing rejection had steroid resistant rejection and were given tacrolimus rescue therapy.

In the immunologically high risk group, 41% had at least one episode of rejection in the first three months post-transplant, of which 56% were steroid resistant. In the immunologically normal risk group, 31% had at least one episode of rejection in the first three months, of which 31% were steroid resistant.

In corroboration of the earlier analysis, the incidence of acute rejection has been lower in the Nottingham Renal Unit patients since the beginning of 1997 when the immunosuppressive policy was altered to Neoral (7mg/kg/day), azathioprine (1.5mg/kg/day) and prednisolone (20mg) as initial therapy. Before that, the acute rejection rate was nearer to 50%.

5. DISCUSSION AND CONCLUSIONS

The clinical trial evidence demonstrates that immunosuppressive regimens containing tacrolimus or mycophenolate mofetil significantly reduce the incidence and severity of acute rejection within the first year post-transplantation. These studies were neither designed nor powered to demonstrate long-term improvements in graft survival; in fact studies with very large numbers of patients would be required and these are not realistic. Many studies have shown, however, that the number and severity of acute rejection episodes correlates with the development of chronic rejection, which will, therefore, influence graft survival and subsequent return to dialysis.

In demonstrating the cost and consequences of using tacrolimus and mycophenolate mofetil in the first year following transplantation, certain caveats have to be made. Within the UK healthcare system reduced in-patient bed stay and staff costs do not translate easily to real cost savings. This would not be the case in insurance funded health schemes where every part of the process may be individually costed and paid for separately.

It becomes even more difficult in realising long-term cost savings, which may be intangible. These include the positive clinical and economic benefits of prolonged graft survival. If the graft is functioning well, fewer out-patient visits and diagnostic tests/procedures are required, and the patient can live with a good quality of life and with good occupational rehabilitation. Poor transplant function with chronic rejection results in more clinic visits, more diagnostic tests/procedures, and the inevitable need for dialysis and re-transplantation. A failed transplant is very expensive and has been calculated by others at £94,000 per patient per year, which includes not only the costs associated with the recipient (extra immunosuppressive therapy, resumption of dialysis and continuation of dialysis), but also the denial of that kidney for another dialysis dependent patient in whom it may have worked better.[29] Therefore, long-term graft survival is one of the primary aims of transplantation and meeting this goal can be helped by effective immunosuppressive protocols alongside other strategies to reduce morbidity.

As discussed in Section 3.4 there are also other long-term cost savings which are difficult to measure accruing from steroid-sparing immunosuppressive protocols. This possibility is more likely with tacrolimus and mycophenolate mofetil regimens where there has been less rejection and, therefore, less need for long-term steroid therapy. The use of steroids long-term is undoubtedly associated with increased morbidity which includes bone problems

(osteopoenia, fractures, avascular necrosis) and cataracts. Prednisolone and azathioprine have been used for over 30 years in clinical transplantation and, as such, are cheap, so there are few direct cost savings to be made. Savings come from the associated reduced morbidity.

It is known that there is an increased risk of acute rejection in the first six months post-transplantation and that the incidence after one year is low. It can be argued that more potent immunosuppression should be given to cover this high risk period with conversion to conventional treatment thereafter. Thus, the extra costs of tacrolimus or mycophenolate mofetil would be concentrated in the first year. There is as yet no published evidence looking at conversion from tacrolimus or mycophenolate mofetil.

There are now recognised guidelines for converting patients from tacrolimus to cyclosporin which are safe, but, as with any change of immunosuppression, it could precipitate an episode of acute rejection. There are also issues of patient compliance: tacrolimus is a small tablet whereas cyclosporin is relatively large, and if patients are stable on one drug they may be reluctant to change. Likewise, it would be straightforward to convert patients from mycophenolate mofetil to azathioprine with consequent cost savings; because the patient would still be receiving cyclosporin, the risk of rejection would be low.

Conversions as described above should be safe where:

- graft function is stable;
- the patient is immunologically low risk (good HLA match with low cytotoxic antibodies);
- the patient has had little or no rejection.

However, where these criteria are not met, there would be an increased risk of acute rejection associated with conversion.

When the new agents are compared with the Sandimmun formulation of cyclosporin, tacrolimus is estimated to be potentially cost neutral and result in an average of 4.4 episodes of acute rejection avoided per annum in a 'typical' health authority. Similarly, mycophenolate mofetil was shown to have an additional cost of £26,000 (£19,000-£32,000) per year and result in an average of 5.9 episodes of acute rejection avoided per annum in a 'typical' health authority.

Revising the estimates to take account of the improved performance of the Neoral formulation of cyclosporin compared with Sandimmun produces a reduced estimate of marginal benefit for both tacrolimus and mycophenolate mofetil. Accordingly, tacrolimus is no longer cost neutral, but would be estimated to cost approximately £12,500 more per annum and prevent an average of only 1.4 episode of acute rejection in a 'typical' health authority. Estimating the marginal effect for mycophenolate mofetil is more difficult since mycophenolate mofetil is used in addition to cyclosporin. The marginal cost-effectiveness may remain as estimated earlier, or reduce further to an extra cost of £37,600 together with only 2.9 episodes of acute rejections avoided per annum.

Acute rejection after renal transplantation is uncommon after one year. When it does occur, it is associated with a poor prognosis for graft survival and may be caused by poor patient compliance. This will be the same for the new, as well as the conventional, immunosuppressive strategies.

The treatment of steroid resistant or refractory rejection has been assumed in this paper to be with polyclonal or monoclonal antibodies. However, it is clear that the majority of UK renal transplant units are increasingly using tacrolimus in place of antibody therapies in this situation since it is effective, more patient friendly, and can be given by mouth as an out-patient.[3,4]

The high withdrawal rate, due to side-effects in both the tacrolimus and mycophenolate mofetil studies, has previously been alluded to and it is clear that side-effects are principally dose dependent. Patients and their medical attendants are always extra vigilant in clinical trials and patients are withdrawn and the drug discontinued at an earlier stage than might normally happen in routine clinical practice if side-effects are observed. Once experience has been gained in the use of a new drug, the clinician has more confidence in continuing to use it or to reduce the dose depending on response and side-effects. As a result of the tacrolimus studies, lower maintenance doses are now recommended once a therapeutic response has been obtained. The withdrawal rates for side-effects in the mycophenolate mofetil studies were greater in the 3mg than the 2mg group and, as a result, 1mg twice daily is now recommended.

It should be noted that this report focuses on renal transplantation in adults. Children justify special consideration because one of the major benefits of transplantation in children is to enable them to grow satisfactorily, incidentally saving on potentially expensive treatments,

such as, growth hormone therapy, and for them to achieve their school and developmental potential. It is essential that the best graft function possible is achieved and the use of these newer agents would enable a reduction of acute rejection. This may, in turn, reduce the incidence of chronic rejection and the need for the child to undergo further transplants either in late childhood or early adulthood. A lot of focus in the document is on saving kidneys in the long-term from rejection and this is of major importance in children.

Body image considerations are also of major importance in children and may be a factor in non-compliance with treatment which particularly affects the adolescent group. Therefore, drugs which do not result in excess hair growth or enlarged gums or major changes in body image are to be encouraged. These are further reasons to consider tacrolimus or mycophenolate mofetil with reduced steroid dosage in the future.

The analysis of drug costs presented in this report is based on typical drug doses for an adult population and, since doses are based upon body size, does not apply directly to children where doses are likely to be markedly less. Furthermore, since children may be travelling from further afield to a single regional centre, the cost of travel is likely to be very relevant as increased out-patient and in-patient attendance will lead to increased cost. An economic analysis for the use of these new drugs in a paediatric population is, therefore, likely to be improved in comparison to their adult population analysis.

It is clear that tacrolimus and mycophenolate mofetil are potent immunosuppressive agents and, as such, may increase the risk of infectious complications and malignancy. One important principle of transplantation is to establish the balance between under and over immunosuppression; on the one hand to minimise the risk of rejection whilst on the other minimising the risks of infectious complications and malignancy. Since approximately 50% of patients will not experience acute rejection, it can be argued that this group can be maintained on conventional cyclosporin based therapy, accepting the morbidity associated with the potential long-term usage of steroids. It is the groups which experience severe, recurrent or late rejection which would particularly benefit from tacrolimus or mycophenolate mofetil based immunosuppression. Although this group cannot be predicted accurately, there are certain factors which render an individual immunologically at high risk; these include:

- loss of previous transplant to acute rejection;
- the presence of more than 50% cytotoxic antibodies;
- third or subsequent transplant.

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