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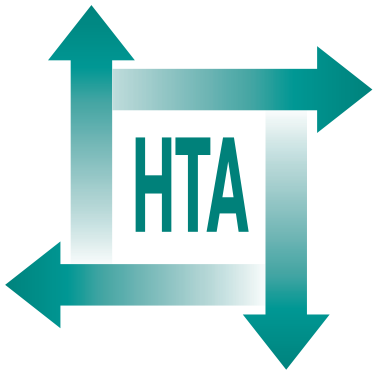

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A systematic review and economic model of the clinical and cost-effectiveness of immunosuppressive therapy for renal transplantation in children

G Yao,[1] E Albon,[2] Y Adi,[2] D Milford,[3] S Bayliss,[2] A Ready,[4] J Raftery[5] and RS Taylor[2*]

[1] Health Economics Facility, Health Services Management Centre, University of Birmingham, UK

[2] Department of Public Health and Epidemiology, University of Birmingham, UK

[3] Department of Nephrology, Birmingham Children's Hospital, UK

[4] Department of Nephrology, Queen Elizabeth Hospital, Birmingham, UK

[5] National Coordinating Centre for Health Technology Assessment, University of Southampton, UK

* Corresponding author

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Abstract

A systematic review and economic model of the clinical and cost-effectiveness of immunosuppressive therapy for renal transplantation in children

G Yao,[1] E Albon,[2] Y Adi,[2] D Milford,[3] S Bayliss,[2] A Ready,[4] J Raftery[5] and RS Taylor[2*]

[1] Health Economics Facility, Health Services Management Centre, University of Birmingham, UK
[2] Department of Public Health and Epidemiology, University of Birmingham, UK
[3] Department of Nephrology, Birmingham Children's Hospital, UK
[4] Department of Nephrology, Queen Elizabeth Hospital, Birmingham, UK
[5] National Coordinating Centre for Health Technology Assessment, University of Southampton, UK
* Corresponding author

Objectives: To review the clinical and cost-effectiveness of basiliximab, daclizumab, tacrolimus, mycophenolate mofetil (MMF), mycophenolate sodium (MPS) and sirolimus as possible immunosuppressive therapies for renal transplantation in children.
Data sources: Electronic databases were searched up to November 2004.
Review methods: Data from selected studies were extracted and quality assessed. An economic model [Birmingham Sensitivity Analysis paediatrics (BSAp)] was produced based on an adaptation of a model previously developed for the assessment of the cost-effectiveness of immunosuppressants in adults following renal transplant.
Results: For the addition of basiliximab, one unpublished paediatric randomised control trial (RCT), reported that the addition of basiliximab to tacrolimus-based triple therapy (BTAS) failed to significantly improve 6-month biopsy-proven acute rejection (BPAR), graft function, graft loss and all-cause mortality. No significant difference between groups was seen in 6-month or 1-year or longer graft loss, all-cause mortality and side-effects. In a meta-analysis of adult RCTs, the addition of basiliximab to a ciclosporin, azathioprine and steroid regimen (CAS) significantly reduced short-term BPAR. There was no significant difference in short- or long-term graft loss, all-cause mortality or side-effects. One adult RCT was included for the addition of daclizumab to CAS, which reported reduced 1-year BPAR, although no difference between groups was seen in either 1- or 3-year graft loss, all-cause mortality and side-effects. For tacrolimus versus ciclosporin, one unpublished paediatric RCT found that a regimen of tacrolimus, azathioprine and a steroid (TAS) reduced 6-month BPAR and improved graft function [glomerular filtration rate (GFR)] compared with CAS. This improvement in BPAR with tacrolimus was as shown in the meta-analysis of adult RCTs. There was evidence, particularly in children, that in comparison with ciclosporin, tacrolimus may reduce long-term graft loss, although there is no benefit on total mortality. The total level of withdrawal in children was reduced in children receiving tacrolimus. Adult RCTs showed an increase in post-transplant diabetes mellitus with tacrolimus. For MMF versus azathioprine, a meta-analysis of adult RCTs showed MMF [regimen of ciclosporin, MMF and a steroid (CMS)] to reduce 1-year BPAR compared with azathioprine (CAS). There was evidence, particularly in children, that in comparison with azathioprine, tacrolimus may reduce long-term graft loss, although there is no benefit on total mortality. There was an increase in the level of cytomegalovirus infection with MMF, although the overall level of withdrawal due to adverse events was not different to that of azathioprine-treated adults. No study comparing MPS with azathioprine (CAS) was identified. In an adult RCT comparing MMF with MPS, there was no significant difference between groups in 1-year efficacy or side-effects. One unpublished paediatric RCT assessed the addition of sirolimus to CAS. BPAR, graft loss and all-cause mortality were not reported. In two adult RCTs, compared with azathioprine, sirolimus reduced 1-year BPAR, reduced graft function (as assessed by an increased serum creatinine) and increased the level of hyperlipidaemia. No significant differences were seen in other efficacy

and side-effect outcomes. On an adult RCT comparing sirolimus with ciclosporin, there were no significant differences between groups in 1-year efficacy or side-effects with the exception of an increased level of hyperlipidaemia with sirolimus substitution. Both the assessment group and drug companies assessed the cost-effectiveness of the newer renal immunosuppressants currently licensed in children using an adaptation (BSAp) of the Birmingham Sensitivity Analysis (BSA) model. This model is based on a 10-year extrapolation of 1-year BPAR results sourced from paediatric RCTs or adult RCTs (where paediatric RCTs were not available). The addition of basiliximab and that of daclizumab to CAS was found to increase quality-adjusted life-years (QALYs) and decreased overall costs, a finding that was robust to sensitivity analyses. The incremental cost-effectiveness ratio (ICER) of replacing ciclosporin with tacrolimus was highly sensitive to the selection of the hazard ratio for graft loss from acute rejection, dialysis costs and the incorporation (or not) of side-effects. The ICERs for tacrolimus versus ciclosporin ranged from about £46,000/QALY to about £146,000/QALY. Although sensitive to varying the hazard ratio for graft loss with acute rejection, the ICER for replacing azathioprine with MMF remained in excess of £55,000/QALY.

Conclusions: In general, compared with a regimen of ciclosporin, azathioprine and steroid, the newer immunosuppressive agents consistently reduced the incidence of short-term biopsy-proven acute rejection. However, evidence of the impact on side-effects, long-term graft loss, compliance and overall health-related quality of life is limited. Cost-effectiveness was estimated based on the relationship between short-term acute rejection levels from RCTs and long-term graft loss. Both the addition of daclizumab and that of basiliximab were found to be dominant strategies, that is, regarding cost savings and increased QALYs. The incremental cost-effectiveness of tacrolimus relative to ciclosporin was highly sensitive to key model parameter values and therefore may well be a cost-effective strategy. The incremental cost-effectiveness of MMF compared with azathioprine, although also sensitive to model parameter, was unattractive. There is a particular need for RCTs to assess the use of MMF, MPS and daclizumab for renal transplantation in children where no such evidence currently exists. Future comparative studies need to report not only on the impact of the newer immunosuppressants on short- and long-term clinical outcomes but also on side-effects, compliance, healthcare resource, costs and health-related quality of life.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Cadaveric transplant A transplant kidney removed from someone who has died.

Calcineurin inhibitor Ciclosporin or tacrolimus.

Cold ischaemia time Period during which a donated kidney is transported in ice from donor to recipient. Duration is related to extent of of kidney damage.

Cytomegalovirus A virus that normally causes only a mild 'flu-like' illness. In people with a kidney transplant, CMV can cause a more serious illness, affecting the lungs, liver and blood.

Donor A person who donates an organ to another person (the recipient).

1-Haplotype identical HLA antigens are inherited as a set called a 'haplotype' from one or both parents. 1-Haplotype identical is not a 'perfect' HLA match; a 2-halotype identical is a perfect HLA match.

Heart-beating donor A donor kidney where the heart is still beating in the donor after brain death has occurred. Most, but not all, cadaveric transplants come from heart-beating donors.

Living related transplant A kidney donated by a living relative of the recipient. A well-matched living related transplant is likely to last longer than either a living unrelated transplant or a cadaveric transplant.

Living unrelated transplant A kidney transplant from a living person who is biologically unrelated to the recipient.

Nephritis A general term for inflammation of the kidneys. Also used as an abbreviation for glomerulonephritis.

Recipient In the context of transplantation, a person who receives an organ from another person (the donor).

Rejection The process whereby a patient's immune system recognises a transplant kidney as foreign and tries to destroy it. Rejection can be acute or chronic.

Renal replacement therapy Dialysis or kidney transplantation.

List of abbreviations

AZA	azathioprine
BAS	basiliximab
BCAS	regimen of basiliximab, ciclosporin, azathioprine and a steroid
BNF	British National Formulary
BPAR	biopsy-proven acute rejection
BSA	Birmingham Sensitivity Analysis
BSAp	BSA paediatrics
BTAS	regimen of basiliximab, tacrolimus, azathioprine and a steroid
CAN	chronic allograft nephropathy
CAS	regimen of ciclosporin, azathioprine and a steroid
CI	confidence interval
CIC	ciclosporin
CMS	regimen of ciclosporin, MMF and a steroid
CMsS	regimen of ciclosporin, MPS and a steroid
CMV	cytomegalovirus
CRS	regimen of ciclosporin, sirolimus (Rapamune) and a steroid
DAC	daclizumab
DARE	Database of Abstracts of Review of Effects
DCAS	regimen of daclizumab, ciclosporin, azathioprine and a steroid
EBV	Epstein–Barr virus
EQ-5D	EuroQoL instrument
ESRF	end-stage renal failure
GFR	glomerular filtration rate
HLA	human leucocyte antigen
HR	hazard ratio
ICER	incremental cost-effectiveness ratio
ITT	intention-to-treat
MMF	mycophenolate mofetil
MPS	mycophenolate sodium
NAPRTCS	North American Paediatric Renal Transplant Cooperative Study
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Clinical Excellence
NRR	National Research Register
OHE HEED	Office of Health Economics Health Economic Evaluation Database
PTDM	post-transplant diabetes mellitus
PTLD	post-transplant lymphoproliferative disease
QALY	quality-adjusted life-year
RAS	regimen of sirolimus, azathioprine and a steroid
RCAS	regimen of sirolimus, ciclosporin, azathioprine and a steroid
RCS	regimen of sirolimus (Rapamune), ciclosporin and a steroid
RCT	randomised controlled trial
RMR	Rapamune Maintenance Regimen
RR	relative risk
RS	regimen of sirolimus (Rapamune) and a steroid
ScHARR	School of Health and Related Research
SD	standard deviation
TAC	tacrolimus
TAS	regimen of tacrolimus, azathioprine and a steroid
TMS	regimen of tacrolimus, MMF and a steroid
UNOS	United Network of Organ Sharing

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

The prevalence of end-stage renal failure in the UK paediatric population varies from 13.6 per million in the under 4-year-old population to 53.4 per million in the under 18-year-old population. Renal transplantation has established itself as the optimum treatment for end-stage renal failure. The goal of immunosuppression is to maintain graft and patient survival without exposing the patient to the risks of excessive immunosuppression or nephrotoxicity related to the use of immunosuppressant drugs. The current mainstay of therapy in children in the UK is a triple immunosuppression consisting of a calcineurin inhibitor (ciclosporin or tacrolimus), a DNA proliferation inhibitor (usually azathioprine) and steroids.

Objective

The objective was to review the clinical and cost-effectiveness of basiliximab, daclizumab, tacrolimus, mycophenolate mofetil (MMF), mycophenolate sodium (MPS) and sirolimus as possible immunosuppressive therapies for renal transplantation in children.

Methods

We searched for systematic reviews of randomised controlled trials (RCTs) undertaken in adults, children or both, systematic reviews of non-randomised comparative studies undertaken in children and RCTs undertaken in adults, children or both. A variety of bibliographic sources were used and database searches were undertaken up to November 2004. Studies were assessed for inclusion according to predefined criteria. Data extraction and quality assessment were also undertaken.

An economic model [Birmingham Sensitivity Analysis paediatrics (BSAp)] was developed based on an adaptation of a model previously developed for assessment of the cost-effectiveness of immunosuppressants in adults following renal transplant.

Number and quality of studies and direction of evidence

Clinical effectiveness

Addition of basiliximab

One unpublished paediatric RCT, four adult RCTs and six non-randomised comparative studies were included. The paediatric RCT reported that the addition of basiliximab to tacrolimus-based triple therapy (BTAS) failed to significantly improve 6-month biopsy-proven acute rejection (BPAR) [relative risk (RR) 0.93, 95% CI: 0.53 to 1.65], graft function, graft loss and all-cause mortality. No significant difference between groups was seen in 6-month or 1-year or longer graft loss, all-cause mortality and side-effects. In a meta-analysis of adult RCTs, the addition of basiliximab to a ciclosporin, azathioprine and steroid regimen (CAS) significantly reduced short-term BPAR (RR 0.61, 95% CI: 0.46 to 0.80). There was no significant difference in short- or long-term graft loss, all-cause mortality or side-effects.

Addition of daclizumab

One adult RCT was included. The addition of daclizumab to CAS reduced 1-year BPAR (RR 0.63, 95% CI: 0.42 to 0.94). No difference between groups was seen in either 1- or 3-year graft loss, all-cause mortality and side-effects.

Tacrolimus versus ciclosporin

One unpublished paediatric RCT, nine adult RCTs and two paediatric non-randomised comparative studies were included. The paediatric RCT found that a regimen of tacrolimus, azathioprine and a steroid (TAS) reduced 6-month BPAR (RR 0.42. 95% CI: 0.26 to 0.69) and improved graft function [glomerular filtration rate (GFR)] compared with CAS. This improvement in BPAR with tacrolimus was as shown in the meta-analysis of adult RCTs. There was evidence, particularly in children, that in comparison with ciclosporin, tacrolimus may reduce long-term graft loss, although there is no benefit on total mortality. The total level of withdrawal in children was reduced in children receiving tacrolimus. Adult RCTs showed an increase in post-transplant diabetes mellitus with tacrolimus.

MMF versus azathioprine

Seven adult RCTs and three paediatric non-randomised comparative studies were included. A meta-analysis of adult RCTs showed MMF [regimen of ciclosporin, MMF and a steroid (CMS)] to reduce 1-year BPAR (RR 0.60, 95% CI: 0.47 to 0.76) compared with azathioprine (CAS). There was evidence, particularly in children, that in comparison with azathioprine, tacrolimus may reduce long-term graft loss, although there is no benefit on total mortality. There was an increase in the level of cytomegalovirus infection with MMF, although the overall level of withdrawal due to adverse events was not different to that of azathioprine-treated adults.

MPS versus azathioprine

No study comparing MPS with azathioprine (CAS) was identified. In an adult RCT comparing MMF with MPS, there was no significant difference between groups in 1-year efficacy or side-effects.

Sirolimus

One unpublished paediatric RCT and three adult RCTs were included. The paediatric RCT assessed the addition of sirolimus to CAS. BPAR, graft loss and all-cause mortality were not reported. Two adult RCTs compared sirolimus with azathioprine. Compared with azathioprine, sirolimus reduced 1-year BPAR (pooled RR 0.60, 95% CI: 0.45 to 0.80), reduced graft function (as assessed by an increased serum creatinine) and increased the level of hyperlipidaemia. No significant differences were seen in other efficacy and side-effect outcomes. One adult RCT compared sirolimus with ciclosporin. There were no significant differences between groups in 1-year efficacy or side-effects with the exception of an increased level of hyperlipidaemia with sirolimus substitution.

Cost-effectiveness

Both the assessment group and drug companies assessed the cost-effectiveness of the newer renal immunosuppressants currently licensed in children using an adaptation (BSAp) of the Birmingham Sensitivity Analysis (BSA) model initially developed by the assessment group to inform the National Institute for Health and Clinical Excellence (NICE) guidance on the use of the newer renal immunosuppressive drugs for adult renal transplant recipients. This model is based on a 10-year extrapolation of 1-year BPAR results sourced from paediatric RCTs or adult RCTs (where paediatric RCTs were not available).

Both the addition of basiliximab and that of daclizumab to CAS were found to increase quality-adjusted life-years (QALYs) and decreased overall costs, a finding that was robust to sensitivity analyses. The incremental cost-effectiveness ratio (ICER) of replacing ciclosporin with tacrolimus was highly sensitive to the selection of the hazard ratio for graft loss from acute rejection, dialysis costs and the incorporation (or not) of side-effects. The ICERs for tacrolimus versus ciclosporin ranged from about £46,000/QALY to about £146,000/QALY. Although sensitive to varying the hazard ratio for graft loss with acute rejection, the ICER for replacing azathioprine with MMF remained in excess of £55,000/QALY.

Limitations of the calculations

There are substantive differences in the incremental costs per QALY results in this report compared with industry submissions for MMF. These differences reflect, principally, variations in parameter values for BPAR and drug doses/costs.

Conclusions

We found limited RCT evidence of the benefits and harms of the use of newer immunosuppressive agents (basiliximab, daclizumab, mycophenolate mofetil/sodium, tacrolimus and sirolimus) in children with kidney transplants, although, in some cases, there was instead evidence from non-randomised comparative studies in children and RCTs in adults. In general, compared with a regimen of ciclosporin, azathioprine and steroid, the newer immunosuppressive agents consistently reduced the incidence of short-term biopsy-proven acute rejection. However, evidence of the impact on side-effects, long-term graft loss, compliance and overall health-related quality of life is limited. Cost-effectiveness was estimated based on the relationship between short-term acute rejection levels from RCTs and long-term graft loss. Both the addition of daclizumab and that of basiliximab were found to be dominant strategies, that is, regarding cost savings and increased QALYs. The incremental cost-effectiveness of tacrolimus relative to ciclosporin was highly sensitive to key model parameter values and therefore may well be a cost-effective strategy. The incremental cost-effectiveness of MMF compared with azathioprine, although also sensitive to model parameter, was unattractive.

Need for further research

There is a particular need for RCTs to assess the use of MMF, MPS and daclizumab for renal

transplantation in children where no such evidence currently exists. Future comparative studies need to report not only on the impact of the newer immunosuppressants on short- and long-term clinical outcomes but also on side-effects, compliance, healthcare resource, costs and health-related quality of life.

Chapter 1
Background

Description of underlying health problem

Renal failure and reasons for transplantation

End-stage renal failure (ESRF) occurs when the kidneys are no longer able to function, so that the patient would die, and necessitates lifelong and/or life-saving intervention in the form of dialysis or kidney transplantation.[1]

Kidney transplantation is the treatment of choice for ESRF because, if successful, quality and duration of life are better than those achieved with long-term dialysis.[2] In 1992, the cost of transplantation was calculated to be £11,600 for the transplant procedure, with each subsequent year of a successful transplant costing £4000 per annum.[3] In contrast, the cost per annum for dialysis was calculated to be £21,000 in the National Institute for Health and Clinical Excellence (NICE) appraisal of home versus hospital haemodialysis (£21,000 and £22,000 for haemodialysis in a satellite unit and hospital, respectively).[4] The increased cost of transplantation in children relates primarily to the increased length of hospital stay. Successful kidney transplantation is reliant on the use of immunosuppressant agents.

Renal transplant procedures

Kidney grafts can come from living or dead (cadaveric heart beating or non-heart beating) donors. Where the donor is living, both the donor and recipient are in hospitals in the same city or, in some units, in the same hospital, so the transplant can be performed quickly after retrieval. With a cadaveric kidney, the donor may be several hundred miles from the recipient. In most transplants, the recipient receives only one kidney, but in rare circumstances, particularly if the donor is less than ideal, two kidneys may be transplanted.[5]

The quality of retrieved organs is particularly important because a higher quality kidney graft is associated with increased patient survival.[6] This creates additional responsibility when one centre is retrieving a kidney for another. In all cases, the time between retrieval of kidneys and transplantation needs to be kept to a minimum. Injury to the kidney can occur during the period of removal of the organ from the donor (warm ischaemia), during storage of the organ (cold ischaemia)[6] or at the time of implantation (anastamosis time). The minimisation of ischaemic injury optimises the subsequent performance of the transplanted kidney. Prolonged cold ischaemia is associated with reduced 5-year graft survival.[7]

Most kidneys are now retrieved from heart beating donors as part of a multi-organ donor procurement.[8] Some centres in Europe are attempting to increase the number of organs available by retrieving from non-heart beating donors.[9] An increasing number of reports indicate that kidneys from this source can function adequately but there are no plans for these organs to be routinely used for paediatric recipients. There is an increase in postoperative dialysis requirements because of delayed graft function and the retrieval process is more complex than is the case with heart beating donors.[10]

Rejection of transplanted organs

Rejection, acute or chronic, remains a major cause of graft dysfunction and loss. Immunosuppressive agents therefore play a key role in the prevention of rejection.[9] Rejection may occur as acute episodes that are managed with intensive short-term treatment, usually with steroids, or rejection may be chronic causing gradual deterioration of the graft.[9] Some 30% of UK paediatric patients experience biopsy-confirmed acute rejection by 1 year after renal transplantation.[8]

Acute rejection usually occurs in the first few weeks after transplantation. The response is cell mediated with a vascular component and leads to injury or destruction of the transplanted organ.[11] In the majority of patients who experience an acute rejection, it is reversed by immunosuppressive drugs. Acute rejection episodes predispose a recipient to chronic rejection and possible graft loss. Late and severe episodes of acute rejection are particularly threatening to the graft.[12]

Chronic rejection [chronic allograft nephropathy (CAN)] is a gradual process with variable onset

and rate of progression. It may develop as early as a few months after transplantation or emerge after several years.[11] The incidence of CAN varies and approximately 30% of renal transplant recipients experience this process. CAN is diagnosed by renal transplant biopsy in a patient with progressively worsening graft function and is notoriously difficult to treat. In the majority of cases, it eventually leads to complete loss of function of the transplanted organ, necessitating a return to dialysis or re-transplantation.[12] CAN is a multi-factorial process in which tissue damage occurs as a result of low-grade, continuous rejection exacerbated by viral infections, episodes of acute rejection and the toxic effects of certain immunosuppressive drugs. It is characterised by a slow decline in graft function, ultimately leading to chronic renal failure.[11]

One-year graft survival in adults has steadily improved over the last two decades and is now over 90% in low-risk patients. Impressive improvements in short- and long-term graft survival have been reported in children.[13,14] A decade ago, it was believed that children had poorer graft survival rates than adults; however, 1-year graft survival rates ranging from 89 to 96% in children after 1 year or longer have recently been reported in North America.[15] Longer term graft survival appears to vary by age; those aged 10 years and under appear to have the best 5-year graft survival (70–90%) whereas those aged 11–17 years have the poorest (60–75%). The reasons for this decline are not entirely known, but a contributing factor may be poor compliance with their immunosuppressive regimens.[16]

Epidemiology

Registries on paediatric kidney transplantation are held by UK Transplant (UK Renal Registry)[8] and the North American Paediatric Renal Transplant Cooperative Study (NAPRTCS) (a voluntary registry of US and Canadian paediatric renal transplant centres, started in 1987) and the United Network of Organ Sharing (UNOS) (mandatory registry of all renal transplants in the USA started in 1987).[15] The UK Renal Registry defines the 'paediatric population' as both infants and children under 15 years of age plus adolescents aged between 15 and 18 years. The remainder of this report uses the term 'children' (or 'paediatric' population) to include all individuals of 18 years or less.

The prevalence of ESRF in the UK paediatric population varies from 13.6 per million in the under 4-year-old population to 53.4 per million in the under 18-year-old population. The latter figure will almost certainly be an underestimate due to the direct referral of young people between ages 15 and 18 years to adult services.[15] The male to female ratio for ESRF is 1.5:1 and the take-on rate by ethnicity is 7 (whites), 21 (Asian) and 4.5 (blacks) per million of the population. However, a greater proportion of Asians remain on dialysis although a smaller proportion of Asians undergo dialysis than whites.

From the 2003 Renal Registry Report,[8] the total number of patients being cared for in the 13 UK paediatric units in April 2002 was 804. Of these, 793 patients were below the age of 20 years, of whom 760 were below 18 years of age and 622 were below 16 years of age.

In contrast to adult practice, most children with ESRF will be suitable for transplantation. Many paediatric renal transplant centres have a minimum body weight requirement of 10 kg or minimum age of 21–24 months for children undergoing transplantation. However, guidelines vary and some centres will undertake transplantation at any age.[8] At the end of 2002, 612 paediatric patients were in receipt of a transplant in UK.[8]

Current service provision

Categories of immunosuppressive therapy

The overall aim of immunosuppression therapy is to prevent mortality by prolonging graft survival without exposing the patient to the risks of excessive immunosuppression or toxicity related to the use of immunosuppressant therapy.[15]

Immunosuppression treatment following kidney transplantation can be categorised into prevention of graft rejection (initial and maintenance therapy) and the treatment of graft rejection ('rescue' therapy).

- Initial (or induction) therapy is a short course of intensive immunosuppression beginning before surgery and continued for 2–3 months after the transplant operation.
- Maintenance therapy is the treatment that is given long term, for the entire duration of the survival of the kidney graft.
- Acute rejection therapies are short courses during maintenance where therapies are adjusted temporarily or permanently following

an episode of acute rejection (this aspect of renal immunosuppression is outwith the scope of this report and will not be discussed further).

Newer immunosuppressive agents

Agents traditionally used as maintenance therapy in renal transplantation have included a combination of ciclosporin (a calcineurin inhibitor), azathioprine (a DNA proliferation inhibitor) and prednisolone (a steroid) – 'triple therapy'. During the last decade, a number of new immunosuppressive agents have been introduced into renal transplantation, leading to a variety of different regimens. In general, these newer agents have more potent immunosuppressive activity than their older counterparts. While this may reduce the incidence of rejection, the risk of infection [particularly cytomegalovirus and Epstein–Barr virus (EBV)], post-transplant lymphoproliferative disease and other malignancy may also be increased.

Complications of long-term immunosuppression include increased risk of developing infections, cancer [post-transplant lymphoproliferative disease (PTLD)] and specific side-effects of each medication. Common infections caused by suppression of the immune system include: viral [herpes, cytomegalovirus (CMV), EBV]; opportunistic protozoal; fungal; and bacterial.[17] As immunosuppression is at its highest level in the first 6-months after transplantation, this is also the peak period for infections in these patients. Nevertheless, they are at higher risk for infections than the general population throughout their post-transplant life.[18]

The side-effects of immunosuppressives include high blood pressure, excessive hair growth, hand tremors, mood swings, weight gain and diabetes mellitus. Some side-effects are temporary and resolve as the body adjusts to the medication and some will continue for as long as the medication is taken.[18]

The newer immunosuppressive agents under consideration in this report are tacrolimus (a calcineurin inhibitor), mycophenolate mofetil (MMF) and mycophenolate sodium (MPS) (both DNA proliferation inhibitors), sirolimus (a proliferation signal inhibitor) and basiliximab and daclizumab (both interleukin-2 inhibitors). The license indication and dosing details of these newer agents are summarised in *Table 1*. In summary, at present, basiliximab, daclizumab, tacrolimus and MMF are licensed in the UK for use in children whereas sirolimus and MPS are not. In March 2005, the US Food and Drug Administration agreed to the use of sirolimus in children.

Current UK practice

NICE issued guidance (No. 85) for the use of the immunosuppressive agents in adults in September 2004. However, there are currently no nationally agreed clinical guidelines on the combination of drugs given for immunosuppressive therapy in children. As a result, a variety of different immunosuppressive regimens are currently used in UK paediatric renal transplant units. Nevertheless, the current mainstay of therapy in children in the UK is a triple immunosuppression consisting of a calcineurin inhibitor (ciclosporin or tacrolimus), a DNA proliferation inhibitor (usually azathioprine) and steroids. Only a very small proportion (<5%) of UK paediatric renal transplant patients receive sirolimus or induction immunosuppressive therapy using antibody preparations.[8]

Considerations in children

Children represent a distinct group of organ transplant candidates. They differ from their adult counterparts in several important aspects, including the underlying etiology of organ failure, the complexity of the surgical procedure, the pharmacokinetic properties of immunosuppressants, the immune response following organ transplantation, the measures of success of the transplant procedure, the amount and the degree of comorbid conditions and the susceptibility to post-transplant complications, especially infections.

Organ transplantation can never be considered fully successful for children unless they grow and develop as normally as possible after transplantation.[15,19] Growth retardation often occurs in children with chronic renal insufficiency and the use of steroids in children may also retard growth (although the mechanism is unknown).[19,20] One long-term goal for immunosuppressive protocols in children is steroid-free regimens.

As is common in many childhood chronic conditions, compliance with medication is a major problem in transplanted patients, the problem being greatest among the adolescent population. The problem is likely to be greatest with those medications that are complex to administer or are associated with adverse side-effects.[21]

TABLE I *Newer immunosuppressive therapies – use in children*

Generic name	Trade name	Manufacturer	Mode of action	Licensed indication	Recommended dose	Price
Basiliximab	Simulect	Novartis	Interleukin-2 inhibitor	Prophylaxis of acute organ rejection in *de novo* allogeneic renal transplantation in adult and paediatric patients. To be used concomitantly with ciclosporin microemulsion- and corticosteroid-based immunosuppression, in patients with panel reactive antibodies <80%, or in a triple maintenance immunosuppressive regimen containing ciclosporin microemulsion, corticosteroids and either azathioprine or mycophenolate mofetil	*By injection* <35 kg, 10 mg within 2 h before transplant surgery and repeated 4 days after surgery; ≥ 35 kg, 20 mg within 2 h before transplant surgery and repeated 4 days after surgery	10-mg vial = £758.69, 20-mg vial = £842.38
Daclizumab	Zenapax	Roche	Interleukin-2 inhibitor	Prophylaxis of acute organ rejection in *de novo* allogeneic adult and paediatric renal transplantation and is to be used concomitantly with an immunosuppressive regimen including ciclosporin and corticosteroids in patients who are not highly immunised	*By intravenous injection* 1 mg/kg within a 24-h period before transplantation, then 1 mg/kg every 14 days for a total of 5 doses	Concentrate 5 mg/ml, 5 ml = 223.68
Tacrolimus	Prograf	Fujisawa/Astellas	Calcineurin inhibitor	Primary immunosuppression in liver and kidney allograft adult and paediatric recipients and liver and kidney allograft rejection resistant to conventional immunosuppressive regimens. Prograf is not licensed for use with Cellcept or Simulect	*By mouth* 300 μg/kg daily in 2 divided doses *Or by intravenous injection* Over 24 h, 0.05 mg/kg	Capsules: 500 μg, 50-capsule pack = £65.69; 1 mg, 50-capsule pack = £85.22, 100-capsule pack = £170.43; 5 mg, 50-capsule pack = £314.84 Concentrate: 1-ml ampoule = £62.05

continued

TABLE I *Newer immunosuppressive therapies – use in children (cont'd)*

Generic name	Trade name	Manufacturer	Mode of action	Licensed indication	Recommended dose	Price
Mycophenolate mofetil (MMF)	Cellcept	Roche	DNA proliferation inhibitor	Indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in adult and paediatric patients (>2 years old) receiving allogeneic renal, cardiac or hepatic transplants. Cellcept is not licensed for use with Prograf	*By mouth or intravenous infusion* 2–18 years (and body surface area >1.25 m^2) 600 mg/m^2 twice daily (max. 2 g daily)	Capsule: 250 mg, 100-capsule pack = £87.33 Tablets: 500 mg, 50-tablet pack = £87.33 Oral suspension: 175 ml = £122.25 I.v. infusion: 500 mg vial = £9.69 (not licensed in children)
Mycophenolate sodium (MPS)	Myfortic	Novartis	DNA proliferation inhibitor	Indicated in combination with ciclosporin microemulsion and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal transplants. Adults only	*By mouth* 720 mg twice daily starting within 72 h of transplantation	Tablets: 180 mg, 120-tablet pack = £122.49, 360 mg, 120-tablet pack = £244.97
Sirolimus	Rapamune	Wyeth	Proliferation signal inhibitor	Adults only. Indicated for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving a renal transplant. Recommended that Rapamune be used initially in combination with ciclosporin microemulsion and corticosteroids for 2–3 months, then may be continued as maintenance therapy with corticosteroids only if ciclosporin can be progressively discontinued	*By mouth* Initially 6 mg, after surgery, then 2 mg once daily for 2–3 months	Tablets: 1 mg, 30-tablet pack = £90.00; 2 mg, 30-tablet pack = £180.00 Oral solution: 60 ml = £169.00

Data from BNF No. 49 (March 2005).

Clinical trials in paediatric populations and the hierarchy of evidence

Prospective randomised controlled trials (RCTs) provide the highest level of evidence to compare therapeutic regimens. Whereas a number of RCTs of immunosuppression in adults have been conducted, a previous systematic review by the authors of this report found the paediatric RCT literature to be extremely sparse.[22]

At that time, only one published RCT undertaken specifically in children was identified. In this European multicentre trial, children following renal transplantation were randomised to tacrolimus-based triple therapy (azathioprine and steroid) or ciclosporin-based triple therapy. Recently, one additional paediatric RCT has been published comparing OKT3 induction therapy with intravenous ciclosporin in children receiving a triple therapy of ciclosporin or tacrolimus, azathioprine or MMF, and a steroid. The only other paediatric RCT is a US National Institutes of Health-sponsored trial conducted by NAPRTCS. OKT3 induction therapy was compared with 3 days of intravenous ciclosporin in 285 paediatric recipients who all received oral ciclosporin, steroids and azathioprine or MMF.[16] A recent publication of this US trial study reported no difference between the two groups in outcomes up to 4 years post-transplantation.[23]

Two adult RCTs of sirolimus have included a small number of children. Ettenger and Grimm included 12 children out of 719 in their RCT of sirolimus compared with azathioprine.[24] The US multicentre sirolimus registration study enrolled only three of the 576 enrolled subjects under the age of 18 years.[25] This lack of RCT evidence raises the question as to what might constitute 'best evidence' for assessing the comparability of immunosuppression regimens where no paediatric RCT data are available, such as MMF compared with azathioprine. Two potential sources of such secondary evidence are RCTs of the immunosuppressive regimen in adults and non-RCT comparisons undertaken in children. Both of these secondary sources of evidence have their advantages and disadvantages. Drugs are likely to have a different bioavailability, pharmacokinetics and side-effect profile in children than adults. However, we would argue that the body of empirical evidence adds to the bias (up to a 30% overestimation or underestimation of a therapy's effect)[26] of non-RCT evidence strongly in favour of the use of RCT evidence in adults. A number of recent reviews of the efficacy and safety of immunosuppressive agents in paediatric transplantation, in the absence of paediatric RCTs, have focused on trial evidence from adults.[27,28]

Surrogate outcomes and prediction of long-term graft survival

RCTs have almost uniformly reported short-term outcomes such as acute rejection rates as a surrogate marker for long-term graft survival.[22] However, the question of surrogate outcomes is a contentious one and there has been considerable debate as to the relative merits of acute rejection as compared to measures of graft function, such as serum creatinine and glomerular filtration rate (GFR).[23] A systematic review by the authors of this report found evidence that acute rejection and serum creatinine is predictive of future 5-year or longer graft survival in adults. The authors reported that the pooled hazard ratio (HR) for allograft survival based on an acute rejection episode was 1.95 [95% confidence interval (CI): 1.42 to 2.67) and 1.69 (95% CI: 1.29 to 2.22) for a raised serum creatinine. Little evidence was found for measures of graft function (GFR or creatinine clearance) as predictors of long-term graft survival.

This previous systematic review excluded children. Therefore, the original searches (MEDLINE, EMBASE and CENTRAL) were updated (up to May 2005) and re-run (see Appendix 1 for search strategies). In addition, recent annual reports of a number of national renal registries (UNOS, NAPRTCS, Australia and New Zealand Dialysis and Transplant Registry, European Renal Association Registry and UK Renal Register reports) were checked for suitable data. Out of 810 potential titles and abstracts, two studies were identified that met the inclusion criteria, that is, reported a quantitative association between acute rejection or a measure of graft function and graft survival at 5 years or longer based on a multivariate analysis.

Ishitanti and colleagues[29] undertook a retrospective multivariate analysis using data from the UNOS registry on 2418 children with living-related renal transplants ranging in age from 0 to 18 years with graft survival up to 7 years. They reported an HR of 1.41 (95% CI: 1.15 to 1.74) for those individuals who were treated for an acute rejection before discharge compared with those who were not. This study failed to assess either

serum creatinine or GFR. Vats and colleagues[30] reported a retrospective analysis based on 10-year graft survival data from 290 children from a single US centre receiving both cadaveric and living renal transplants. Multivariate analysis showed that biopsy-confirmed acute rejection prior to discharge was associated with increased graft loss (HR 6.258, $p = 0.0001$). Serum creatinine at discharge was found not to be an independent predictor of graft survival.

In summary, this updated review of surrogate outcome predictors in children appears to support the findings that acute rejection is a strong predictor of future graft loss. However, at this time, there is little evidence in children to support or refute the predictive value of measures of graft function such as serum creatinine or GFR.

It is well documented that associations between surrogate and final outcomes based on observational evidence may not extrapolate directly to RCTs. For example, observational cross-sectional studies show a strong relationship between levels of blood pressure and cardiovascular risk. However, an intervention that reduces blood pressure will not necessarily lead to an improvement in cardiovascular disease. To investigate the level of extrapolation between observational data and RCTs for this review, we compared the change in surrogate levels to the change in graft survival seen in the paediatric RCT by Filler and colleagues[31] (i.e. ciclosporin versus tacrolimus in a steroid and azathioprine regimen). In this trial, an improvement in 2-year graft survival with tacrolimus ($p = 0.04$) was associated with improvements in both GFR and the incidence in acute rejection at 6 months to 1 year in the tacrolimus group. Although only one trial, this finding does appear to support the use of early post-transplant (6–12 months) acute rejection as a surrogate predictor of long-term graft survival in the paediatric population. More trial-based evidence is required to establish the role of serum creatinine and GFR as surrogate markers of long-term paediatric graft survival.

Chapter 2

Decision problem

Renal transplantation has established itself as the optimum treatment for ESRF. The goal of immunosuppression is to maintain graft and patient survival without exposing the patient to the risks of excessive immunosuppression or nephrotoxicity related to the use of immunosuppressant drugs.

In 2004, NICE upheld an appeal on its adult renal immunosuppressives guidance that there had been insufficient review of the evidence base in children.

The aim of this assessment report was to establish the clinical effectiveness (harms and benefits) and cost-effectiveness of four of the newer immunosuppressive drugs for renal transplantation, namely basiliximab, daclizumab, tacrolimus and mycophenolate (mofetil and sodium), and of sirolimus in children.

Questions to be addressed by this report

The following specific questions will be addressed compared with triple therapy regimen of ciclosporin, azathioprine and a steroid (CAS) for children with kidney transplantation.*

1. What is the clinical effectiveness and cost-effectiveness of the addition of daclizumab [regimen of daclizumab, ciclosporin, azathioprine and a steroid (DCAS)] or basiliximab [regimen of basiliximab, ciclosporin, azathioprine and a steroid (BCAS)]?
2. What is the clinical effectiveness and cost-effectiveness of tacrolimus as a replacement for ciclosporin [regimen of tacrolimus, azathioprine and a steroid (TAS)]?
3. What is the clinical effectiveness and cost-effectiveness of mycophenolate (mofetil or sodium) as a replacement for azathioprine [regimen of ciclosporin, MMF and a steroid (CMS) or regimen of ciclosporin, MPS and a steroid (CMsS)]?
4. What is the clinical effectiveness and cost-effectiveness of the addition of sirolimus (Rapamune) [regimen of sirolimus, ciclosporin, azathioprine and a steroid (RCAS)], as a replacement for azathioprine [regimen of ciclosporin, sirolimus (Rapamune) and a steroid (CRS)] or ciclosporin [regimen of sirolimus, azathioprine and a steroid (RAS)]?

*The choice of comparator regimen of CAS was discussed and agreed at the outset of this assessment at the consultee's meeting. Although a number of UK paediatric renal units may now routinely include newer immunosuppressive agents (particularly tacrolimus and MMF), CAS represents a minimum standard of comparative care.

Chapter 3

Assessment of clinical effectiveness

Methods

Methodological approach

The previous systematic review of newer immunosuppressant drugs by the authors of this report identified very little RCT evidence for clinical effectiveness in children.[22] In order to establish the clinical effectiveness of particular renal immunosuppressive therapy strategies in children, it was therefore necessary to consider alternative approaches to evidence identification. The following evidence framework was used:

- *Level-1 evidence:* findings from RCTs carried out in children with kidney transplants. This could include RCTs undertaken solely in children, or RCTs where a subgroup analysis in children was reported.
- *Level-2 evidence:* where level-1 evidence was not available, use of findings from RCTs undertaken in adults with kidney transplants.
- *Level-3 evidence:* findings from non-randomised comparative evidence collected in children with kidney transplants. Level-3 evidence was used to complement and check the consistency of level-2 evidence (where level-1 evidence was not available).

Search strategy

The starting point of this review was the RCT evidence identified in our previous systematic review. We searched for systematic reviews of RCTs undertaken in adults, children or both, systematic reviews of non-randomised comparative studies undertaken in children and RCTs undertaken in adults, children or both. A variety of sources were used:

- Bibliographic databases: Cochrane Library (Update Software) 2004 Issue 4 [CDSR, CENTRAL, Database of Abstracts Reviews of Effects (DARE)]; MEDLINE (Ovid) 1996–2004 November week 3; MEDLINE In-Process at 3 December 2004; EMBASE (Ovid) 1980–2004 week 48; and CINAHL (Ovid) 1982–2004 November week 4. All were searched for the years 2002–4. Details of specific search strategies are given in Appendix 2.
- Citation lists of all included RCTs and systematic reviews.
- Citations in the industry submissions to NICE.
- The National Research Register (NRR) Issue 4 2004 and Current Controlled Trials Register for ongoing trials.

Studies on costs, quality of life, cost-effectiveness and modelling were identified from the following sources:

- Bibliographic databases: MEDLINE (Ovid) 1966–November week 3 2004; EMBASE (Ovid) 1980–2004 week 48; Cochrane Library (Update Software) 2004 Issue 4 [NHS Economic Evaluation Database (NHS EED) and DARE]; and Office of Health Economics Health Economic Evaluation Database (OHE HEED) December 2004 issue.
- Industry submissions.
- Internet sites of national economic units.

No language or age restrictions were applied to the searches. Details of search strategies are given in Appendix 2. All references were exported to Reference Manager version 11 (ISI, Carlsband, CA, USA).

Inclusion and exclusion criteria

Three reviewers (EA, YA and RT) independently scanned all the titles and abstracts and identified the potentially relevant articles to be retrieved. Where there was uncertainty, full text copies of papers were obtained. Studies were considered eligible if they met the following inclusion criteria:

- *Study design*: RCTs, systematic reviews (with or without meta-analyses) of RCTs, systematic reviews of non-randomised comparative studies, cost studies and formal economic evaluations.
- *Population*: recipients of first or subsequent kidney transplant (either live donor or cadaver donor) (the inclusion of non-randomised comparative studies and economic evaluations was restricted to studies conducted in children/adolescents).
- *Intervention(s)*: see *Table 2*.
- *Comparator(s)*: see *Table 2*.
- *Outcomes:* data were collected on one or more of the following outcomes: all-cause mortality; graft loss; graft function (i.e. serum creatinine or GFR); incidence of biopsy-proven acute

TABLE 2 *Intervention and comparative renal immunosuppressive therapy*

	Intervention	Comparator
Initial therapy[a]	Daclizumab or basiliximab	Placebo or no therapy[b]
Maintenance therapy	Mycophenolate mofetil (MMF), or mycophenolate sodium (MPS), or sirolimus (Rapamune), or tacrolimus in any of the following regimen combinations: BCAS DCAS TAS CMS CMsS RAS RCAS CRS	*Triple therapy*[b] comprising ciclosporin + azathioprine + steroid(s): CAS

[a] In addition to maintenance therapy.
[b] No comparator restriction was applied to the selection of paediatric RCTs and paediatric non-RCTs.

rejection; growth in children (i.e. height and weight); drug switching (as a result of intolerance, side-effects or patient preference where switching is defined as changing from intervention to comparator drug or comparator to intervention drug); specific side-effects adverse effects [i.e. CMV infection, post-transplant diabetes mellitus (PTDM), hyperlipidaemia and PTLD; withdrawal due to adverse events] (these specific outcomes were chosen following discussion with our clinical advisors); withdrawal due to adverse events; total withdrawals; health-related quality of life; compliance; and costs or cost-effectiveness.

Studies were excluded if they included more than one intervention drug; included an intervention drug in the comparator arm; set out to examine a strategy of drug tapering or switching; the trial had not finished recruiting; reported only baseline characteristics or only follow-up results for a small proportion (<50%) of the trial participants; involved multiple organ transplants; recruited patients with failed or failing renal transplants (rescue therapy) such as chronic allograft nephropathy; or only compared different doses of the same drug.

Data extraction and quality

A single reviewer (EA, YA or RT) independently extracted trial characteristics, aspects of trial quality and outcome results from included studies into predefined data extraction and quality assessment forms (Appendix 3). A second reviewer checked data extraction. Any discrepancies were resolved by discussion and, if necessary, by involvement of a third reviewer.

The quality of RCTs was assessed qualitatively based on the methods of randomisation and allocation concealment, blinding, loss to follow-up and intention-to-treat (ITT) analysis. An overall Jadad score[32] was also applied to each study (see Appendix 3). The quality of non-randomised comparative studies was assessed according to the primary forms of bias (i.e. selection, assessment, performance and attrition bias).

Data presentation, synthesis and analysis

Any information specified by manufacturers as 'commercial-in-confidence' has been removed and indicated by '**[Confidential information removed]**'.

A detailed tabular summary of the characteristics (i.e. patients, intervention, comparator and outcomes) and methodological quality of all included studies was undertaken. Outcome results are reported separately for each drug comparison by study design (RCT or non-RCT) and by two age categories (children and adult).

Where possible, meta-analysis was undertaken to combine the outcomes results across RCTs within each age category and drug comparison. Fixed-effects meta-analysis was used except in those situations where there was evidence of statistical heterogeneity using the χ^2 or Cochran's Q test ($p < 0.10$), when a random effects model was employed instead. Binary and continuous outcomes are expressed as relative risks (RRs) and weighted mean differences, respectively, and expressed as point estimates and 95% CIs. All analyses were undertaken using StataV.8 (Stata

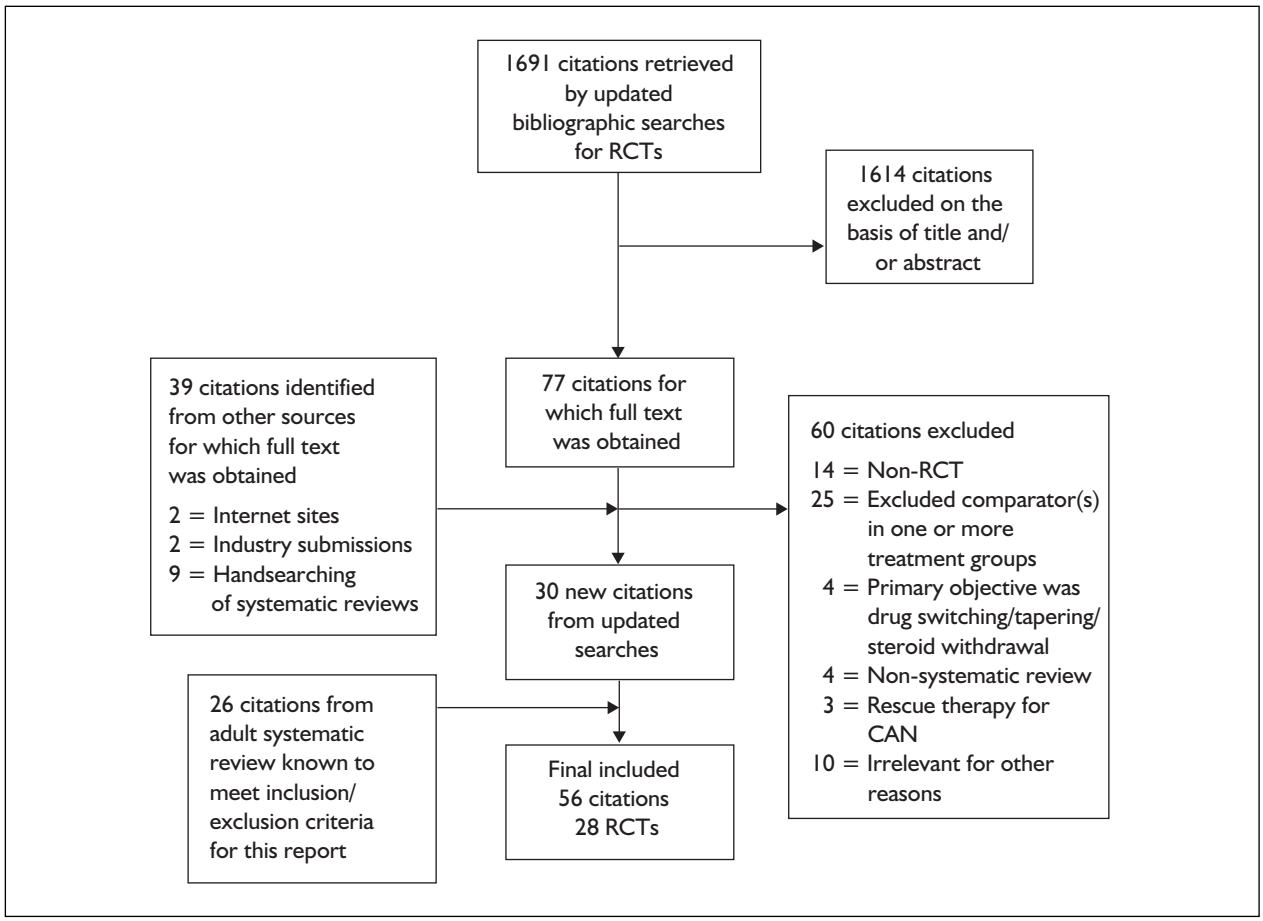

FIGURE 1 *Summary of search process and results for RCTs*

Corporation, College Station, TX, USA) or Stats Direct statistical software (www.StatsDirect.com).

Results

Quantity of evidence

Figure 1 shows the QUOROM flow diagram summarising the inclusion and exclusion process for the selection of RCTs. In addition to reviewing the previous systematic review by the assessment group for potential trials, the contents of other systematic reviews were also examined in detail.[33–44] Twelve systematic reviews were identified by our searches (Appendix 4). The primary studies that were included in these systematic reviews were checked and those fulfilling our inclusion/exclusion criteria were included in this review.

Following this process, 28 RCTs (three paediatric RCTs and 25 adult RCTs) were included in this report. The breakdown of RCT by drug comparisons and age categories is summarised in *Table 3*. Details of included RCTs are provided in Appendices 5–10.

The findings from these RCTs are summarised for each of the newer immunosuppressive drugs in the following sections.

Addition of daclizumab

Paediatric randomised controlled trials

There were no RCTs (published or unpublished) carried out in a child or adolescent population.

Adult randomised controlled trials

One RCT of daclizumab versus placebo in combination with ciclosporin, azathioprine and steroid met the inclusion/exclusion criteria for this review.[45–50] A total of 260 adults were recruited from centres outside the UK.

Tables 4 and *5* summarise the characteristics and quality of this trial. Daclizumab was used under the licensed dosage and regimen. Patients were first-time recipients of a cadaveric renal graft. Outcomes were reported at 6 and 12 months and

TABLE 3 *Details of included RTs*[a]

	All RCTs	Level-1 Paediatric RCTs	Level-2 Adult RCTs	Mixed adult and paediatric RCTs
Daclizumab	1 (6)	0	1 (6)	0
Basiliximab	5 (9)	1 (2)	4 (7	0
Mycophenolate mofetil	7 (10)	0	7 (10)	0
Mycophenolate sodium	1 (1)	0	1 (1)	0
Tacrolimus	10 (22)	1 (5)	9 (17)	0
Sirolimus	4 (8)	1 (1)	2 (5)	1 (2)
Total	28 (56)	3 (8)	24 (46)	1 (2)

[a] Number of RCT citations in parentheses.

TABLE 4 *Adult RCT daclizumab versus placebo – trial characteristics*

Authors, year [trial name]	No. of patients	Interventions, dose/day	Co-therapies	Mean age (years)	Male (%)	Graft type	First graft (%)	Follow-up
Vincenti *et al.*, 1998[45–50] [Phase III Daclizumab Study Group]	260	DAC vs placebo, 1 mg/kg	CIC + AZA + steroid	47/47	59/60	Cadaveric	100/100	6 months, 12 months, 3 years

AZA, azathioprine; CIC, ciclosporin; DAC, daclizumab.

TABLE 5 *Adult RCT daclizumab versus placebo – trial quality*

Authors, year [trial name]	Method of randomisation stated	Method of allocation concealment stated	Blinding	ITT analysis stated	Loss to follow-up (%) stated	Jadad score
Vincenti *et al.*, 1998[45–50] [Phase III Daclizumab Study Group]	No	No	Double blind	Yes	No	2

3 years. Details of methods were not fully reported, resulting in a low quality score, despite the trial being double blind and analysed according to ITT.

Use of daclizumab in adults resulted in a reduction in biopsy-proven acute rejection (BPAR) at 6 months compared with placebo. There was no significant difference in graft loss and all-cause mortality at 12 months with daclizumab (*Table 6*). There was no difference in 6-month serum creatinine between the daclizumab and placebo treatment groups.

No significant differences were observed in any of the above efficacy outcomes at 3 years follow-up.

Incidence of CMV infection at 6 months was not significantly different between the daclizumab and placebo groups (15/126 versus 14/134, respectively). Hyperlipidaemia, PTDM, PTLD, and withdrawals due to adverse events were not reported. Therefore, no tabulation of these side-effect results is presented for daclizumab.

Health-related quality of life was not reported by this trial.

Paediatric non-randomised controlled studies

Bibliographic searches and review of industry submissions to NICE failed to identify any systematic review or comparative non-randomised studies of the use of daclizumab in children.

TABLE 6 *Adult RCT daclizumab versus placebo efficacy outcomes at 12 months*

	No. of RCTs, *N*	Daclizumab, *n*/*N* (%)	Placebo, *n*/*N* (%)	RR (95% CI)	Heterogeneity *p*-value
BPAR	1[a]	28/126 (22.2)	47/134 (35.1)	0.63 (0.42 to 0.94)	NA
Graft loss	1	6/126 (4.8)	13/134 (9.7)	0.49 (0.19 to 1.25)	NA
All-cause mortality	1	3/126 (2.4)	5/134 (3.7)	0.64 (0.16 to 2.62)	NA
		Daclizumab, mean (SD), *N*	**Placebo, mean SD, *N***	**Mean difference (95% CI)**	
Serum creatinine (μmol/l)	1[a]	150 (60), 126	150 (60), 134	0 (–15 to 15)	NA

NA, not applicable.
[a] Outcome reported at 6 months follow-up.

TABLE 7 *Paediatric RCT basiliximab versus no therapy – trial characteristics*

Authors, year	*N*	Interventions, dose/day	Co-therapies	Mean age (years)	Male (%)	Graft type	First graft	Follow-up
Grenda *et al.*, 2004[51,52]	197	BAS vs no therapy, 10–20 mg	TAC + AZA + steroid	12/11	63/61	Cadaveric/ living	96/94	6 months

BAS, basiliximab; TAC, tacrolimus.

Summary

- No RCT evidence was found of the use daclizumab in paediatric renal transplant recipients.
- One RCT in adults was found that compared daclizumab with placebo as part of concomitant immunosuppression using ciclosporin, azathioprine and steroids. The quality of reporting was judged to be poor. A significant reduction in BPAR was demonstrated for daclizumab compared with placebo at 6 months. BPAR was not reported at 12 months. There were no other significant differences for the outcomes reported at either 6 or 12 months, or 3 years. Little information on side-effects sought for this review was reported.
- There were no systematic reviews or primary non-randomised comparative studies of daclizumab in the paediatric population.

Addition of basiliximab

Paediatric randomised controlled trials

One RCT comparing basiliximab with no therapy in a paediatric population was identified by our searches.[51,52] The study was unpublished and available only in abstract form; however, the full trial report was provided in the Fujisawa/ Astellas submission to NICE. Concomitant triple therapy of tacrolimus, azathioprine and steroid was given to subjects in both treatment arms. A total of 197 children and adolescents up to 18 years of age were recruited from six European centres.

Tables 7 and *8* summarise the characteristics and quality of this trial. The majority of patients were first-time recipients of a cadaveric renal graft. Outcomes were reported at 6 months only. The method of randomisation was unclear.

There were no significant differences in BPAR, graft loss, all-cause mortality or serum creatinine levels at 6 months in the basiliximab group compared with the no therapy group in the paediatric population (*Table 9*). **[Confidential information removed]**

Given the short trial duration, the number of events was small. There were no significant differences in the incidence of CMV infection (classed as a serious adverse event), post-transplant diabetes mellitus and lymphoproliferative disease, or withdrawals due to adverse events at 6 months (*Table 10*). Hyperlipidaemia and drug switching were not reported.

TABLE 8 *Paediatric RCT of basiliximab versus no therapy – trial quality*

Authors, year	Method of randomisation stated	Method of allocation concealment stated	Blinding	ITT analysis stated	Loss to follow-up (%) stated	Jadad score
Grenda *et al.*, 2004[51,52]	**[Confidential information removed]**					3

TABLE 9 *Paediatric RCT basiliximab versus no therapy – efficacy outcomes at 6 months*

	No. of RCTs	Basiliximab, *n/N* (%)	No therapy, *n/N* (%)	RR (95% CI)	Heterogeneity *p*-value
BPAR	1	19/102 (18.6)	19/95 (20.0)	0.93 (0.53 to 1.65)	NA
Graft loss	1	5/102[a] (4.9)	5/95 (5.3)	0.93 (0.28 to 3.12)	NA
All-cause mortality	1	0/102 (0)	0/95 (0)	Not calculable	NA
		Mean difference between groups (95% CI)			
Serum creatinine (mmol/l)	1	4.5 (–6.26 to 15.26)			NA

[a] Four graft losses were reported in a more recent conference abstract;[51] five graft losses were reported in the unpublished full company report.[52]

TABLE 10 *Paediatric RCT basiliximab vs no therapy – side-effects at 6 months*

	No. of RCTs	Basiliximab, *n/N* (%)	No therapy, *n/N* (%)	RR (95% CI)	Heterogeneity *p*-value
CMV infection	1	**[Confidential information removed]**			NA
PTDM	1	5/102 (4.9)	4/95 (4.2)	1.16 (0.32 to 4.21)	NA
PTLD	1	**[Confidential information removed]**			NA
Hyperlipidaemia	0	**[Confidential information removed]**			NA
Withdrawals due to adverse events	1	**[Confidential information removed]**			NA
Drug switching due to adverse events	0	**[Confidential information removed]**			NA

Growth and health-related quality of life outcomes were not reported.

Adult randomised controlled trials

Four RCTs of basiliximab versus placebo or no therapy in 500 adults were identified that met our inclusion criteria (two RCTs versus placebo,[53–56] two RCTs versus no therapy.[57–59] All four trials used a triple therapy combination of ciclosporin + azathioprine + steroids in both treatment arms.

Tables 11 and *12* summarise the trial characteristics and quality, respectively. All trials used basiliximab under the licensed dosage and regimen. Only 12 patients were randomised in the trial reported by Bingyi and colleagues.[53] Outcome reporting was patchy at 6 and 12 months, and only one trial reported outcomes beyond 1 year. The quality of reporting was very poor, with the exception of that of Ponticelli and colleagues,[54–56] which was judged to be a good-quality trial.

Use of basiliximab in adults resulted in a reduction in BPAR at 12 months compared with placebo or no therapy. There was no significant difference in graft loss, all-cause mortality and serum creatinine levels at 12 months with basiliximab compared with placebo or no therapy (*Table 13*).

In the trial reporting 3-year outcomes,[57] a borderline statistically significant difference was

TABLE 11 *Adult RCTs basiliximab versus placebo or no therapy – trial characteristics*

Authors, year	No. of patients	Interventions, dose/day	Co-therapies	Mean age (years)	Male (%)	Graft type	First graft	Follow-up
Folkmane *et al.*, 2001[58,59]	48	BAS vs no therapy, 20 mg	CIC + AZA + steroid	40/45	NR	Cadaveric	NR	6 and 12 months
Sheashaa *et al.*, 2003[57]	100	BAS vs no therapy, 20 mg	CIC + AZA + steroid	33/33	88/82	Living	100/100	6 and 12 months, 3 years
Bingyi *et al.*, 2003[53]	12	BAS vs placebo, 20 mg	CIC + AZA + steroid	Range 35–59/ 36–54	66/83	Cadaveric	NR	12-months
Ponticelli *et al.*, 2001[54–56]	340	BAS vs placebo, 20 mg	CIC + AZA + steroid	44 BAS, 44 placebo	66/69	Cadaveric/ Living	93/94	6 and 12 months

NR, not reported.

TABLE 12 *Adult RCTs basiliximab versus placebo or no therapy – trial quality*

Authors, year	Method of randomisation stated	Method of allocation concealment stated	Blinding	ITT analysis stated	Loss to follow-up (%) stated	Jadad score
Folkmane *et al.*, 2001[58,59]	No	No	No	Yes	No	1
Sheashaa *et al.*, 2003[57]	No	No	No	Yes	No	1
Bingyi *et al.*, 2003[53]	No	No	Unclear	Yes	No	1
Ponticelli *et al.*, 2001[54–56]	No	Yes (central list of treatment codes)	Double blind	Yes[a]	Yes (10% at 6 months)	4

[a] Fully randomised sample $n = 344$ or 345 but reports results for full analysis sample $n = 340$.

TABLE 13 *Adult RCTs basiliximab versus placebo or no therapy – efficacy outcomes at 12 months*

	No. of RCTs	Basiliximab, *n*/*N* (%)	Placebo or no therapy, *n*/*N* (%)	RR (95% CI)	Heterogeneity *p*-value
BPAR	3[a]	54/241 (22.4)	91/247 (36.8)	0.61 (0.46 to 0.80)	0.94
Graft loss	2	18/191 (9.4)	23/197 (11.7)	0.81 (0.45 to 1.45)	0.89
All-cause mortality	1	4/168 (2.4)	5/172 (2.9)	0.82 (0.22 to 3.00)	NA
		Mean difference between groups (95% CI)			
Serum creatinine (mmol/l)	3	–4.18 (–12.22 to 3.87)			0.30

[a] Includes one trial with outcomes at 6 months.

observed for a reduction in BPAR with basiliximab (RR 0.72, 95% CI: 0.53 to 0.99). Graft loss (RR 0.50, 95% CI: 0.10 to 2.61) and all-cause mortality (RR 0.33, 95% CI: 0.01 to 7.99) at 3 years were not significantly different.

Side-effects were poorly reported at all follow-up points by all four included studies (*Table 14*). The incidence of CMV infection (reported at 6 months only) was no different between those receiving basiliximab or no induction therapy. PTDM was only reported by Bingyi and colleagues[53] at 12 months, where there was no evidence of the condition in any of the 12 patients. Sheashaa and colleagues[57] reported incidence of PTDM at 3 years. There was no statistical difference between treatment groups (RR 0.57, 95% CI: 0.18 to 1.83).

Two trials report the incidence of PTLD and only one case was found in the control arm. None of the four trials reported incidence of hyperlipidaemia or drug switching due to adverse events. Withdrawal due to adverse events was only reported by Ponticelli and colleagues[54–56] where there was no significant difference between treatment groups. Health-related quality of life was not reported.

Paediatric non-randomised controlled studies

Our bibliographic searches did not identify any published systematic review of non-randomised studies of basiliximab compared with placebo or no therapy as part of a triple immunosuppressive regimen. The submission by Novartis to NICE contained an unpublished systematic review by the School of Health and Related Research (ScHARR) at the University of Sheffield.[60] Electronic bibliographic searches of nine databases were carried out during December 2004–February 2005. No restrictions were applied, but several filters were used to search specifically for high-quality effectiveness studies in children. Six retrospective, comparative non-RCTs were identified (a single

TABLE 14 *Adults RCTs basiliximab versus placebo or no therapy – side-effects at 12 months*

	No. of RCTs	Basiliximab, *n/N* (%)	No therapy, *n/N* (%)	RR (95% CI)	Heterogeneity *p*-value
CMV infection	2[a]	33/191 (17.3)	28/197 (14.2)	1.21 (0.77 to 1.93)	0.79
PTDM	1	0/6 (0)	0/6 (0)	NA	NA
PTLD	2	0/174 (0)	1/178 (0.6)	NA	NA
Hyperlipidaemia	0	NR	NR	NA	NA
Withdrawals due to adverse events	1[b]	1/168	3/172	0.34 (0.04 to 3.25)	NA
Drug switching due to adverse events	0	NR	NR	NA	NA

[a] Both trials report 6-month data only.
[b] 6-month data only.

TABLE 15 *Paediatric non-RCTs basiliximab versus no therapy – study characteristics*

Authors, year	No. of patients	Interventions, dose/day	Co-therapies	Mean age (years)	Male (%)	Graft type	First graft	Follow-up
Duzova *et al.*, 2003[61]	43	BAS vs no therapy, 20 mg maximum	CIC or TAC+ AZA or MMF + steroid	15/15	60/57	Cadaveric/ living	NR	6 and 12 months
Pape *et al.*, 2002[62]	77	BAS vs no therapy, 0/20 mg	CIC + steroid	8/7	58/72	Cadaveric/ living	88/79	1 and 2 years
Swiatecka-Urban *et al.*, 2001[63]	32	BAS vs no therapy, 20 mg maximum	TAC + steroid	15/15	54/75	Cadaveric/ living	NR	12 months

citation each), three of which compared basiliximab with no therapy and did not involve anti-thymocyte globulin (ATG), anti-lymphocytic globulin (ALG) or anti-thymocyte globulin (equine) (ATGAM) interventions.[61–63] These will therefore be commented on further. The characteristics of these studies are reported in *Table 15*.

Biases (selection, performance, detection and attrition) introduced during study design, conduct and analysis may have influenced the internal validity of the trials, making it necessary to interpret results with caution. Few demographics were reported for treatment groups at baseline. Reports of side-effects and withdrawals were patchy.

In the two-centre study reported by Duzova and colleagues,[61] age, sex and proportion of live/cadaveric grafts appeared similar between the basiliximab and no therapy treatment groups. This study involved triple co-therapy of ciclosporin or tacrolimus plus azathioprine or MMF plus steroid; however, a breakdown of the numbers in each combination was not reported and may not have been evenly distributed between the basiliximab and no therapy arms. Study withdrawals at 12 months were significantly different between groups (30% basiliximab versus 0% no therapy). Patient ages ranged from 7 to 21 years with no outcomes reported for subgroups.

In Pape and colleagues' study,[62] reporting of basic demographics at baseline was minimal, but appeared similar between both groups. Patients in the control group were selected from the same centre and during the same study period as those in the treatment group. Rates of withdrawal were not reported.

The study by Swiatecka-Urban and colleagues[63] compared 24 basiliximab-treated patients with a historical control group of eight patients. The quality of this study was particularly poor since the historical control may have differed systematically from the intervention group. Age appeared similar in each group, but the proportion of male to female (54 versus 75% male), cadaveric to living (62 versus 25% cadaveric) and proportions of African-American/Hispanic/Caucasian (54 versus 0% African-American) were very different between the two treatment arms. Patient ages ranged from 7 to 21 years with no outcomes reported for subgroups.

Table 16 shows the results for BPAR at 12 months. Duzova and colleagues[61]also reported BPAR at 6 months (0/17 versus 6/23; RR 0.10; 95% CI: 0.01 to 1.70) and Pape and colleagues[62] at 24 months (7/48 versus 10/29; RR 0.42; 95% CI: 0.18 to 0.99). Only the study by Pape and colleagues showed a borderline statistically significant difference in incidence of BPAR between the basiliximab and no basiliximab groups.

All-cause mortality at 12 months (observation period reported by Pape and colleagues 1.7 ± 0.8 months) was 0 for both the basiliximab and no therapy groups in all three studies.

Graft loss at 12 months was not significantly different between the group receiving basiliximab and the group that did not, in all three studies (*Table 17*).

Side-effects were not assessed in the review by ScHARR but are summarised in *Table 18*. Duzova and colleagues[61]and Swiatecka-Urban and colleagues[63]commented that no adverse event was considered attributable to basiliximab, whereas Pape and colleagues[62] do not make any comment.

TABLE 16 *Paediatric non-RCTs basiliximab versus no therapy – BPAR at 12 months*

Authors, year	Basiliximab, *n*/*N* (%)	No therapy, *n*/*N* (%)	RR (95% CI)
Duzova *et al.*, 2003[61]	1/14 (7)	6/23 (26)	0.27 (0.04 to 2.04)
Pape *et al.*, 2002[62]	7/48 (15)	4/26 (15)	0.95 (0.31 to 2.94)
Swiatecka-Urban *et al.*, 2001[63]	6/24 (25)	3/8 (38)	0.67 (0.22 to 2.07)

TABLE 17 *Paediatric non-RCTs basiliximab versus no therapy – graft loss at 12 months*

Authors, year	Basiliximab, *n*/*N* (%)	No therapy, *n*/*N* (%)	RR (95% CI)
Duzova *et al.*, 2003[61]	0/14 (0)	3/23 (13)	0.23 (0.01 to 4.12)
Pape *et al.*, 2002[62]	3/48 (6)	2/26 (8)	0.81 (0.14 to 4.56)
Swiatecka-Urban *et al.*, 2001[63]	3/24 (13)	2/8 (25)	0.50 (0.10 to 2.48)

TABLE 18 *Paediatric non-RCTs basiliximab versus no therapy – side-effects at 12 months*

Authors, year	CMV infection BAS % vs no therapy %	PTDM BAS % vs no therapy %	PTLD BAS % vs no therapy %	Withdrawals due to adverse events BAS % vs no therapy %
Duzova *et al.*, 2003[61]	0 vs 0	NR	NR	NR
Pape *et al.*, 2002[61]	6 vs 21	NR	0 vs 0	NR
Swiatecka-Urban *et al.*, 2001[63]	3/6[a] vs -	2[b] vs NR	0 vs 0	NR

[a] Three or six CMV negative at transplantation – all patients were CMV positive at transplantation.
[b] Only one patient remained on insulin.

The poor level of reporting prevents analysis. None of the three comparative studies report quality of life or growth in the paediatric population.

Summary

- One RCT compared basiliximab with no therapy in a paediatric population. The trial scored poorly using the Jadad scale since the trial was an open-label design. There were no significant differences in BPAR, graft loss or all-cause mortality at 6 months for basiliximab versus no therapy in children. **[Confidential information removed]**
- Four RCTs of basiliximab versus placebo or no therapy were carried out in 500 adults. The quality of reporting was very poor, with the one exception of the study by Ponticelli and colleagues.[54–56] Use of basiliximab in adults resulted in a reduction in BPAR at 12 months compared with placebo or no therapy. There was no significant difference in graft loss and all-cause mortality at 12 months.
- There was one unpublished systematic review in the Novartis submission to NICE. This identified three relevant non-RCTs of basiliximab versus no therapy in the paediatric population. Reporting in these three studies was poor, and the study design was also very weak. One study employed the use of a historical control group. Results from all three studies should be interpreted with caution. None of the studies showed a statistically significant difference in incidence of BPAR or graft loss between the basiliximab and no basiliximab groups at 12 months. Mortality was zero for both treatment groups in all three studies. Little information on the side-effects sought for this review was reported.

Tacrolimus versus ciclosporin

Paediatric randomised controlled trials

One published multicentre paediatric RCT (18 centres in nine European countries, including the UK) was identified comparing TAS with the triple therapy of CAS.[64] The initial follow-up of this study was up to 6 months. However, there have been three subsequent publications reporting 1,[65] 3[66] and 4-year follow-ups.[31]

A total of 204 patients were randomly assigned to receive tacrolimus (n = 105) or ciclosporin (n = 99). The trial characteristics are summarised in *Table 19*. The RCT was judged to be of good methodological quality (Jadad score 4) as summarised in *Table 20*. There were a significant number of withdrawals with only 137/204 patients (67%) completing 6 months follow-up; 57 patients were subsequently withdrawn, 23 from the tacrolimus arm and 34 from the ciclosporin group. The reasons for withdrawal were adverse effects, protocol deviations and graft loss. In the 1-year data,[65] a further 52 patients were added, bringing the total number in 1 year to 178. It is not clear if these added patients were part of the originally randomised patients.

At the 6-month follow-up, the incidence of BPAR was significantly lower in the patients who received tacrolimus compared with those who were treated with ciclosporin. However, there was no statistical difference in graft loss or all-cause mortality (*Table 21*). Mean serum creatinine decreased similarly in both arms at 6 months. GFR at 6 months calculated according to the Schwartz equation was not significant (p = 0.09) but was statistically significant at 1 year in favour of tacrolimus (p = 0.003).

At the 1-year follow-up, patient survival was similar to the 6-month follow-up (3/103 tacrolimus versus 3/93 ciclosporin, p = 0.90). No significant difference was shown in graft survival in the tacrolimus arm compared with the ciclosporin arm. In the tacrolimus arm there were 10/103 graft losses versus 17/93 ciclosporin (p = 0.082). The mean GFR with tacrolimus was 62.5 versus ciclosporin GFR 56.4 (p = 0.003). Seven patients

TABLE 19 *Paediatric RCT tacrolimus versus ciclosporin – trial characteristics*

Authors, year	No. of patients	Interventions, dose/day	Co-therapies	Mean age (years)	Male (%)	Graft type	First graft	Follow-up
Trompeter *et al.*, 2002[64]	204	0.3 mg/kg	AZA + steroid	10.5/10.1	62/60	Cadaveric/ living	7.8/12.9	6 months to 4 years

TABLE 20 *Paediatric RCT tacrolimus versus ciclosporin – trial quality*

Authors, year	Method of randomisation stated	Method of allocation concealment stated	Blinding	ITT analysis stated	Loss to follow-up (%) stated	Jadad score
Trompeter *et al.*, 2002[64]	Yes	Yes	No	Analysis was not by ITT for BPAR	Yes (33 at 6 months)	4

TABLE 21 *Paediatric RCT tacrolimus versus ciclosporin – efficacy outcomes at 6 months*

	No. of RCTs	Tacrolimus, *n*/*N* (%)	Ciclosporin, *n*/*N* (%)	RR (95% CI)	Heterogeneity *p*-value
BPAR	1	17/94[a] (18.1)	37/86[a] (43.0)	0.42 (0.26 to 0.69)	NA
Graft loss	1	8/103 (7.7)	15/93 (16.1)	0.48 (0.22 to 1.08)	NA
All-cause mortality	1	3/103 (2.9)	3/93 (3.2)	0.9 (0.21 to 3.84)	NA
Serum creatinine (μmol/l) (SD)	1	90.91 (34.2) *N* = 103[b]	86.09 (26.8) *N* = 93[b]	NA	

[a] The denominators (*N*) for both tacrolimus and ciclosporin refer to biopsied patients only (94/103 and 86/93, respectively, were biopsied from full sample).
[b] Assumed ITT population.

had died by the 2-year follow-up, 3/103 tacrolimus versus 4/93 ciclosporin. This was not a statistically significant difference between the two treatments. Graft loss only became significant at 2 years, 10/103 tacrolimus versus 19/93 ciclosporin (p = 0.03). The GFR (calculated according to the Schwarz equation) was 64.9 tacrolimus versus 51.7 ciclosporin (p = 0.0002). At the 3-year follow-up, patient survival was 95% in both arms. Graft loss did not differ significantly (86% tacrolimus versus 78% ciclosporin, p = 0.11). GFR was not reported at 3 years. Tacrolimus therapy resulted in a significantly lower incidence of acute rejection, 36% versus ciclosporin therapy 59.1% (p = 0.003). However, this analysis is based on 128 subjects from an original randomisation sample of 204. This analysis does not take into account those who were lost to follow-up or those who died. Finally, at the 4-year follow-up, patient deaths were 5/103 with tacrolimus and 4/93 with ciclosporin (p = 0.90). The graft loss was 11/103 in the tacrolimus group but 20/93 for those receiving ciclosporin (p = 0.03). GFR at 4 years was significantly better in transplant recipients who received tacrolimus, 71.5 vs 53.0 (p = 0.001). There were no significant differences in side-effects between tacrolimus and ciclosporin (*Table 22*). Although CMV infection was not reported, the incidence of infections during the first 6 months was similar in both treatment groups at 68.9% (tacrolimus) and 64.5% (ciclosporin). There was an increase in the level of total withdrawals with ciclosporin compared with tacrolimus.

Adult randomised controlled trials

Nine RCTs in a total of 1664 adults were identified that compared tacrolimus with a triple therapy of CAS. Doses of tacrolimus and ciclosporin were similar across trials (*Table 23*). Follow-up ranged between 6 months and 6 years.

The RCTs were poorly reported and therefore were judged to be of poor methodological quality

TABLE 22 *Paediatric RCT tacrolimus versus ciclosporin – side-effects at 6 months*

	No. of RCTs	Tacrolimus, *n/N* (%)	Ciclosporin, *n/N* (%)	RR (95% CI)	Heterogeneity *p*-value
CMV infections	1	NR	NR	NA	NA
PTDM	1	3/103 (2.9)	2/93 (2.1)	1.35 (0.23 to 7.93)	NA
PTLD	1	1/103 (1.0)	2/93 (2.1)	0.45 (0 .04 to 4.89)	NA
Hyperlipidaemia[a]	1	NR	NR	NA	NA
Total withdrawals	1	23/103 (22.3)	34/93 (36.6)	0.61 (0.39 to 0.96)	NA
Withdrawal due to adverse events	1	10/103 (9.7)	14/93 (15.0)	0.64 (0.30 to 1.38)	NA
Drug switching due to adverse events	1	0/103 (0)	5/93 (5.4)	0.08 (0.004 to 1.47)	NA

[a] The mean serum cholesterol levels dropped in the TAC group from 4.88 (2.2) mmol/l at baseline to 4.32 (1.48) mmol/l at 6 months. The mean serum cholesterol levels increased in the CIC group from 4.73 (2.2) mmol/l at baseline to 5.02 (1.92) mmol/l at 6 months.

TABLE 23 *Adult RCTs tacrolimus versus ciclosporin – trial characteristics*

Authors, year [trial name]	No. of patient	Interventions, dose/day	Co-therapies	Mean age (years)	Male (%)	Graft type	First graft	Follow-up
Shapiro *et al.*, 1991[67]	57	TAC 0.15 mg/kg vs CIC	AZA + steroid	36.5/39.4	NR	NR	100	1 year
Mayer *et al.*, 1997 [European Tacrolimus Multicentre Renal Study][68–71]	448	TAC 0.1 mg/kg vs CIC	AZA + steroid	46.6/45.8	65/63	Cadaveric	90	1, 4 and 5 years
Radermacher *et al.*, 1998[72]	41	TAC 0.2–0.3 mg/kg vs CIC	AZA + steroid	41.3/47.1	63/	Cadaveric	89	1 year
Van Duijhoven *et al.*, 2002[73]	23	TAC 0.2–0.3 mg/kg vs CIC	AZA + steroid	45.4/47.8	73/75	Cadaveric	82	1 year
Jurewicz *et al.*, 1999 [Welsh Transplant Research Group][74–76]	232	TAC 0.2 mg/kg vs CIC	AZA + steroid	44/48	49.5/48.5	Cadaveric	80	1, 3 and 6 years
Sperschneider *et al.*, 2001[77–80]	560	TAC 0.3 mg/kg vs CIC	AZA + steroid	42.4/43.8	70/63	Cadaveric/ living	93	6 months
Toz *et al.*, 2004[81]	35	TAC 0.2 mg/kg vs CIC	AZA + steroid	35/30	59/67	Cadaveric/ living	NR	1 year
Campos *et al.*, 2002 [Brazilian Tacrolimus study Group][82]	166	TAC 0.2 mg/kg vs CIC	AZA + steroid	40.5/40.9	48/55	Cadaveric/ living	94	1 year
Murphy *et al.*, 2003[109]	102	TAC 0.2 mg/kg vs CIC	AZA + steroid	45/45	61.5/70	Cadaveric/ living	88	1 year

TABLE 24 *Adult RCTs tacrolimus versus ciclosporin – trial quality*

Authors, year	Method of randomisation stated	Method of allocation concealment stated	Blinding	ITT analysis stated	Loss to follow-up (%) stated	Jadad score
Shapiro *et al.*, 1991[67]	No	No	No	No	No	1
Mayer *et al.*, 1997[68–71]	No		No	Yes	Yes (30% at 12 months)	2
Radermacher *et al.*, 1998[72]	No	Yes (central allocation)	No	No	Yes (17% at 12 months)	2
Van Duijhoven *et al.*, 2002[73]	No	Yes (sealed envelopes)	No	No	Yes (21% at 12 months)	1
Jurewicz *et al.*, 1999[74–76]	No	No	No	No	No	1
Sperschneider *et al.*, 2001[77–80]	Yes (central randomisation)	No	No	Yes	Yes (14.5% at 6 months)	2
Toz *et al.*, 2004[81]	No	No	No although BPAR were evaluated blind	Yes	No	1
Campos *et al.*, 2002[82]	No	No	No	No	No	1
Murphy *et al.*, 2003[83]	No	No	No	No	No	1

TABLE 25 *Adult RCTs tacrolimus versus ciclosporin – efficacy outcomes at 12 months*

	No. of RCTs	Tacrolimus, *n*/*N* (%)	Ciclosporin, *n*/*N* (%)	RR (95% CI)	Heterogeneity *p*-value
BPAR	6	213/848 (25.1)	261/650 (40.1)	0.61 (0.53 to 0.71)	0.17
Graft loss	6	82/771 (10.6)	56/594 (9.4)	0.97 (0.66 to 1.43)	0.34
All-cause mortality	5	41/754 (5.4)	24/576 (4.2)	1.27 (0.77 to 2.08)	0.36
		Mean difference between groups (95% CI)			
Serum creatinine (μmol/l)	3	–7.81 (–16.52 to 0.89)			0.76

with a Jadad score of 1 or 2 (*Table 24*). Few trials reported the method of randomisation and concealment. Trials were either open or there were no details about blinding stated. ITT was stated in 3/9 RCTs and the loss to follow-up was reported in only 4/9 trials.

The 12-month outcomes pooled across studies are summarised in *Table 25*. Although there was evidence of a significant reduction in BPAR with tacrolimus compared with ciclosporin at 1 year, there were no significant differences in graft loss, all-cause mortality or serum creatinine.

There was no significant difference in side-effects between tacrolimus and ciclosporin with the exception of PTDM, which was significantly increased with tacrolimus (*Table 26*). There was a lower level of drug switching with patients receiving tacrolimus than ciclosporin.

Two trials provided follow-up of 3 years or more, by Mayer[68,69] and Jurewicz.[74,75] No significant differences were observed by either trial in all-cause mortality, graft loss or graft function between tacrolimus- and ciclosporin-treated patients at long-term follow-up.

TABLE 26 *Adult RCTs tacrolimus versus ciclosporin – side-effects at 12 months*

	No. of RCTs	Tacrolimus, *n/N* (%)	Ciclosporin, *n/N* (%)	RR (95% CI)	Heterogeneity *p*-value
CMV infection	3	68/616 (11.0)	48/440 (10.9)	0.92 (0.65 to 1.29)	0.73
PTDM	4	44/726 (6.1)	14/547 (2.6)	2.38 (1.32 to 4.31)	0.95
PTLD	0	–	–	–	–
Hyperlipidaemia	1	12/286 (4.2)	24/271 (8.8)	0.47 (0.24 to 0.93)	NA
Withdrawal due to adverse events	3	116/641 (18.1)	83/466 (17.8)	0.68 (0.18 to (2.56)	<0.0001
Drug switching due to adverse events	2	4/371 (1.1)	39/352 (11.1)	0.10 (0.04 0.27)	0.08

Paediatric comparative non-randomised controlled studies

Bibliographic searches identified no systematic review of non-randomised comparative studies of tacrolimus compared with ciclosporin in children. However, from a review of company submissions to NICE, two comparative non-randomised studies in paediatric patients were identified.

A study by Garcia and colleagues[84] was cited in the Fujisawa/Astellas submission to NICE. It reports 24 renal transplants in paediatric patients aged 2–18 years. There were two groups: group 1 (n = 12), regimen of basiliximab, tacrolimus, azathioprine and a steroid (BTAS) and group 2 (n = 12), CMS. The two groups did not differ significantly in gender, ethnicity, aetiology of renal failure or origin of the donor. These patients were followed up for 3 months to assess the effect of different treatment on acute rejection and safety measures.

Results for BPAR episodes were 1/12 (8%) in group 1 versus 2/12 (17%) in group 2 and there were no statistically significant differences between the two groups. There were no deaths reported in either group. Graft survival was 100 versus 80%, which was a non-significant difference.

Infection and adverse events for group 1 were 4/12 CMV versus 0/12 in group 2, (p = 0.04) and hyperglycaemia in group 1 was 1/12 versus 0/12 in group 2.

Despite the small sample size and a rather small event rate of acute episodes in which there was no statistical differences, the authors concluded that group 1 (BTAS) had a lower rate of acute rejection. The study did not report how the patients were selected or what was done to reduce selection bias, no blinded outcome assessment was carried out and loss to follow-up was not reported.

The study by Neu and colleagues[85] was a retrospective, unmatched cohort study based on the US NAPRTCS registry. This study was sited in the Novartis submission to NICE. Patients were treated either with ciclosporin or tacrolimus in combination with MMF and steroid at 30 days post-transplant in 2–21-year-olds. At least 1 year of follow-up data were available in the database. Those under 2 years of age were excluded. There were 986 participants (out of 1762 of all transplants reported to NAPRTCS during 1997–2000) and patients were significantly imbalanced in respect of several population characteristics at baseline (race, transplant age, induction therapy and year of transplant).

No difference was reported in acute rejection (time to acute rejection) between tacrolimus- and ciclosporin-treated patients at 1 year follow-up. There was no difference in graft survival or risk of graft failure in patients treated with tacrolimus or ciclosporin. At 2 years follow-up, all-cause mortality was 4/220 (1.8%) tacrolimus versus 4/766 (0.5%) ciclosporin (RR 3.76, 95% CI: 0.89 to 15.81). However, tacrolimus was associated with significantly improved graft function at the 1- and 2-year follow-up.

This comparative non-randomised study design is more likely to be affected by selection bias, loss to follow-up and non-blinded assessment.

Table 27 summarises the characteristics of these two comparative non-randomised studies.

Summary

- One good-quality multicentre RCT in children comparing tacrolimus with ciclosporin with 4 years of follow-up was identified. At the 6-month follow-up this trial reported a significant reduction in BPAR and improvement in graft function (GFR) with tacrolimus

TABLE 27 *Paediatric non-RCTs tacrolimus versus ciclosporin – efficacy outcomes*

	Patient survival (%)	Acute rejection (%) (95% CI)	RR acute rejection	Graft survival (%)	Serum creatinine (mg/dl GFR) or creatinine clearance (ml/min)
Garcia *et al.*, 2002[84]	100/100	1/12 (8.0%) vs 2/12 (17.0%) ($p = 0.60$)	NR	100/90.0 ($p = 0.30$)	71 ml/min/1.73 m^2 vs 82 ml/min/1.73 m^2
Neu *et al.*, 2003[85]					
At 1-year follow-up		Kaplan–Meier estimate time to acute rejection 29.1 vs 29	aRR 1.01 (0.77 to 1.31)	96.8 vs 97.9 ($p = 0.60$)	89.1 ml/min/1.73 m^2 (SE 2.64) vs 78.6 ml/min/1.73 m^2 (SE 1.07) ($p = 0.0003$)
At 2-year follow-up		($p = 0.84$)	aRR 0.67 (0.56 to 0.79)	91.4 vs 95.1 ($p = 0.15$)	96.7 ml/min/1.73 m^2 (SE 3.33) vs 73.2 ml/min/1.73^2 (SE 1.48), ($p < 0.0001$)

aRR, adjusted relative risk for baseline characteristics; SE, standard error.

compared with ciclosporin. Significant graft survival gains in favour of tacrolimus were observed from 2 years of follow-up although there were no differences in overall mortality. There was no evidence of difference in the reviewed side-effect profile of the two drugs. However, the proportion of children withdrawing due to adverse events was significantly lower for tacrolimus.

- Nine adult RCTs (1664 patients) comparing tacrolimus with ciclosporin in an azathioprine and steroid regimen were included. The methodological reporting of these trials was poor. At 1 year there was a reduction in BPAR levels with tacrolimus compared with ciclosporin, although there was no significant difference in either graft loss or all-cause mortality. PTDM levels were increased with tacrolimus compared with ciclosporin, although there was no difference in the proportion of patients withdrawing due to adverse events between groups. The level of drug switching with tacrolimus was lower than with ciclosporin. There was no significant difference in graft loss or all-cause mortality in trials with follow-up beyond 1 year.
- No data were found comparing the health-related quality of life of renal transplant recipients receiving either ciclosporin or tacrolimus.

Mycophenolate mofetil versus azathioprine

Paediatric randomised controlled trials

No (published or unpublished) RCTs comparing MMF with azathioprine in paediatric renal transplant recipients were found.

Adult randomised controlled trials

Seven RCTs in 1273 adults were identified that compared MMF with azathioprine within a triple therapy regimen of ciclosporin and steroids.[58,59,80,86–88,90,91]

The characteristics and quality of these trials are summarised in *Tables 28* and *29*, respectively. All trials assessed the (licensed) dose of 2 g/dose of MMF. The MMF Acute Renal Rejection (ARR) Study Group also included a 3 g/day dose of MMF. As no significant dose effect was reported by this trial, the outcome results of this trial were aggregated across doses.

The majority of patients across the adult RCTs were first-time recipients and received a cadaveric graft. All trials reported outcomes at either 6 or 12 months. In addition, the MMF ARR Study Group trial, Tricontinental Study Group trial and the trial by Tuncer and colleagues[89] reported outcomes at 3 years or later.

Due to poor reporting, the trials overall scored low on the Jadad scale (median score across trials 1 out of 5).

MMF significantly reduced BPAR compared with azathioprine at 12 months. There was no significant difference in graft loss, all-cause mortality or serum creatinine at 1 year (*Table 30*). Across the three trials with follow-up data at 3 years there was no significant difference in either graft loss (pooled RR 0.72, 95% CI: 0.52 to 1.01) or all-cause mortality (pooled RR 0.83, 95% CI: 0.56 to 1.23).

TABLE 28 *Adult RCTs MMF versus azathioprine in triple therapy regimen – trial characteristics*

Authors, year	No. of patient	Interventions, dose/day	Co-therapies	Mean age (years)	Male (%)	Graft type	First graft	Follow-up
Folkmane *et al.*, 2001[58,59]	48	MMF 2 g vs AZA	CIC + steroid	45/41	NR	Cadaveric	NR	6 months and 1 year
Tricontinental MMF Renal Transplantation Study Group, 1996[86]	503	MMF 2 and 3 g vs AZA	CIC+ steroid	46/47	57/67	Cadaveric	78/82	6 months and 1 and 3 years
Miladipour *et al.*, 2002[87]	80	MMF 2 g vs AZA	CIC + steroid	39/37	53/45	NR	NR	6 months
Sadek *et al.*, 2002[88]	319	MMF 2 g vs AZA	CIC+ steroid	44/44	71/60	Cadaveric/ living	100/100	1 year
Tuncer *et al.*, 2002[89]	76	MMF 2 g vs AZA	CIC + steroid	35/41	71/74	Cadaveric/ living	100/100	3 years
MMF Acute Renal Rejection Study Group, 1998[90]	221	MMF 2 and 3 g vs AZA	CIC + steroid	43/44	64/59	Cadaveric/ living	87/91	6 months, and 1 and 3 years
Baltar *et al.*, 2002[91]	26	MMF NR vs AZA	CIC + steroid	51	69	Cadaveric	100/100	6 months and 1 year

TABLE 29 *Adult RCTs MMF versus azathioprine in triple therapy regimen – trial quality*

Authors, year	Method of randomisation stated	Method of allocation concealment stated	Blinding	ITT analysis stated	Loss to follow-up (%) stated	Jadad score
Folkmane *et al.*, 2001[58,59]	No	No	No	No	No	1
Tricontinental MMF Renal Transplantation Study Group, 1996[86]	No	No	Double	Yes	Yes (27% at 6 months)	3
Miladipour *et al.*, 2002[87]	No	No	No	No	No	1
Sadek *et al.*, 2002[88]	Yes (sequential numbers)	Yes	No	No	Yes (37% at 1 year)	3
Tuncer *et al.*, 2002[89]	No	No	No	No	No	1
US Renal Transplant Study Group, 1995[90]	No	No	Double	Yes	Yes (38% at 1 year)	3
Baltar *et al.*, 2002[91]	No	No	No	No	No	1

Side-effects were poorly reported, with no trials reporting levels of PTDM or hyperlipidaemia. The level of CMV infection was significantly higher for MMF than azathioprine. There was no difference in the levels of PTLD or withdrawals due to adverse events (*Table 31*). Trials did not report the proportion of patients who needed to be switched from MMF to azathioprine or azathioprine to MMF due to drug-specific side-effects (or other reasons).

Only the study of Baltar and colleagues[91] reported health-related quality of life. Using the EuroQol instrument (EQ-5D) they observed a small improvement in the mean EQ-5D score following

TABLE 30 *Adult RCTs MMF versus azathioprine – efficacy outcomes at 12 months*

	No. of RCTs	MMF, *n*/*N* (%)	Azathioprine, *n*/*N* (%)	RR (95% CI)	Heterogeneity *p*-value
BPAR	3[a]	102/552 (18.5)	110/348 (31.6)	0.60 (0.47 to 0.76)	0.95
Graft loss	6	39/701 (5.5)	63/530 (11.4)	0.46 (0.29 to 1.10)[b]	0.01
All-cause mortality	4	24/650 (3.7)	19/479 (3.9)	0.91 (0.50 to 1.64)	0.58
		Mean difference between groups (95% CI)			
Serum creatinine (μmol/l)	4	2.6 (–4.9 to 10.2)			0.08

[a] Includes one trial with outcomes at 6 months.
[b] Random effects meta-analysis.

TABLE 31 *Adult RCTs MMF versus azathioprine – side-effect at 12 months*

	No. of RCTs	MMF, *n*/*N* (%)	Azathioprine, *n*/*N* (%)	RR (95% CI)	Heterogeneity *p*-value
CMV infection	4[a]	105/687 (15.2)	58/510 (11.3)	1.43 (1.02 to 2.01)	0.41
PTDM	0	NR	NR	NA	NA
PTLD	2	6/448 (1.3)	4/270 (1.5)	1.10 (0.30 to 4.01)	0.77
Hyperlipidaemia	0	NR	NR	NA	NA
Withdrawals due to adverse events	3	81/612 (13.2)	55/431 (12.7)	1.00 (0.73 to 1.40)	0.16
Drug switching due to adverse events	0	NR	NR	NA	NA

[a] Includes one trial with outcomes at 6 months.

immunosuppression therapy (pretherapy, 0.84, SD 0.16; 1 year post, 0.87, SD 0.19). They did not report EQ-5D by treatment group.

Paediatric non-randomised controlled studies

No published systematic review of non-randomised controlled studies of MMF compared with azathioprine in children was identified from our literature searches. However, two industry submissions to NICE were found to contain reviews of this issue. The Novartis submission contained an unpublished systematic review by ScHARR.[92] This review identified three non-randomised studies comparing MMF and azathioprine. The Roche Cellcept (MMF) submission to NICE contained a non-systematic review that identified one non-randomised study.[93] As this study was included by the ScHARR review, the remainder of this section focuses on the ScHARR systematic review.

The ScHARR review appeared to employ a rigorous methodology, searching a number of electronic bibliographies using a detailed search strategy (up to January 2005), and a single unblinded reviewer selected studies based on explicit inclusion criteria. Given that identified studies were all non-randomised, the author(s) of the ScHARR report decided to report the results of each study separately and not to combine across studies. Four studies were judged to meet the inclusion criteria of the review, by Antoniadis and colleagues[94] Steffen and colleagues,[95] Staskewitz and colleagues[96] and Jungraithmayr and colleagues.[97,98] Although the study of Steffen and colleagues[95] was excluded by the ScHARR authors (as it was only available in abstract form), the data from this study, for the purposes of the present report, have been included. In addition, the ScHARR review reported Staskewitz and colleagues[96] and Jungraithmayr and colleagues[97,98] as different studies when, in fact, they represent different analyses from the same historical control study. Our own searches identified one additional non-randomised comparative study, by Benfield and colleagues.[99] In summary, we included a total of four non-randomised studies of MMF compared with azathioprine (*Table 32*).

TABLE 32 *Paediatric non-RCTs MMF versus azathioprine – trial characteristic*

Authors, year [Design]	Participants: Mean age (years) Male (%)	Interventions: No. of patients Dosage	Co-therapies	Graft type	Follow-up
Antoniadis *et al.*, 1998[94] [Non-randomised prospective controlled trial]	10 NR	MMF (n = 7) (target 600 mg/m^2 BSA) vs AZA (n = 7)	CIC + steroids	Living	1 and 3 years
Benfield *et al.*, 1999[99] [Historical control study]	10.7/8.8 56/61	MMF (n = 36) (initially 1g/m^2/day)	OKT3 + CIC + steroids	Cadaveric/ living	6 and 12 months
Staskewitz *et al.*. 2001[96] Jungraithmayr *et al.*, 2003/2004[97,98] [Historical control study]	11.5/9.9 65/59	MMF (n = 86) (target 600 mg/m^2 BSA b.d.) vs AZA (n = 54)	CIC + steroids	Cadaveric	6 months and 1 and 3 years
Steffen *et al.*, 2003[95] [Retrospective registry analysis]	<18 NR	MMF (NR) vs AZA	NR	NR	1 year

b.d: twice per day; BSA: body surface area; NR: not reported.

TABLE 33 *Paediatric non-RCTs MMF versus azathioprine – BPAR*

Time	Study	MMF	Azathioprine
6 months	Antoniadis *et al.*, 1998[94]	0/7 (0%)	3/7 (43%)
	Benfield *et al.*, 1999[99]	NR	NR
6 months	Staskewitz *et al.*, 2001[96]	10/65 (15%)	14/54 (26%)[b]
1 year		34/86 (39%)[a]	32/54 (60%)[a]
3 years		38/86 (44%)[b,c]	32/54 (59%)[c]

[a] Read from Kaplan–Meier curve.
[b] Indicates statistically significant at the 5% level (favoured arm marked).
[c] Actuarial rates reported in text of paper.

The quality of the three studies was assessed as poor, with none taking appropriate measures to eliminate selection bias (concealment of the assignment schedule), performance bias or detection bias (blinding).[92] The historical control design of the Staskewitz and Jungraithmayr studies is a major limitation. Although the baseline characteristics [human leucocyte antigen (HLA) match and type of transplant] of the two groups appeared similar, the children receiving MMF were younger (mean age 11.5 years, SD 3.6 years versus mean age 9.9 years, SD 4.7 years; $p < 0.05$). Acute rejection events were not collected prospectively in both groups and were defined clinically and not by biopsy confirmation.

The outcome results of studies are summarised in the following text and tables.

BPAR levels at 6 and 12 months with MMF were lower than with azathioprine (*Table 33*). At 6 months there was a reduction in the pooled BPAR with MMF (RR 0.39, 95% CI: 0.19 to 0.79).

Only a small number of patients died by up to 3 years of follow-up and there was little evidence of a difference between azathioprine and MMF (*Table 34*). At 1 year or longer following transplant, the level of graft loss was significantly lower with MMF (*Table 35*). The one study that reported graft function[96] found no significant difference in serum creatinine between MMF and azathioprine (azathioprine mean 89 µmol/l, SD 40 µmol/l versus MMF mean 79 µmol/l, SD 31 µmol/l) at 1 year.

The reporting of side-effects across the three studies was poor and no overall assessment of

TABLE 34 *Paediatric non-RCTs MMF vs azathioprine – all-cause mortality*

Time	Study	MMF	Azathioprine
6 months	Antoniadis *et al.*, 1998[94]	0/7	0/7
12 months	Benfield *et al.*, 1999[99]	2/36 (6%)	4/31 (13%)
6 months 1 year 3 years	Staskewitz *et al.*, 2001[96]	0/86 0/86 1/86 (1.1%)	1/54 (1.9%) 3/54 (5.6%) 3/54 (5.6%)

TABLE 35 *Paediatric non-RCTs MMF versus azathioprine – graft loss*

Time	Study	MMF	Azathioprine
6 months	Antoniadis *et al.*, 1998[94]	0/7 (0%)	0/7 (0%)
12 months	Benfield *et al.*, 1999[99]	4/36 (11%)	6/31 (19%)
6 months 1 year 3 years	Staskewitz *et al.*, 2001[96]	1/65 (2%)[a] 1/65 (2%)[b] 1/65 (2%)[a,b]	9/54 (17%) 9/54 (17%) 11/54 (20%)[b]

[a] Indicates statistically significant at the 5% level; favoured arm marked.
[b] Actuarial rates reported in text of paper.

TABLE 36 *Paediatric non-RCTs MMF versus azathioprine – side-effects at 1 year*

Time	Study	MMF	Azathioprine
CMV infection	Antoniadis *et al.*, 1998[94] Staskewitz *et al.*, 2001[96]	3/7 (43%) 13/65 (20%)	5/7 NR
PTLD	Staskewitz *et al.*, 2001[96]	1/65 (2%)	NR
PTDM		NR	NR
Withdrawals due to adverse events		NR	NR
Drug switching ciclosporin to tacrolimus	Staskewitz *et al.*, 2001[96]	4/65 (6%)	1/54 (2%)

side-effects was presented in the ScHARR review. The Staskewitz study only reported side-effects for the transplant recipients receiving MMF. Results are summarised in *Table 36*.

No studies reported on the quality of life or growth of children.

Summary

- No RCT evidence comparing MMF with azathioprine in paediatric renal transplant recipients was found.
- Seven RCTs compared MMF with azathioprine in a triple-based regimen (ciclosporin plus steroids) in adult renal transplant recipients. The quality of these trials is difficult to assess due to their poor level of reporting. Pooling across trials revealed a significant reduction in the level of BPAR with MMF compared with azathioprine at 1 year (RR 0.60, 95% CI: 0.47 to 0.76). There was no significant difference between MMF and azathioprine in 1-year graft loss, all-cause mortality or serum creatinine. At 3 years there was no significant difference in all-cause mortality or graft loss.
- An unpublished systematic review of non-randomised studies comparing MMF with azathioprine was presented in the Novartis submission to NICE. This review identified three studies to which an additional study was added. As these four non-randomised studies were subject to a number of biases (i.e.

selection, performance and assessment bias), their reported outcome differences may be unreliable. Although the direction and effect of these studies appeared similar to those reported in the adult RCTs, the magnitude of the MMF effect appeared to be higher. Compared with azathioprine, MMF was found to reduce significantly both 6-month BPAR (RR 0.39, 95% CI: 0.19 to 0.79) and graft loss at 6 months, 1 year and 3 years.
- Drug side-effects and adverse events were poorly reported. In adult RCTs, MMF was associated with significantly increased risk of CMV infection compared with azathioprine (RR 1.43, 95% CI: 1.02 to 2.01), although there was no difference in withdrawals due to adverse events.
- No data were found comparing the health-related quality of life of renal transplant recipients receiving either MMF or azathioprine.
- Few data were reported on drug switching. A single non-randomised study indicated that more patients switched (i.e. from tacrolimus to ciclosporin) with MMF than with azathioprine.

Mycophenolate sodium (MPS) versus azathioprine and MPS versus MMF

Paediatric randomised controlled trials

No (published or unpublished) RCTs comparing MPS with azathioprine or MPS with MMF in paediatric renal transplant recipients were found.

Adult randomised controlled trials

No (published or unpublished) RCTs comparing MPS with azathioprine in adult renal transplant recipients were found. One trial comparing MPS with MMF was reported in the Novartis submission to NICE.[100]

This trial (Study B301) was a 1-year double-blind, double-dummy, randomised, multicentre, parallel group study of the efficacy, safety and tolerability of MPS (n = 213) versus MMF (n = 210) in *de novo* renal transplant patients. Patients were randomised within 48 hours after transplantation to either MMF (2 g/day) or MPS (1.4 g/day), as part of a triple immunosuppressive therapy utilising ciclosporin and prednisolone. The trial was powered for equivalence. At 12 months, there was no significant difference in graft loss (MPS 28.6% versus MMF 28.1%) or BPAR (MPS 22.5% versus MMF 24.3%). The treatments were reported to have a comparable incidence of side-effects and there was no significant difference in withdrawals due to adverse events (MPS 16.9% versus MMF 13.8%). Drug switching and quality of life were not reported.

Paediatric non-randomised controlled studies

No systematic review or primary non-randomised studies comparing MPS with azathioprine in paediatric (or adult) renal transplant recipients were found from bibliographic searches. An unpublished systematic review (searching up to January 2005) included in the Roche Cellcept submission[93] confirmed that there were no paediatric comparative studies of MPS versus azathioprine, either randomised or non-randomised. This systematic review also found no paediatric comparative studies of MPS versus MMF, randomised or non-randomised.

Summary

- No evidence (randomised or non-randomised) comparing MPS with azathioprine or MPS with MMF in paediatric renal transplant recipients was found.
- No evidence (randomised or non-randomised) comparing MPS with azathioprine in adult renal transplant recipients was found.
- One RCT comparing MPS with MMF in adults found the level of BPAR, graft loss, all-cause mortality and side-effect profiles of the two therapies at 1 year post-transplant to be similar. No data were reported on health-related quality of life or drug switching.

Sirolimus

A previous systematic review of the use of sirolimus in renal transplant recipients by the authors of this report concluded that, unlike the other newer immunosuppressive drugs considered here, there was no one specific regimen where sirolimus has been focused.[101] In this report, RCTs were identified that used sirolimus in recipients of renal transplants in four alternative ways:[101] as an alternative to azathioprine;[102] as an alternative to ciclosporin;[103] the addition of sirolimus to calcineurin-based triple therapy;[104] and the addition of sirolimus to ciclosporin-based dual therapy followed by the withdrawal (or not) of ciclosporin.[22] In our previous adult assessment report we argued for the exclusion of the ciclosporin withdrawal regimen.[22] This was because the regimen was licensed based on an RCT that was designed to examine the question of the effectiveness of ciclosporin sparing rather than the effectiveness of the addition of sirolimus *per se*. However, given both the criticism we received for omitting this RCT in the previous report and given that ciclosporin withdrawal is a stated part of the current licence indication for sirolimus [see the section 'Newer immunosuppressive agents' (p. 3)], RCT evidence for all four strategies is presented in this report.

TABLE 37 *Paediatric RCT addition of sirolimus – trial characteristics*

Trial	No. of patient	Interventions, dose/day	Co-therapies	Mean age (years)	Male (%)	Graft type	First graft (%)	Follow-up
Wyeth 0468E1-217-US (unpublished)	**[Confidential information removed]**	Sirolimus[a] + CIC or TAC + steroid	CIC or TAC + steroid ± AZA or MMF	**[Confidential information removed]**			NR	6 months and 1, 2 and 3 years

[a] To achieve trough level 5–15 ng/ml.

TABLE 38 *Paediatric RCT addition of sirolimus – trial quality*

Trial	Method of randomisation stated	Method of allocation concealment stated	Blinding	ITT analysis stated	Loss to follow-up (%) stated	Jadad score
Wyeth 0468E1-217-US (unpublished)	**[Confidential information removed]**					

Paediatric randomised controlled trials

One (unpublished) RCT of the use of sirolimus in paediatric renal transplant recipients was found (*Tables 37* and *38*). In this North American multicentre, open-label RCT, 102 children with a history of previous acute rejection were randomised to receive either a ciclosporin- or tacrolimus-based triple regimen with or without the addition of sirolimus. A commercial-in-confidence version of the full clinical trial report (trial reference 0468E1-217-US) was obtained on request from the drug manufacturer, Wyeth.[102] Details of this trial are provided below. A second paediatric RCT was mentioned in the Wyeth submission to NICE ("Study 315 was designed as a 2 part, randomised, double blind clinical trial in which corticosteroids were to be eliminated from the immunosuppressive regime of paediatric renal allograft recipients who remained free of acute rejection at 6 months post-transplantation"). According to the manufacturer, this trial has only recently completed recruiting and has not yet been analysed. Therefore, no further information is presented on this trial.

In addition, two adult RCTs recruited a small proportion of renal transplant recipients aged 18 years or younger. A brief summary of the paediatric trial and the paediatric data from the two adult trials follows.

US Rapamune Study[106] [Sirolimus versus azathioprine)

Twelve of the 719 enrolled renal transplant recipients were between 12 and 18 years of age. Of these 12, six were randomly assigned to receive sirolimus 2 mg/day, three to receive sirolimus 5 mg/day and the remaining three were assigned to azathioprine. All subjects also received ciclosporin and steroids. Two of the nine subjects receiving sirolimus developed acute rejection episodes (non-biopsy confirmed); these occurred in the 2 mg/day group. No rejection episodes occurred in the group receiving azathioprine. No subjects died or experienced graft loss. Two individuals in the azathioprine group and the one in the 5 mg/day sirolimus group withdrew due to adverse events. The point of follow-up at which these outcomes occurred was not reported.

Rapamune Global Study Group[104] (sirolimus versus placebo)

Three of the 576 enrolled transplant recipients in this trial were younger than 18 years.[103] Of these, one was randomly assigned to each of the three treatment groups: sirolimus 2 mg/day, sirolimus 5 mg/day and placebo. All subjects also received ciclosporin and steroids. Only the individual in the placebo group withdrew from treatment prematurely. None died or had graft loss or BPAR.

TABLE 39 *Paediatric RCT addition of sirolimus – efficacy outcomes at 12 months (or 6 months)*

	Sirolimus, *n*/*N*	Control, *n*/*N*	RR (95% CI)
BPAR	**[Confidential information removed]**		
Graft loss	**[Confidential information removed]**		
All-cause mortality	**[Confidential information removed]**		
	***N*, mean (SD)**	***N*, Mean (SD)**	**Mean difference (95% CI)**
Serum creatinine (μmol/l)	**[Confidential information removed]**		
Glomerular filtration rate (ml/min, 1.72 m^2), mean (SD)	**[Confidential information removed]**		

TABLE 40 *Paediatric RCT addition of sirolimus – side-effects at 12 months (or 6 months)*

	Sirolimus, *n*/*N*	Control, *n*/*N*	RR (95% CI)
CMV infection	**[Confidential information removed]**		
PTDM	**[Confidential information removed]**		
PTLD	**[Confidential information removed]**		
Hyperlipidaemia (hypercholesterolaemia)	**[Confidential information removed]**		
Withdrawals due to adverse events	**[Confidential information removed]**		

The point of follow-up at which these outcomes occurred was not reported.

Paediatric trial 0468E1-217-US (addition of sirolimus)[102]
This RCT enrolled paediatric and adolescent renal graft recipients at higher immunological risk of graft failure by virtue of their having had one or more episodes of acute rejection and/or biopsy evidence of chronic allograft nephropathy before qualifying for study participation. Individuals aged 20 years or younger were 2:1 randomised to receive either sirolimus combined with a calcineurin inhibitor (ciclosporin or tacrolimus) and steroid or calcineurin inhibitor and steroid alone. Although individuals in the sirolimus group could not receive azathioprine or MMF, this therapy was allowed in the non-sirolimus group. **[Confidential information removed]** (*Tables 39* and *40*).

Adult randomised controlled trials

Four RCTs of the use of sirolimus in adults were included. Two trials compared sirolimus with azathioprine,[105,106] and one trial compared sirolimus with ciclosporin.[107] One trial [Rapamune Maintenance Regimen (RMR) Study] assessed the impact of a 3-month period of sirolimus plus ciclosporin and steroid and then randomised patients to continue sirolimus and steroid either continuing or stopping ciclosporin.[25] Although the RMR trial did not formally meet our inclusion criteria, it was included on the basis that it is the pivotal trial upon which the current license for sirolimus is based. Characteristics, quality and outcome results of the four studies are provided in Appendix 10 and are summarised in *Tables 41–44*.

Outcomes of trials are reported below according to the three differing uses of sirolimus.

Sirolimus versus azathioprine
At 1-year follow-up, there was evidence of a decrease in pooled BPAR and increase in pooled serum creatinine with sirolimus compared with azathioprine (*Table 43*). There was no significant difference in graft loss or all-cause mortality. The Rapamune US Study Group also reported 2-year follow-up results. No significant difference in graft loss or all-cause mortality was seen at 2 years. There were no significant differences in side-effect outcomes at 1 year (*Table 44*). Neither trial reported patient health-related quality of life or drug switching.

Sirolimus versus ciclosporin
There was no statistically significant difference in 1-year efficacy outcomes between the sirolimus- and ciclosporin-treated groups (*Table 45*). There was evidence of an increased incidence of hyperlipidaemia with sirolimus (*Table 46*). This trial did not report patient health-related quality of life or drug switching.

TABLE 41 *Adult RCTs sirolimus – trial characteristics*

Authors, year	No. of patients	Interventions, dose/day	Co-therapies	Mean age (years)	Male (%)	Graft type	First graft	Follow-up
Versus azathioprine								
Kahan, 2000[106] [Rapamune US Study Group]	719	Sirolimus (2 mg and 5 mg/day) vs AZA	CIC + steroid	46/46	68/57	Cadaveric/ living	100	1 year
Machado *et al.*, 2004[105]	70	Sirolimus (2 mg/day) vs AZA	CIC + steroid	36/33	66/66	Living	100	1-year
Versus ciclosporin								
Groth *et al.*, 1999[107] [Sirolimus European Renal transplantation Study Group]	83	Sirolimus[a] + vs CIC	AZA + steroid	48/42	71/60	Cadaveric	100	1 year
Addition of sirolimus with ciclosporin removal								
Johnson *et al.*, 2001[25] [RMR study]	430	Sirolimus[b] (2 mg/day) + ciclosporin vs Sirolimus (2 mg/day) + ciclosporin withdrawal	Steroid	42/44	62/27	Cadaveric/ living	91	1, 2 and 4 years

[a] 16–24 mg/m^2/day followed by 8–12 mg/m^2/day.
[b] All patients underwent a 3-month period of treatment post-transplant of sirolimus (2 mg/day), ciclosporin and steroid.

TABLE 42 *Adults RCTs sirolimus – trial quality*

Authors, year [trial name]	Method of randomisation stated	Method of allocation concealment stated	Blinding	ITT analysis stated	Loss to follow-up (%) stated	Jadad score
Versus azathioprine						
Kahan 2000[106] [Rapamune US Group]	Yes	Yes (telephone)	Double blind	Yes	Yes (2%)	5
Machado *et al.*, 2004[105]	No	No	No	Yes	NR	1
Versus ciclosporin						
Groth *et al.*, 1999[107] [Sirolimus European Renal transplantation Study Group]	No	Yes (central computer)	No	Yes	NR	2
Addition of sirolimus with ciclosporin removal						
Johnson *et al.*, 2001[25] [RMR Study]	Yes (computer)	Yes (telephone)	No	Yes	NR	3

TABLE 43 *Adult RCTs sirolimus vs azathioprine – efficacy outcomes at 12-months*

	No. of RCTs	Sirolimus, *n/N* (%)	Azathioprine, *n/N* (%)	RR (95% CI)	Heterogeneity *p*-value
BPAR	2	106/593 (19)	55/196 (28)	0.60 (0.45 to 0.80)[a]	0.64
Graft loss	2	37/593 (6)	10/196 (5)	1.14 (0.58 to 2.27)[a]	0.92
All-cause mortality	2	35/593 (6)	6/196 (3)	1.85 (0.77 to 4.42)[a]	0.65
				Mean difference (95% CI)	
Serum creatinine (μmol/l)	2			28.7 (18.8 to 38.5)[a]	0.20

[a] Calculated by authors of this report.

TABLE 44 *Adult RCTs sirolimus versus azathioprine – side-effects at 12 months*

	No. of RCTs	Sirolimus, *n/N* (%)	Azathioprine, *n/N* (%)	RR (95% CI)	Heterogeneity *p*-value
CMV infection	2	6/593 (1)	3/194 (1.5)	0.68 (0.17 to 2.77)[a]	0.60
PTDM	1	2/35 (6)	2/35 (6)	1.00 (0.15 to 6.72)[a]	NA
PTLD		NR	NR		
Hyperlipidaemia	2	209/596 (35)	44/194 (23)	1.57 (1.19 to 2.07)[a]	0.12
Withdrawals due to adverse events	2	54/593 (9)	18/196 (9)	1.04 (0.63 to 1.73)[a]	0.29
Drug switching due to adverse events		NR	NR		

[a] Calculated by authors of this report.

TABLE 45 *Adult RCTs sirolimus versus ciclosporin – efficacy outcomes at 12 months*

	No. of RCTs	Sirolimus, *n/N* (%)	Ciclosporin, *n/N* (%)	RR (95% CI)	Heterogeneity *p*-value
BPAR	1	17/41 (41)	16/42 (38)	1.14 (0.67 to 1.94)[a]	NA
Graft loss	1	1/41 (2)	4/42 (9)	0.26 (0.03 to 2.19)[a]	NA
All-cause mortality	1	0/41 (0)	2/42 (5)	0.20 (0.01 to 4.13)[a]	NA
		***N*, mean (SD)**	***N*, Mean SD**	**Mean difference (95% CI)**	
Serum creatinine (μmol/l)	1	18,116 (38)	24,134 (38)	–18 (–41 to 5)[a]	NA

[a] Calculated by authors of this report.

Addition of sirolimus followed by removal of ciclosporin

In the RMR trial, *de novo* renal graft recipients were randomised to ciclosporin withdrawal (or not) following a 3-month pretreatment period of sirolimus in a triple therapy regimen.

At 1 year, although there was no difference in graft loss or all-cause mortality, there was a higher rate of BPARs in the ciclosporin withdrawal group compared with the no withdrawal group (*Table 47*). Graft function (as assessed by a lower serum creatinine level) was better in the ciclosporin withdrawal group, a result that was maintained at 4 years follow-up. There were no statistically significant differences in side-effects or withdrawals due to adverse events between the two groups at 12 months follow-up (*Table 48*). Although

TABLE 46 *Adults RCT sirolimus versus ciclosporin – side-effects at 12 months*

	No. of RCTs	Sirolimus, *n*/*N* (%)	Ciclosporin, *n*/*N* (%)	RR (95% CI)	Heterogeneity *p*-value
CMV infection	1	6/41 (15)	5/42 (12)	1.22 (0.41 to 3.71)	NA
PTDM	1	1/41 (2)	1/42 (2)	1.02 (0.07 to 15.9)	NA
PTLD	1	0/41	0/42	Not calculable	
Hyperlipidaemia	1	18/41 (44)	6/42 (14)	3.07 (1.36 to 6.96)	NA
Withdrawals due to adverse events	1	NR	NR		
Drug switching due to adverse events	1	NR	NR		

TABLE 47 *Adult RCT sirolimus and ciclosporin versus ciclosporin removal (RMR trial) – efficacy outcomes at 12 months*

	No. of RCTs	Sirolimus + ciclosporin withdrawal, *n*/*N* (%)	Sirolimus + no ciclosporin withdrawal, *n*/*N* (%)	RR (95% CI)	Heterogeneity *p*-value
BPAR	1	21/215 (10)	9/215 (4.)	2.33 (1.09 to 4.98)[a]	NA
Graft loss	1	6/215 (3)	9/215 (4)	0.67 (0.24 to 1.84)[a]	NA
All cause mortality	1	6/215 (3)	4/215 (2)	1.50 (0.43 to 5.24)[a]	NA
		***N*, mean (SD)**	***N*, mean (SD)**	**Mean difference (95% CI)**	
Serum creatinine (μmol/l)	1	215,142 (62)	215,158 (62)	–16 (–28 to –4)[a]	NA

[a] Calculated by authors of this report.

the numbers of patients with hyperlipidaemia were not reported, there was no statistically significant difference between groups in the mean serum cholesterol or triglyceride levels. Health-related quality of life and drug switching as a result of side-effects or adverse events were not reported.

Paediatric non-randomised controlled studies

Bibliographic searches and review of the company submissions did not identify any systematic reviews or non-randomised comparative studies of the use of sirolimus in children with kidney transplants.

Summary

- One paediatric RCT was identified that assessed the addition of sirolimus to ciclosporin- or tacrolimus-based immunosuppression in renal transplant recipients of age 18 years or less who had experienced one or more previous acute rejections. The quality of this trial was judged to be poor with evidence of selection and performance bias. **[Confidential information removed].**
- Two RCTs compared sirolimus with azathioprine in a triple-based regimen (ciclosporin and steroids) in adult renal transplant recipients. The quality of one RCT was judged to be good whereas the other was judged to be too poorly reported to assess its quality. Compared with azathioprine, sirolimus was associated with a decreased incidence of 1-year BPAR and an increase in serum creatinine.
- One RCT compared sirolimus with ciclosporin in a triple-based regimen (ciclosporin and steroids) in adult renal transplant recipients. The quality of this trial was difficult to judge as it was poorly reported. There was no statistically significant difference in the incidence of 1-year BPAR between sirolimus and ciclosporin, although there was evidence of an increased level of hyperlipidaemia in sirolimus-treated individuals.
- One RCT assessed the current licensed indication for sirolimus, that is, the addition of sirolimus with the withdrawal of ciclosporin at 3 months. The quality of this trial was judged to be moderate. Ciclosporin withdrawal was associated with a higher level of BPAR and lower serum creatinine at 1- and 4-year follow-up than that with no withdrawal.

TABLE 48 *Adult RCT sirolimus and ciclosporin versus ciclosporin removal (RMR trial) – side-effects at 12 months*

	No. of RCTs	Sirolimus + ciclosporin withdrawal, *n*/*N* (%)	Sirolimus + no ciclosporin withdrawal, *n*/*N* (%)	RR (95% CI)	Heterogeneity *p*-value
CMV infection	1	6/215 (3)	5/215 (2)	1.20 (0.37 to 3.87)[a]	NA
PTDM	1	6/215 (3)	3/215 (1)	2.00(0.51 to 7.89)[a]	NA
PTLD	1	NR	NR		NA
Hyperlipidaemia	1	NR	NR[b]		
Withdrawals due to adverse events	1	37/215 (17)	30/215 (14)	1.40 (0.90 to 2.19)[a]	NA
Drug switching due to adverse events	1	NR	NR		

[a] Calculated by this report author.
[b] No significant difference in mean serum cholesterol and triglyceride levels.

- Health-related quality of life and drug switching due to side-effects were not reported by any of these trials.
- No systematic reviews (published or unpublished) of non-comparative studies examining the use of sirolimus were found.

Chapter 4

Assessment of cost-effectiveness

Assessment of existing cost-effectiveness literature

Bibliographic searches for cost studies and economic evaluations identified 202 citations (MEDLINE 59, EMBASE 73, NHS EED 29 and OHE HEED 41). Based on an assessment of title/abstract, none were judged to meet the inclusion criteria for this review.

Review of company economic evaluations

Three of the four companies submitted paediatric cost-effectiveness models, Wyeth being the exception. Wyeth in its submission referred to the economic model that it had previously submitted for the adult renal immunosuppressives appraisal. *Table 49* summarises the company submissions and the drugs modelled.

The three company-submitted models were based on the Birmingham Sensitivity Analysis (BSA) adult model which the assessment group had previously developed to assess the cost-effectiveness of different immunosuppressive regimens in adults post-renal transplantation. This model is summarised below. An electronic copy of the BSA model was made available to the companies early in the assessment process and several meetings were held between the assessment group, company representatives and NICE staff to discuss modelling strategies. Companies were free to make changes as appropriate to the model, but use of the same model as a starting point was seen as likely to increase transparency and reduce scope for disagreement. This section first outlines the original BSA model, then critiques each company model before comparing company models (structure, input parameter and results).

TABLE 49 *Company submissions: inclusion of model (yes/no) and drugs modelled*

Company	Drugs	Economic analysis submitted
Fujisawa/Astellas	Tacrolimus	Yes
Novartis	Ciclosporin	No
	MPS	No
	Basiliximab	Yes
Roche	MMF	Yes
	Daclizumab	Yes
Wyeth	Sirolimus	No[a]

[a] Wyeth referred to its economic analysis submitted for adult immunosuppression.[22]

Original BSA model

The BSA model was developed by the Birmingham group with the NICE Decision Support Unit following the submission of the adult renal immunosuppressives assessment reports. Its results were used to inform NICE's guidance on renal immunosuppressants in adults in September 2004.

Key features of the BSA model include:

- A Markov model with three states – functioning graft; graft failed/dialysis; and death. Results in terms of of incremental cost per quality-adjusted life-year (QALY) over a 10-year time horizon from a healthcare perspective. Costs and QALYs were discounted at 6 and 1.5%, respectively
- Ten year patient and graft survivals are predicted using one of two possible surrogate outcomes, either acute rejection rates or serum creatinine levels both at 12 months follow-up.
- The relationship between these surrogates (acute rejection, creatinine) and graft failure based on survival analysis, using HRs for each surrogate.
- Patients could die with a functioning graft or post graft-failure, on dialysis. The probability of death for those with a functioning graft was that of the relevant age group in the general population. For those on dialysis, it was based on an audit of UK transplantation.

The choice of surrogate and its baseline HR was based on a systematic review of observational studies linking surrogates to graft survival. Criteria for inclusion of studies in this review were follow-up data for at least 5 years and use of multivariate analysis to control for confounding factors. This

review identified as statistically significant predictors: BPAR within 12 months (HR 1.96, 95% CI: 1.69 to 2.37) and serum creatinine levels at 12 months (HR 1.69, 95% CI: 1.32 to 2.17).

Years spent with either a functioning graft or on dialysis were translated into QALYs by multiplication by a utility score for each state (range 0–1). The review of the adult company submissions to NICE showed that estimates of the utility values of functioning graft and dialysis varied from 0.41 to 0.68 for dialysis and from 0.74 to 0.92 for functioning graft. The BSA model used a value of 0.5 for dialysis and 0.75 for functioning graft.

Each drug cost was taken from its sponsoring company's submission. Dialysis was costed at just over £21,000 per year, based on previous guidance by NICE. The cost of treating each episode of acute rejection was put at £4600, based on amalgamating the various adult company submission estimates.

The BSA model was structured to consider side-effects associated with drug regimens. Side-effects were assumed to lead to switching drugs. However, lack of relevant data by drug prevented full use of this facility. Instead, side-effects were assumed to occur in a fixed percentage of patients with a penalty in terms of loss of quality of life and cost. Default values were set at 10% of patients, the quality of life loss was set to –0.1 QALY and the cost penalty was set to £200. The penalties applied only to one cycle (year), after which a drug switch was assumed to restore the quality of life to the original state pre-side-effects.

Sensitivity analysis explored the effects of varying key assumptions, focusing on issues to do with the HR for acute rejection and the impact of dose reductions of ciclosporin when used with MMF.

Novartis economic model

The Novartis submission included a model-based economic evaluation of the addition of basiliximab in a triple CAS therapy, that is, CASB versus CAS. No cost-effectiveness analysis for MPS was undertaken although the Novartis submission argued for its therapeutic equivalence to MMF. MPS is licensed for adults but not children. For adults the cost of MPS is similar to that of MMF. As therapeutic dosages have yet to be defined for children, no such comparison is possible.

The Novartis submission used the same HR (i.e. 1.96) linking acute rejection to graft survival as in the adult BSA model. As in the BSA model, the time frame was 10 years. Changes to the BSA included the following. First, the clinical effect of basiliximab on BPAR was taken from a published meta-analysis of adult RCTs.[37] Second, the BSA model was reconfigured to allow a distribution (normal distribution for no induction therapy and log-normal for induction) around the pooled odds ratio. Third, mortality, which in BSA was based on age 35 years, was also altered to run from age 10 years (minimum) for 10 years. Fourth, a new parameter was added – body mass – to allow dosages to be adjusted to age/mass. Dosages of CAS were as in the Trompeter/Filler paediatric RCT of ciclosporin versus tacrolimus[64] [see the section 'Tacrolimus versus ciclosporin' (p. 20)], and dosage of basiliximab were taken as licensed indications (20 mg for <35 kg, 40 mg for >35 kg). The Novartis submission noted that the Trompeter/Filler RCT had ciclosporin dosage at 7 mg/kg, well above the licensed dose of 4–6 mg /kg, resulting in higher prices for ciclosporin. Similarly, the Novartis submission claimed that the tacrolimus dosage in the Trompeter trial at mean 0.21 mg/kg underestimated the cost of tacrolimus. However, although the licensed initial dose in the British National Formulary (BNF) is 0.3 mg/kg, this has to be titrated in maintenance therapy.

The results of the Novartis model give a QALY gain of 0.06 for basiliximab over 10 years, with a reduced cost (greater in the younger age groups), indicating dominance for basiliximab. Cost savings were of the order of £2000 and £3000 for children over or under 35 kg, respectively.

The key potential criticism of the basiliximab cost-effectiveness analysis undertaken by Novartis is its use of acute rejection data sourced from adult and not paediatric trials. However, given the absence of published RCTs on basiliximab in children, this approach seems reasonable.

Fujisawa/Astellas economic model

The Fujisawa/Astellas submission explored the cost-effectiveness of tacrolimus to ciclosporin (combined with azathioprine and ciclosporin) based on the BSA model. The submission used the same HR (i.e. 1.96) linking acute rejection to graft survival for adults in the BSA model. The BSA model was amended to cover two age groups (<13 and 13–18 years). Other amendments included:

1. a distribution around the probability of acute rejection based on clinical trial data
2. switching of drugs due to side-effects or acute rejection

3. inclusion of other costs for functioning grafts
4. dosages adjusted to age by annual cycles
5. additional health states due to switching (i.e. switching from CAS to TMS, TAS to CAS and TAS to TMS).
6. transition cost of moving to the graft failure states.
7. changed assumptions in the model assumptions including the following:
   (a) the <13-year-old age group starting in the model aged 7 years, and in 13–18-year-old group, starting at 15 years
   (b) a maximum of one acute rejection event per annual cycle
   (c) all drug switches occurring at end of cycle
   (d) switched patients having no acute rejection event or side-effects (justified on the basis of most acute rejections occurring in year 1).

The submission used the same HR (i.e. 1.96) linking acute rejection to graft survival for adults in the BSA model. 'Expanded bottom-up costs' were used, including co-medications, laboratory test diagnoses, visits and consultations and hospital admissions. The use of each was estimated by an expert panel of clinicians. Unit costs were from BNF, NHS Reference Costs and Personal Social Services Research Unit (PSSRU), plus data from several hospitals. The cost of an acute rejection event was put at around £1000, dialysis at £30,000 per annum and nephrectomy at £3000. The costs of side-effects were put at £48 for cosmetic and £533 for diabetes mellitus.

Dosages were maintenance not initial dose, with the dosages of ciclosporin, tacrolimus, azathioprine and sirolimus as in the Trompeter RCT, but with a different dose in year 1 compared with the following 9 years, and also different by age group. Dosages were adjusted with weight each year. Weight/age data for dose adjustment were drawn from the US Centers for Disease Control and Prevention.

The acute rejection rate in each arm was based for the first year on the Trompeter RCT, supplemented with unpublished data from the same trial for years 2–4 extrapolated up to 10 years. The incidence of switching was based on an expert panel of clinicians, which had 43–44% CAS patients switching to TAS, followed by 11–16% switching from TAS to TMS, with low levels of switching from other regimens. Only those side-effects that would necessitate switching were included. Switching was also allowed as a result of an acute rejection event.

Results showed an incremental cost-effectiveness ratio (ICER) of about £18,000 for the <13-year-old age group and about £31,000 for the 13–18-year-old age group. When side-effects were excluded, these rose to about £119,000 and about £147,000, respectively.

A number of different sensitivity analyses were carried out, indicating that the ICERs were highly sensitive to the assumptions on side-effects.

The principle criticisms of the Fujisawa/Astellas model were as follows:

- Major reliance on the estimates of a clinical expert group, particularly on side-effects, which had major impact on ICERs.
- Lack of clear links between sensitivity analysis and base-case results (particularly between cohort simulation and probabilistic analyses, which give very different ICERs). The probabilistic sensitivity analysis was limited in having distributions only on one parameter.
- Unduly complex model with two age groups each ageing each year, and also extrapolation of dosages and acute rejections for each of the 10 years modelled.

Roche economic model

The Roche submission undertook cost-effectiveness analysis of both the addition of daclizumab to ciclosporin triple therapy and MMF compared with azathioprine. The Roche submission used the same adapted BSA model for both analyses. The following BSA model adaptations were made.

The submission used the same HR (i.e. 1.96) linking acute rejection to graft survival for adults in the BSA model. For the MMF–azathioprine comparison, the model relied heavily on a single non-randomised comparative study[96] undertaken in children. Estimation of dosages was indirect via the National Diet and Nutrition survey, due to lack of data on mean weight in the Staskewitz study. The model used a 12-month acute rejection level of 59% for CAS compared with 28% for CMS, based on Staskewitz and colleagues. It should be noted that this model used clinical acute rejection and not biopsy-confirmed acute rejection [see the section 'Mycophenolate mofetil versus azathioprine' (p. 25)]. Utility scores for dialysis and functioning graft were taken as 0.65 and 0.85, respectively. It was assumed that there were no side-effect differences between MMF and azathioprine. In contrast, our meta-analysis of adult RCTs found a statistically significant increase

in CMV infection with MMF [see the section 'Mycophenolate mofetil versus azathioprine' (p. 25)].

MMF was shown to be more effective and less costly than azathioprine. The higher drug cost of MMF was offset by reduced time on dialysis, which was in turn driven by the relatively large difference in acute rejection. Inclusion of the acute rejection rates used in the original BSA model (of 34 versus 19%) gave an ICER of about £17,000. The cost-effectiveness of MMF was robust to a number of one-way sensitivity analyses (i.e. based on cost of dialysis, rate of acute rejection, utility, HR and mortality).

The principle criticism of the Roche MMF cost-effectiveness analysis was the reliance on a non-randomised comparative study[96] [see the section 'Mycophenolate mofetil versus azathioprine' (p. 25)] albeit in children. Clinically defined acute rejection (rather than biopsy-confirmed) events were used in the cost-effectiveness analysis.

The Roche submission also used the adapted BSA model for the assessment of the cost-effectiveness of daclizumab. The BPAR level was sourced from an adult RCT by Vincenti and colleagues.[49] It was concluded that the addition of daclizumab was dominant, a conclusion that was robust in all sensitivity analyses except that of low acute rejection gain where the ICER became approximately £12,000.

Wyeth economic model

Wyeth did not submit an economic model in children. Instead, they referred to a cost-effectiveness model analysis undertaken in their previous submission to NICE on renal immunosuppressants in adults. This analysis, which predated the BSA model, was different. Our critique of the Wyeth model from the previous adult review is reproduced in Appendix 12 and summarised here.

The Wyeth model assessed the cost-effectiveness of a strategy of sirolimus (Rapamune) combined with ciclosporin and a steroid (RCS) versus a strategy of sirolimus with steroid alone (RS). The data came from the RMR trial (see the section 'Mycophenolate sodium (MPS) versus azathioprine and MPS versus MMF' (p. 30). It should be noted that this analysis did not address the effectiveness of sirolimus *per se* but instead the effectiveness of ciclosporin withdrawal (or not) when taking a sirolimus-based regimen.

The key elements of the Wyeth adult model were as follows:

- reliance on serum creatinine levels (rather than acute rejection) as the surrogate outcome for graft loss
- inclusion of a wide range of costs based on a database from a single UK centre.

The assessment group designed the adult BSA model for adults to allow either acute rejection or serum creatinine to be used as the surrogate outcome, but not both. When the serum creatinine values from the RMR trial were used in the original BSA model, it was found that RCS was dominant compared with CS. Given that the RMR trial did not directly address the effectiveness of sirolimus, the assessment group did not model the results of the RMR trial [see the section 'Assessment group economic assessment' (p. 41)].

Comparison of company model features, inputs and results

The general structure, inputs and results of the three submitted company models are summarised in *Tables 50–52*.

Summary

- The three company paediatric economic models were based on the assessment group's BSA model that was initially developed to assess the cost-effectiveness of newer immunosuppressant drugs in adult renal transplant recipients.
- Cost-effectiveness analyses in children were undertaken by the companies for the strategies of BCAS versus CAS (Novartis), DCAS versus CAS (Roche), CMS versus CAS (Roche) and TAS versus CAS (Fujisawa/Astellas).
- Each company populated their model with their own particular clinical outcome and cost parameter values. However, all companies used an acute rejection-based prediction of long-term graft loss using a mean HR of 1.96 sourced from the adult BSA model. The only company to apply a substantive structural adaptation to the BSA model was Fujisawa/Astellas, who formally included side-effects.
- The results of each company model were favourable to their respective immunosuppressive drug, three claiming dominance over competitor products and one quoting ICERs ranging from £18,000 to £31,000/QALY. Sensitivity analysis was

TABLE 50 *General company model characteristics*

	Fujisawa/Astellas	Novartis	Roche
Manufactured drugs	Tacrolimus	Basiliximab and MPS	Daclizumab and MMF
Comparisons modelled	TAS vs CAS	BTAS/BCAS vs CAS/TAS	DCAS vs CAS CMS vs CAS
Model basis	BSA	BSA	BSA
Population and subgroups	<13 years (start age 7 years) ≥ 13–18 years (start age 15 years)	Age NR <35 kg and >35 kg	11 year, 41 kg
Time horizon	10 years post-transplantation	10 years post-transplantation	10 years post-transplantation
Probabilistic sensitivity analysis	2nd-order Monte Carlo (also cohort) on clinical outcomes (not costs)	No	Daclizumab no MMF yes
Sensitivity analyses	One-way: side-effects; starting age; utility, HR for graft failure; dialysis cost	One-way: body weight	One-way: acute rejection; cost; dialysis cost; utility; HR for graft failure; dialysis
Discounting	6% costs and 1.5% outcomes	NR – as BSA	6% costs and 1.5% outcomes

TABLE 51 *Model clinical parameter values and source and assumptions*

	Fujisawa/Astellas	Novartis	Roche
Baseline graft survival	88% at 1 year UK Transplantation	As BSA	As BSA
All-cause mortality		Actuarial life tables, initial age 10 years	Age-specific mortality
Acute rejection levels	Filler *et al.*[31] paediatric RCT – assumed constant acute rejection risk >4 years and across age subgroups acute rejection at 1 year TAS 33.9/41.4%, CAS 44.2/67.7%	From BMJ meta-analysis (adult) RR 0.56 (95% CI: 0.44 to 0.72) Apply to normally distributed acute rejection on CAS/TAS	DCAS vs CAS, Vincenti *et al.*[49] adult RCT DCAS 28%/CAS 47% CMS vs CAS Staskewitz *et al.*[96] paediatric non-RCT CMS 27.7%/CAS 59.3%
Acute rejection HR	1.96 (95% CI: 1.63 to 2.37)	1.96 (95% CI: 1.63 to 2.37)	1.96 (95% CI: 1.63 to 2.37)
Other surrogates considered?	No	No	No
Handling of side-effects	Drug switching due to diabetes mellitus and cosmetic effects. Sourced from expert panel	Not included	Not included
Utilities:			
Functioning graft	0.75	0.75	0.85
Graft failure/dialysis	0.5	0.5	0.65
Death	0		
Side-effects	–0.1		

common to all models but generally limited in scope and confirming the base-case results. The exception was Fujisawa/Astellas (TAS versus CAS), whose sensitivity analysis indicated the importance of the assumptions on side-effects.

Assessment group economic assessment

We amended the BSA model in order to assess the cost-effectiveness of the newer immunosuppressive drugs in a paediatric population.

TABLE 52 *Base case model results*

	Base case Cohort	Base case Monte Carlo (mean)	Sensitivity analysis
Fujisawa/Astellas	*<13 years* TAS total cost £89,847 CAS total cost £86,222 TAS QALY 5.73 CAS QALY 5.53 ICER £18,002/QALY	*<13 years* TAS total cost £94,120 CAS total cost £88,367 TAS QALY 5.62 CAS QALY 5.47 ICER £25,722/QALY CEAC: 42% at £30,000/QALY	If no side-effects included cohort ICER £119,000/QALY and £147,000/QALY
	≥ 13 years TAS total cost £100,341 CAS total cost £94,211 TAS QALY 5.74 CAS QALY 5.54 ICER £31,121/QALY	*≥ 13 years* TAS total cost £105,675 CAS total cost £97,629 TAS QALY 5.61 CAS QALY 5.47 ICER £86,280/QALY CEAC: 31% at £30,000/QALY	
Novartis	*<35 kg* BTAS/BCAS vs TAS/CAS QALY +0.06 Total costs ~–£3,000 BTAS/BCAS Dominant *>35 kg* BTAS/BCAS vs TAS/CAS QALY +0.06 Total costs ~–£2,000 BTAS/BCAS dominant	Not presented	Not presented

	Base case cohort	Base case Monte-Carlo [mean]	Sensitivity analysis	BSA adult model results
Roche	DCAS total cost £41,390 CAS total cost £45,663 DCAS QALY 6.242 CAS QALY 6.117 DCAS dominant	Not presented	DCAS dominant in all analyses with exception of low acute rejection gain £12,000/QALY	DCAS vs CAS Cost –£3,510 QALY +0.143 DCAS dominant
	CMS total cost £49,800 CAS total cost £55,100 CMS QALY 6.19 CAS QALY 5.90 CMS dominant		CMS dominant in all analyses with exception of low acute rejection gain and RR of mortality from GF £5,000/QALY.	CMS vs CAS Cost £10,086 QALY 0.137 ICER £73,916/QALY
	CMS vs CMsS If assume equivalent efficacy, CMS dominant		If use adult acute rejection, CEAC 86% at £30,000/QALY	

CEAC, cost-effectiveness acceptability curve.

The following seven drug regimens were modelled in comparison with CAS triple therapy:

- CAS versus TAS
- CAS versus CMS
- CAS versus BCAS
- CAS versus DCAS.

In addition, one extra TAS regimen was modelled: CAS versus BTAS.

The intervention drug regimens were selected on the basis of clinical practice, available trial data and current licensing (neither MPS nor sirolimus is currently licensed in children).

The remainder of this section describes the amendments made to the BSA for paediatrics (i.e. the development of the BSA paediatrics (BSAp) model) and reports the cost-effectiveness results for the various newer

immunosuppressive drug regimens based on the BSAp model.

Methods

The adult BSA model was adapted for paediatrics – hereafter referred to as the BSAp model. The following adaptations were made in the development of the BSAp model:

- Use of a paediatric-specific HR of 1.41, 95% CI: 1.15 to 1.74 [see the section 'Surrogate outcomes and prediction of long-term graft survival' (p. 6) for explanation].
- Sourcing of 12-month BPAR levels from RCT evidence in the paediatric population (level-1 evidence). Where paediatric RCT evidence was not available (that is, for MMF and daclizumab), adult RCT data were used (see level-2 evidence). The values used in the BSAp model are summarised in *Table 60*.
- Adjustment of drug dosages (and costs) to reflect licensed indications and also age/weight/body surface area of children.

The BSAp model produces an aggregate ICER per QALY, which is calculated based on two starting ages (3 and 13 years) and corresponding weights. The side-effect component of the model was not used owing to a lack of suitable trial data. Otherwise, the basis of the BSAp model was as described previously for the BSA model. Results are reported as mean and 95% CI based on first-order model uncertainty using a cohort of 10,000 patients. Sensitivity analysis was limited to a one-way analysis based on the 95% CIs around the mean HR for BPAR.

Dosage and unit costs

A key requirement of a paediatric model is that dosages must adjust with weight, which in turn varies with age. The following sections review dosages and cost per dose. Dosage and cost per dose are dealt with separately, for two reasons. First, the adult BSA model did not consider dosages in detail, instead relying on the sponsor company's submitted unit costs. Wide divergences existed between company models as to these unit costs. Second, prices have changed since the adult model was developed in 2003. Between March 2003 and March 2005, the BNF price of ciclosporin fell by 33%, that of MMF by 25% and that of tacrolimus by 8%. The prices of sirolimus, basiliximab and daclizumab remained unchanged.

The company models adjusted dosages for children ageing each year in slightly different ways, as follows:

- Roche had a single group, mean age 11 years, weight 41 kg.
- Novartis had two groups, <35 and >35 kg. Weight and skin surface used for dosage of MMF were based on data for children aged 5, 10 and 15 years. Dosages were updated each year as children aged.
- Fujisawa/Astellas had two groups, aged <13 and 13–18 years (weights not given but appear to be mean 27.6 and 56.8 kg based on averaging the groups aged 3–13 and 13–18 years from the model) (or 33.4 and 58.4 kg if patients start in the model as stated by the company at ages 7 and 15 years).

The doses in terms of milligrams per unit patient weight per day as used by companies are summarised in *Table 53*.

None of the companies provided full rationales for their choice of ages/weights, with the exception of Fujisawa/Astellas, who relied, in the absence of UK data, on US data from DHSS, Centre for Disease Control data (p. 37 of the Fujisawa/Astellas submission). These data, excerpted from the Fujisawa/Astellas model, have been used to establish a mean weight for two groups of 27.6 and 56.8 kg, corresponding to the age groups 3–13 and 13–18 years, respectively. These are the two groups used in the BSAp model.

TABLE 53 *Summary of doses used in company models (Trompeter/Filler RCT[64] doses added for comparison)*

	Azathioprine (mg/kg/day)	Ciclosporin (mg/kg/day)	Tacrolimus (mg/kg/day)	MMF (mg/kg/day)
Roche	1.5	4	NA	1500
Novartis		7	0.2	1400
Fujisawa/Astellas <13 kg	2	7.9	0.2	NA
Fujisawa/Astellas >13 kg	2	5.3	0.2	NA
Trompeter/Filler RCT	1.8	7.03	0.21	NA

The dosages in the company submissions are based on two studies, Trompeter/Filler paediatric RCT, which compared TAS with CAS. This was used by both Novartis and Fujisawa/Astellas. A non-randomised study was used by Roche in its comparison of CMS with CAS, that of Staskewitz and colleagues.[96] The dosages of each of azathioprine, tacrolimus and MMF were consistent across the companies, but the dosage of ciclosporin was less so, for two reasons: different weights and claims for dose reduction by Roche when used with MMF.

The following doses were used in the BSAp model:

- Ciclosporin – based on Trompeter RCT: 7.03 mg/kg
- Tacrolimus – based on Trompeter RCT: 0.21 mg/kg
- MMF – based on Roche submission: 1500 mg daily as in Roche submission (similar to Novartis, 1400 mg)
- Azathioprine – based on Trompeter RCT: 1.8 mg/kg as in Trompeter RCT (agreed by all companies)
- Both basiliximab and and daclizumab are one-off treatments at a specified dose, taken as in the BNF.

MPS was not modelled, since it is not licensed for children.

Cost per milligram

The unit costs from the company models are shown in *Table 54*, along with estimates from BNF No. 49. Roche used eMimms, Novartis either BNF No. 48 or No. 49 (both are cited) and Fujisawa/Astellas used BNF No. 48. However, since several pill/vial sizes are priced in BNF, some assumptions are necessary. For these, the companies were considered to be the most reasonable source of information.

Table 54 summarises the unit costs used in the company models, the most recent net costs from BNF and the values used in the BSAp model. These are discussed below by drug:

- For ciclosporin, several unit costs exist by pill size in the BNF. The lower cost is close to that proposed by Roche, the higher identical with that from Novartis. BSAp uses both £0.027 in its base case and the higher cost in sensitivity analysis.
- For tacrolimus, the BNF ranges from £1.259 to £1.704, again based on 5- and 1-mg pill sizes, are both below that from Novartis of £1.850 and from Fujisawa/Astellas of £1.704. BSAp uses £1.7 per mg.
- For MMF, the BNF cost at £0.006 is double the Roche figure of £0.003. Fujisawa/Astellas and Novartis both used 0.005. BSAp uses £0.005 per mg and explores the lower Roche figure of 0.003 in sensitivity analysis.

For basiliximab, the BNF unit cost is from £42.119 based on a 20-mg vial within 2 hours before surgery and 4 days after surgery; the unit cost is £75.869 based on a 10-mg vial within 2 hours before surgery and 4 days after surgery. BSAp uses the Novartis figure of £42.119 based on BNF No. 48, that is before surgery, its main use.

For daclizumab, the BNF has £8.947 for a 5-mg transfusion. This is used in BSAp.

The dosages and unit costs for the BSAp model are shown in *Table 55*.

Results

The base-case incremental cost per QALY results for the BSAp model are summarised in *Table 56*.

The following subsections discuss the above BSAp cost-effectiveness results and contrast these with the company submissions.

BCAS versus CAS

The result here was a QALY gain of 0.07 at reduced cost, leading to dominance for BCAS over

TABLE 54 *Summary of drug unit prices in company models (£/mg)*

	Azathioprine	Ciclosporin	Tacrolimus	MMF	MPS	Basiliximab	Daclizumab
Roche	0.007	0.018	NA	0.003	NA	NA	NR
Novartis		0.027	1.850	0.005	NA	42.125	NA
Fujisawa/Astellas	0.004	0.017	1.704	0.005	NA	NA	NA
BNF							
Lower	0.004	0.017	1.259	0.006	0.00349	42.119	8.9472
Higher	0.013	0.027	1.704			75.869	
BSAp	0.004		1.704	0.005	0.005	42.119	8.9472

TABLE 55 *Dosages and unit costs in BSAp model*

	Dose (mg/kg/day)	Cost (£/mg)
Ciclosporin	7	0.017/0.027
Ciclosporin in CMS vs CAS	4	0.017/0.027
Tacrolimus	0.2	1.7
AZA	2	0.004
MMF	1500 (mg total)	0.005
Basiliximab	20 (mg total)	42.119
Daclizumab	1	8.9472

TABLE 56 *BSAp base-case cost per QALY results (£)*

	Mean	SD	ICER (mean)
CAS vs TAS			
Incremental cost	13,716	21,036	145,540/QALY
Incremental QALY	0.09	0.50	
CAS vs CMS			
Incremental cost	9,543	16,421	194,559/QALY
Incremental QALY	0.049	0.361	
CAS vs BCAS			
Incremental cost	–1.103	15,660	Dominant
Incremental QALY	0.074	0.37	
CAS vs DCAS			
Incremental cost	–417	15,079	Dominant
Incremental QALY	0.05	0.36	
TAS vs BTAS			
Incremental cost	–451	12,055	Dominant
Incremental QALY	0.038	0.31	

CAS. This result was similar to that of the Novartis model and the adult BSA model.

BTAS versus TAS

BTAS resulted in a mean QALY gain of 0.04 at a reduced cost.

DCAS versus CAS

The result of this comparison was a QALY gain of 0.05 with DCAS and cost reduction leading to dominance. The result is similar to that of the company model and to the model for adults.

TAS versus CAS

The BSAp model generated a QALY gain in favour of TAS of 0.09 over 10 years at an increased cost of about £13,700,000, leading to a mean ICER of about £145,500/QALY. This ICER was well above the company (Fujisawa/Astellas) model which, when side-effects were included, reported an ICER of £18,000–31,000/QALY. However, when side-effects were excluded, the company model had an ICER £119,000–147,000/QALY. Since the BSAp model does not include side-effects, the relevant comparison is with the latter figures. The remaining ICER difference between BSAp and the company model is likely to be due mainly to the different acute rejection rates used in the two models. BSAp used BPAR results (CAS 40% versus TAS 17%) whereas Fujisawa/Astellas used clinical acute rejection rates (TAS 41.5% versus CAS 67.7% for the 13–18-year-old age group), which varied by age group, and by each of the 10 years post-transplantation. The Fujisawa/Astellas model also used somewhat different costs.

The other relevant comparison is with the adult BSA model results, which indicated that tacrolimus was dominant over ciclosporin. However, it is important to note that this BSAp analysis was based on a different HR and different levels of acute rejection. Although the QALY gain in the adult model of 0.11 was similar to that in the paediatric model, the costs of a tacrolimus-based regimen were reduced in the adult model but increased in the paediatric model. The cost changes reflect recent changes in the prices of the

drugs, particularly ciclosporin, the price of which was reduced by 33% between 2003 and 2005, compared with a price cut of 8% for tacrolimus.

CMS versus CAS

The result here is a high mean ICER for CMS compared with CAS of about £195,000/QALY due to a small QALY gain of 0.05 and increased cost of about £16,421.

This contrasts with the Roche submission, which reported CMS as dominant over CAS. When the Roche input values were fed into BSAp, CMS was also found to be dominant. The difference in ICERs was due to Roche's use of the adult HR (1.96) and much higher clinical acute rejection levels than the BPAR figures used in the BSAp model. The BSAp result is broadly similar to that obtained for the BSA model in adults, which gave an ICER of £134,000 based on a QALY gain of 0.07 at an increased cost of £10,000.

The adult renal immunosuppressives appraisal included a BSA model analysis of the CMS versus CAS allowing for ciclosporin sparing with MMF. Limited evidence for a ciclosporin sparing was presented in the Roche submission for this appraisal. However, the Roche economic evaluation of CMS versus CAS in children did not include ciclosporin sparing.

Sensitivity analyses

Sensitivity analyses were conducted to assess the robustness of the base-case results to uncertainty in three parameters: (1) HR of acute rejection; (2) inclusion of side-effects; and (3) dialysis costs.

Varying hazard ratios

In the base-case analysis, the HR for graft loss for acute rejection (1.41) was sourced from a single paediatric observational study. Based on a pooled analysis of adult observational studies, an alternative HR of 1.96 was obtained. The ICERs for each of the drug regimens appeared to decrease slightly with the higher HR (see *Table 57*) although the ICERs for TAS versus CAS and CMS versus CAS remain well above £40,000/QALY.

Incorporating side-effects

The systematic review sought the following side-effects for each drug comparison: CMV infection, PTDM, hyperlipidaemia and PTLD (side-effect categories agreed in consultation with clinical advisors). Although chosen as they represent the more important side-effects, it is recognised that other side-effects are possible, many which are drug specific. Aware of the number of potential side-effects and their varying degrees of impact on children, the authors wanted to derive some 'overall' measure of the negative impact of side-effects in relation to switching drug regimens. Since little information was reported on switching due to adverse events, withdrawal due to adverse events was used as the measure of the overall impact of side-effects in the modelling of cost-effectiveness.

TABLE 57 *Sensitivity analysis – varying hazard ratio*

	ICER (mean) (£/QALY)
CAS vs TAS	
HR 1.41	145,540
HR 1.96	58,801
CAS vs CMS	
HR 1.41	194,559
HR 1.96	76,958
CAS vs BCAS	
HR 1.41	Dominant
HR 1.96	Dominant
CAS vs DCAS	
HR 1.41	Dominant
HR 1.96	Dominant
TAS vs BTAS	
HR 1.41	Dominant
HR 1.96	Dominant

The systematic review revealed few statistically significant side-effect differences for between-drug regimens. Three differences were identified: (1) an increase in the level of PTDM with tacrolimus compared with ciclosporin (6.1 versus 2.6% at 1 year; see *Table 26*, assessment report); (2) an increase in CMV infection with MMF compared with azathioprine (15.3 versus 11.3%; see *Table 31*, assessment report); and (3) an increase in the level of hyperlipidaemia with sirolimus compared with either azathioprine or ciclosporin (35 versus 23% and 44 versus 14%; see *Tables 44* and *46*, assessment report). Only in the case of tacrolimus (versus ciclosporin) was a statistically significant difference found in the withdrawal due to adverse events. The paediatric trial of Trompeter/Filler reported a significantly lower level of total withdrawal in the TAS group than the CAS group (22 versus 37%, *Table 22*). This benefit of tacrolimus was supported by the findings of a lower level of patient switching due to adverse events in the adult trials (1.1 versus 11.1%, from *Table 26*).

Given the findings from our systematic review, it was concluded that the incorporation of side-

effects in the BSAp model was only necessary for the comparison of TAS with CAS. The ICERs for the other drug comparisons are therefore as reported previously (see revised tables, *Tables 56* and *57*).

The adult BSA model was designed to incorporate side-effects. Side-effects were assumed to lead to switching of drugs. However, lack of relevant data by drug prevented full use of this facility. Instead, side-effects were assumed to occur in a fixed percentage of patients with a penalty in terms of loss of quality of life and cost. Default values were set at 10% of patients, the quality of life or utility loss was set to 0.1 QALY and the cost penalty was set to £200 (rationale – limited to one cycle and assuming side-effects are remedied by the switch). The penalties applied only to one cycle (year), after which a drug switch was assumed to restore the quality of life to the original state before side-effects.

In their children's submission, Fujisawa/Astellas assumed that the switch due to side-effects would occur during every cycle of their model. In other words, the utility and cost penalty resulting from side-effects occurred every subsequent cycle post-switch. For the BSAp model, we felt that the more clinically realistic approach was to assume a switch in the initial cycle of the model only. Thus the utility loss of 0.1 QALY was assumed to occur only in the first year. For costs, it was assumed that once switched, patients would pick up the new drug cost associated with their switch, that is, patients switching from tacrolimus to ciclosporin pick up the cost of ciclosporin and vice versa. This approach to costs gets around the difficulty of arriving at the cost of treating specific side-effects. In effect, the assessment group model assumed that the switch 'cures' the side-effects.

Two rates of switching were taken from the systematic review: 22.3% of tacrolimus patients switch to ciclosporin and 36.6% of CAS patients switch to TAS (based on total withdrawal data) or 9.7 versus 15.0% (based on withdrawal due to adverse events). Drug costs were taken as before (see *Tables 54* and *55*).

The ICER was highly sensitive to the incorporation of side-effects, decreasing to a value of about £46,000/QALY when side-effects were included (*Table 58*). Both the Fujisawa/Astellas and assessment group models therefore agree in that they show a reduction in the TAS versus CAS ICER when side-effects are considered. However, given the difference in the way in which side-effects were modelled, the mean ICER of the assessment group model (£46,000/QALY) is higher than that estimated by the Fujisawa/Astellas model (£18,000–31,000/QALY).

Varying dialysis costs

We explored the impact on ICERs of increasing the annual cost of dialysis for paediatric patients from £21,000 to £50,000 and to £80,000. The rationale is that dialysis of paediatric patients tends to have much higher staff-to-patient ratios. Increasing the cost of dialysis would be expected to reduce the ICER by reducing the incremental cost.

The results (*Table 59*) show that for TAS compared with CAS, the ICER fell from £146,000 to £121,000 with dialysis at £50,000 and to £102,000 with dialysis at £80,000. For CMS compared with CAS, the ICER fell from £195,000 to £173,000 with dialysis at £50,000 and to £123,000 with dialysis at £80,000. These figures are without side-effects, which, if included, reduce the ICER for TAS versus CAS to £26,000 at a dialysis cost of £50,000 and to £11,000 at a dialysis cost of £80,000.

General discussion of economic results

As with the BSA results for the adult model, the QALY differences estimated by the BSAp model for children are very small and ranged from 0.002 to 0.15 over 10 years. Such small differences combined with relatively small drug price

TABLE 58 *Sensitivity analysis for CAS versus TAS – incorporation of side-effects*

	Mean difference		ICER (mean) (£/QALY)
	Cost (£)	QALY	
No side-effects	13,716	0.09	145,540
With side-effects:			
22/37%	5,475	0.12	45,753
9.7/15%			92,000

TABLE 59 *Sensitivity analysis – varying dialysis cost*

Dialysis cost (£)	No side-effect: ICER TAS vs CAS (£)	No side-effects: ICER CMS vs CAS (£)	With side-effects: ICER TAS vs CAS (£)
21,000	146,000	195,000	46,000
50,000	121,000	173,000	26,000
80,000	102,000	123,000	11,000

differences for most comparisons can generate ICER values which are unstable and subject to large fluctuations.

Although the price of most drugs compared were relatively similar (ciclosporin, tacrolimus, sirolimus and MMF all cost between £2000 and 3000), one drug, azathioprine, had a much lower cost. Thus the comparison of CMS with CAS involved MMF at a cost per year of £2190 and azathioprine at a cost of £86, a 26-fold difference. A very large advantage in terms of acute rejection would be required to generate a favourable ICER. The BSAp model suggested a high ICER for CMS over CAS of £160,000, not dissimilar to the adult model ICER of approximately £134,000. The company submission claimed dominance for CMS but, as noted above, this was based on questionable acute rejection differences sourced from an observational study. It was also based on an adult rather than paediatric HR.

Summary

- Three companies (Fujisawa/Astellas, Novartis and Roche) submitted economic models based on the assessment group's adult BSA model. These submissions undertook cost-effectiveness analyses for basiliximab (BCAS), tacrolimus (TAS), daclizumab (DCAS) and MMF (CMS) compared with CAS.
- The main adjustment for paediatric patients had to do with dose, which was adjusted to age in both the company and the assessment group's paediatric version of the BSA model (BSAp). This entailed reduced dosages and hence costs in younger age groups.
- All the company models produced results that demonstrated their drug to be either dominant compared with a regimen of CAS or to have an ICER of less than £30,000/QALY compared with CAS.
- The assessment group BSAp obtained results compared with CAS that confirmed the company conclusions that the addition of basiliximab (BCAS) or daclizumab (DCAS) compared with CAS was dominant (i.e. improves QALYs and reduces costs). However, the ICERs associated with CMS versus CAS and TAS versus CAS were all relatively unattractive and exceeded £30,000/QALY. These results were robust to the uncertainty in the HR for acute rejection. The addition of basiliximab was also dominant when compared with a TAS regimen.

TABLE 60 *Summary of parameter values used in BSAp model*

	CAS	Comparator	Source	Range of values used in sensitivity analysis
Risk of BPAR				
CAS vs TAS	0.400	0.170	Assessment group meta-analysis	
CAS vs TMS	0.326	0.185	Assessment group meta-analysis	
CAS vs BCAS	0.368	0.224	Assessment group meta-analysis	
CAS vs DCAS	0.351	0.222	Assessment group meta-analysis	
CAS vs RCAS	0.134	0.123	Assessment group meta-analysis	
TAS vs BCAS	0.200	0.186	Assessment group meta-analysis	
	Age ≤ 13 years	*Age >13 years*		
Costs (£)				
CAS	2,535	4,241	BNF	
TAS	4,500	7,668	BNF	
CMS	5,410	6,346	BNF	
CMS at reduced MMF costs	2,290	5,453	BNF	
Acute rejection episode	4,644	4,644	BNF	
Dialysis	21,060	21,060	BNF	50,000 and 80,000
Utility				
Functioning graft	0.75		Adult assessment report[22]	
Dialysis	0.50		Adult assessment report[22]	
Side-effect	–0.1		Adult assessment report[22]	
Mortality				
Probability of mortality due to graft failure	0.40		Adult assessment report[22]	
Probability of death at dialysis rate	0.0835		Adult assessment report[22]	
Hazard ratio of graft loss with acute rejection episode	1.41 (95% CI: 1.15 to 1.74)		Ishitani *et al.*[29]	1.99
Discounting (%)	1.5 outcomes and 6 costs		NICE guidance	

Chapter 5

Assessment of factors relevant to the NHS and other parties

Kidney transplantation is the treatment of choice for patients with ESRF. If successful, the quantity and quality of life are better than those achieved with long-term dialysis. Given the finite supply of donors, there is therefore a need to identify drug therapies that minimise short-term immunosuppression and maximise the life of the graft.

In September 2004, the NICE issued guidance for the use of newer immunosuppressive drugs in renal transplant recipients. This guidance focused on adults. A recent audit of UK paediatric transplant centres indicates there to be a range of immunosuppressive drug regimens currently being used in children following kidney transplant.[8]

Neither MPS nor sirolimus is currently licensed in the UK for paediatric renal transplant use. Most of the newer immunosuppressants are currently licensed for use in specific combinations and indicated for use in specific combination regimens.

Chapter 6
Discussion

The purpose of this report was to assess the clinical and cost-effectiveness of the newer immunosuppressive agents (basiliximab, daclizumab, tacrolimus, MMF, MPS and sirolimus) for children with kidney transplants.

Main findings

Clinical effectiveness

A relatively small body of RCT evidence was found to exist for the use of the newer immunosuppressive drugs in paediatric renal transplant recipients ('level-1 evidence'). One published RCT compared tacrolimus with ciclosporin and two unpublished RCTs assessed the addition of basiliximab to tacrolimus-based triple therapy and the addition of sirolimus to ciclosporin-based triple or dual therapy alone. For MMF, daclizumab and other applications of sirolimus, only adult RCT evidence ('level-2 evidence') was available. Where possible, non-randomised comparative studies in children ('level-3 evidence') were sought to support the findings of adult-only RCT evidence.

The principal clinical findings by drug regimen of this report can be summarised as follows:

- **Addition of basiliximab (BCAS versus CAS and BTAS versus TAS)**
  [One paediatric RCT; four adult RCTs; six non-randomised comparative studies]
  An unpublished paediatric RCT reported that the addition of basiliximab to TAS (i.e. BTAS versus TAS) failed to improve significantly 6-month BPAR (RR 0.83, 95% CI: 0.53 to 1.65), graft function, graft loss or all-cause mortality **[Confidential information removed]**. No statistically significant difference between groups was seen in either 6-month or 1-year or longer graft loss, all-cause mortality and side-effects. In a meta-analysis of adult RCTs, the addition of basiliximab to CAS (i.e BCAS versus CAS) significantly reduced short-term BPAR (RR 0.61, 95% CI: 0.46 to 0.80). There was no significant difference in short- or long-term graft loss, all-cause mortality or side-effects between the BCAS and CAS groups.
- **Addition of daclizumab (DCAS versus CAS)**
  [One adult RCT]
  The addition of daclizumab to CAS (i.e. DCAS versus CAS) reduced 1-year BPAR (RR 0.63, 95% CI: 0.42 to 0.94) in adults. No difference between groups was seen in either 1- or 3-year graft loss, all-cause mortality or side-effects.
- Tacrolimus versus ciclosporin (TAS vs CAS)
  [One paediatric RCT; nine adult RCTs; two paediatric non-randomised comparative studies]
  A published paediatric RCT found tacrolimus to reduce 6-month BPAR (0.42, 95% CI: 0.25 to 0.68) and improve graft function (GFR) compared with ciclosporin (i.e. TAS versus CAS). The improvement in BPAR with tacrolimus was also shown in the meta-analysis of adult RCTs of TAS versus CAS. There was evidence, particularly in children, that in comparison with CAS, TAS may reduce long-term graft loss, although there is no benefit for total all-cause mortality. The level of withdrawal due to adverse events was reduced in children receiving TAS compared with CAS. Adult RCTs show an increase in PTDM with TAS.
- **MMF versus azathioprine (CMS versus CAS)**
  [Seven adult RCTs; three paediatric non-randomised comparative studies]
  A meta-analysis of adult RCTs showed MMF to reduce 1-year BPAR (pooled RR 0.60, 95% CI: 0.47 to 0.76) compared with azathioprine (i.e. CMS versus CAS). There was no significant difference in either short- or long-term all-cause mortality or graft loss. There was an increase in the level of CMV infection with CMS, although the overall level of withdrawal due to adverse events was not different from that of azathioprine-treated individuals. In children, CMS appears to improve 1-year or longer graft survival.
- **MPS versus azathioprine (CMsS versus CAS)**
  [No comparative evidence]
  One adult RCT compared MMF with MPS (i.e. CMsS versus CMS). There was no significant difference between groups in 1-year efficacy or side-effect outcomes.
- **Sirolimus [RCAS versus CAS; RAS versus CAS; CRS versus CAS]**
  [One paediatric RCT; three adult RCTs]
  One unpublished paediatric RCT assessed the addition of sirolimus (Rapamune) to CAS (i.e.

RCAS versus CAS). BPAR, graft loss and all-cause mortality were not reported. No significant differences between groups were seen in graft function or side-effects. Two adult RCTs compared sirolimus with azathioprine (i.e. CRS versus CAS). Compared with CAS, CRS reduced 1-year BPAR (pooled RR: 0.60, 95% CI: 0.45 to 0.80), reduced graft function (as assessed by an increased serum creatinine) and increased the level of hyperlipidaemia. No significant differences were seen in other efficacy and side-effect outcomes. One adult RCT compared sirolimus with ciclosporin (i.e. RAS versus CAS). There were no significant differences between groups in 1-year efficacy or side-effects, with the exception of an increased level hyperlipidaemia with RAS.

These efficacy and side-effect findings of paediatric and adult RCTs were generally supported by the findings of non-randomised comparative studies where they were available.

Cost-effectiveness

Both the assessment group and the drug companies assessed the cost-effectiveness of the newer renal immunosuppressants in children using an adaptation of the BSA decision analytic model (a model initially developed by the assessment group to inform NICE's guidance on the use of the newer renal immunosuppressive drugs for adult renal transplant recipients). Neither MPS nor sirolimus was modelled as neither is currently licensed in children. The assessment group's BSAp economic model was adapted from the original BSA model in three principal ways: (1) use of a paediatric-specific HR; (2) sourcing of 12-month BPAR levels from RCT evidence in the paediatric population (level-1 evidence); and (3) adjustment of drug dosages (and costs) to reflect licensed indications and also age/weight/body surface area of children. Where paediatric RCT evidence was not available (i.e. MMF, daclizumab and two drug regimens for the use of sirolimus), BPARs were sourced from adult RCT(s) (level-2 evidence). The addition of both basiliximab and daclizumab to CAS increased QALYs and decreased overall costs, a finding that is robust to sensitivity analyses. The ICER of replacing ciclosporin with tacrolimus was highly sensitive to the selection of the HR for graft loss from acute rejection, dialysis costs and the incorporation of side-effects. The ICERs for tacrolimus versus ciclosporin ranged from about £46,000 to about £146,000/QALY. Although sensitive to varying the HR for graft loss with acute rejection, the ICER for replacing azathioprine with MMF remained in excess of £55,000/QALY.

The company models presented cost-effectiveness analyses for the following regimens in children: BCAS versus CAS, DCAS versus CAS, TAS versus CAS and CMS versus CAS. The company model indicated the regimens with their drug to be either 'dominant' (i.e. improved QALYs and reduced costs) or have an ICER below £30,000/QALY. Although the BSAp and company models concur for BCAS, DCAS and TAS versus CAS, this critique of the company's estimate of CMS versus CAS indicates that it is likely to be overoptimistic, driven by inappropriate selection of BPAR levels and drug doses (costs).

Strengths, limitations and uncertainties

This report has two major strengths:

- **Comprehensiveness** – This report undertook a detailed systematic review of the impact of immunosuppressive drugs in children with kidney transplants. Both RCT and non-randomised comparative evidence were sought and, where located, included.
- **Economic model** – A decision analytic (BSA) model was previously developed by the assessment group to explore the cost-effectiveness of the newer renal immunosuppressant drugs in adults. This model allows a synthesis of clinical outcomes and costs within an explicit framework in order to assess the cost–utility of various drug regimens. Both the assessment group and drug manufacturers used the BSA model. We adapted the BSA model to a paediatric population (BSAp) and, where possible, used paediatric-specific outcome and cost input data.

In contrast, certain limitations were placed on this report:

- **Paediatric RCT evidence** – Both the number and coverage of RCTs in children were limited. Clinical outcome findings from RCTs in adults were used in the cost model where no paediatric RCT data were available (i.e. for MMF and daclizumab). The extrapolation of adult evidence to children with the assumption that children are therefore simply 'small adults' is open to criticism. Tacrolimus and ciclosporin, where RCT evidence was available in both children and adults, provides support for this

TABLE 61 *One-year BPAR for tacrolimus versus ciclosporin – comparison of data sources*

	No. of RCTs	Tacrolimus, *n*/*N* (%)[a]	Ciclosporin, *n*/*N* (%)[a]	RR (95% CI)
Paediatric RCT:				
TAS vs CAS	1	17/103 (17%)	37/93 (40%)	0.41 (0.25 to 0.68)
TAS vs BTAS	1	19/95 (20%)	NA	NA
Adult RCTs:				
TAS vs CAS	6	213/848 (25%)	261/650 (40%)	0.61 (0.53 to 0.71)

[a] Combined with azathioprine and a steroid.

approach. *Table 61* shows that the absolute levels of BPAR with TAS and CAS and RR of BPAR between the two drugs were broadly comparable across the two possible sources of RCT evidence.

- **Choice of comparator** – The majority of comparative regimens used in the paediatric RCTs and non-RCTs were ciclosporin combined with azathioprine plus steroid (CAS). The inclusion of adult RCTs was limited to the inclusion of CAS comparators. However, UK practice is increasingly moving towards the routine use of the 'newer' immunosuppressive agents (particularly tacrolimus and MMF). Therefore, CAS may no longer be reflective of current practice of a number of UK paediatric transplant units. In the previous assessment report undertaken by this group, it was found that the magnitude of treatment benefit (as assessed by BPAR) diminished with the addition of more active comparators, for example the absolute risk reduction of TAS compared with CAS was less than TMS compared with CMS.[22] Indeed, in this review a paediatric RCT of BTAS comparing TAS reported no improvement in short-term BPAR. The effect of including other comparative regimens would therefore be to make the relative cost-effectiveness of the newer immunosuppressive agents less attractive than that estimated with CAS.
- **Surrogate outcomes** – The short duration of follow-up of RCTs necessitated the prediction of long-term graft loss and all cause mortality from 1-year BPAR. The authors of this report updated a previous systematic review of the literature in order to source the predictive value of BPAR associated with children [see the section 'Surrogate outcomes and prediction of long-term graft survival' (p. 6)]. We found insufficient evidence to support the predictive use of graft function outcomes (i.e. serum creatinine and GFR).
- **Side-effects** – Side-effects were generally poorly reported in both RCTs and non-randomised comparative studies. It is difficult to quantify the range of side-effects of a given drug into a single estimate. However, in order to assess the potential overall effects of side-effects of TAS and CAS (where there was evidence of a significant difference), we used both the proportion of overall withdrawals and the withdrawals due to adverse events from the Filler trial.[31] Sensitivity analysis was used to assess the effect of incorporating drug side-effects in the BSAp model.
- **Compliance** – It is widely recognised that compliance with medication is a major problem with transplant patients, the problem being greatest amongst the adolescent population. Non-compliance with immunosuppressive therapy is reported to be the commonest cause of late graft loss, with 15–16% of children losing their graft for this reason.[16] The problem of compliance appears to be greatest with those medications that are complex to administer or are associated with adverse side-effects. Those drugs with cosmetic side-effects, such as cushingoid face, acne and hirsutism, are likely to be a particular source of distress to some children and adversely compromise their compliance. Compliance is therefore a potentially important driver of the cost-effectiveness of immunosuppressive regimens. However, drug compliance was not included in the cost modelling in this report, for two reasons. First, compliance with drug immunosuppressive regimens was very poorly reported, if reported at all, across the various clinical studies included in this report. Second, drug compliance is likely to be higher in the clinical trials than the 'real world' setting. Therefore, it could be argued that the cost-effectiveness estimates based on the trial efficacy results are likely to be more optimistic than if compliance had been formally included within the model. Nevertheless, we believe the differential effect of compliance between drug regimens to have a relatively small effect on the ICERs reported here.

Other relevant issues

It is recognised that there are potentially numerous permutations for the use of newer immunosuppressant drugs, particularly when combined with calcineurin sparing or steroid sparing. For example, a recent review of immunosuppressive drugs in renal recipients in children reported that the preliminary reports from centres using steroid-free immunosuppression appeared 'promising'.[108] This regimen was associated with low acute rejection rates, excellent short-term graft and patient survival and marked improvements in growth. However, these benefits came at the expense of the use of relatively more intensive tacrolimus, MMF and sirolimus therapy.

The clinical and cost-effectiveness of the impact of calcineurin- or steroid-sparing strategies were not assessed by this report.

Suggested research priorities

In undertaking this report of newer immunosuppressants for renal transplantation in children, three particular areas for future research were identified, in order of priority:

- **Further RCT evidence** – This report has shown that RCTs of newer immunosuppressant drugs are feasible in children with kidney transplants. There is a particular need for multicentre/multinational RCTs to assess the use of MMF, MPS and daclizumab where no paediatric RCT evidence currently exists. In addition, future paediatric trials need to examine the effectiveness of steroid-free strategies, particularly in terms of growth and the need for immunosuppressive co-therapies.
- **Long-term outcomes** – The main challenges in paediatric transplantation are maintaining and improving growth, improving compliance, reducing adverse effects and minimising chronic decline in graft function. Therefore, studies of much longer outcome measures of the newer drugs are needed.
- **Additional economic evaluations** – This report did not identify any published economic evaluations of the use of the newer immunosuppressants for renal transplantation in children. Future trials need to assess (and report) not only the impact of the newer immunosuppressants on clinical outcomes (including side-effects) but also on drug compliance, healthcare resource(s) and costs. With the increasing reliance of policy-makers on cost–utility evidence, there is a particular need for collection of health-related quality of life data.

Chapter 7
Conclusions

We found limited RCT evidence of the benefits and harms of the use of newer immunosuppressive agents (basiliximab, daclizumab, MMF, MPS, tacrolimus and sirolimus) in children with kidney transplants although, in some cases, there was instead evidence from non-randomised comparative studies in children and RCTs in adults. In general, compared with a regimen of ciclosporin, azathioprine and steroid, the newer immunosuppressive agents consistently reduce the incidence of short-term BPAR. However, evidence of the impact on side-effects, long-term graft loss, compliance and overall health-related quality of life is limited. Cost-effectiveness was estimated based on the relationship between short-term acute rejection levels from RCTs and long-term graft loss. The additions both of daclizumab and basiliximab were found to be dominant strategies, that is, cost saving and with increased QALYs. The incremental cost-effectiveness of tacrolimus relative to ciclosporin was highly sensitive to key model parameter values and therefore may well be a cost-effective strategy. The incremental cost-effectiveness of MMF compared with azathioprine, although also sensitive to model parameters, was unattractive.

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Contribution of authors

Esther Albon (Systematic Reviewer), Yaser Adi (Systematic Reviewer) and Rod Taylor (Reader) applied the inclusion and exclusion criteria to the clinical studies, extracted data, appraised studies and conducted meta-analyses. Sue Bayliss (Information Specialist) carried out the searches. David Milford (Consultant Paediatric Nephrologist) wrote the introduction and background and advised on clinical aspects of the report. Andrew Ready (Consultant Surgeon) also provided clinical advice. Guiqing Yao (Health Economist) adapted the Birmingham Sensitivity Analysis model to children and populated and ran the model. James Raftery (Professor of Health Economics) advised on the modelling and appraised the industry models. All authors contributed to the writing and editing of the report.

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Appendix 1

Search strategies for surrogates review

Database: MEDLINE (Ovid) 1966 to April week 4 2005

1 exp Kidney Transplantation/ or kidney transplant.mp.
2 (renal adj transplant$).mp.
3 (kidney adj transplant$).mp.
4 or/1-3
5 exp Graft Rejection/
6 exp Graft Survival/
7 exp Survival Rate/
8 exp Treatment Outcome/
9 acute rejection.mp.
10 (long adj term adj1 rejection).mp.
11 or/5-10
12 exp "Predictive Value of Tests"/ or predictive value.mp.
13 marker$.mp. or exp Genetic Markers/
14 (predict$ adj3 survival).mp.
15 predictor$.mp.
16 (risk adj3 loss).mp.
17 (monitor$ adj function$).mp.
18 (surrogate adj marker$).mp.
19 exp Glomerular Filtration Rate/ or gfr.mp.
20 (creatinine adj3 rejection).mp.
21 or/12-20
22 4 and 11
23 22 and 21
24 child$.mp. or exp CHILD/
25 exp ADOLESCENT/ or adolescent$.mp.
26 or/24-25
27 23 and 26
28 limit 27 to yr=1993 - 2005

Database: EMBASE (Ovid) 1980 to 2005 week 19

1 kidney transplant$.mp. or exp Kidney Graft/
2 (renal adj transplant$).mp.
3 (kidney adj graft$).mp.
4 or/1-3
5 exp Graft Rejection/
6 exp Graft Survival/
7 exp Survival Rate/
8 exp Treatment Outcome/
9 (acute adj rejection).mp.
10 (long adj term adj1 rejection).mp.
11 or/5-10
12 predictive value.mp.
13 exp GENETIC MARKER/ or marker$.mp. or exp MARKER/
14 (predict$ adj3 survival).mp.
15 predictor$.mp.
16 exp Risk Factor/
17 (risk adj3 loss).mp.
18 (monitor$ adj function$).mp.
19 (surrogate adj marker$).mp.
20 exp Glomerulus Filtration Rate/ or gfr.mp.
21 (creatinine adj3 rejection).mp.
22 or/12-21
23 4 and 11
24 22 and 23
25 Child/
26 Adolescent/
27 or/25-26
28 24 and 27
29 limit 28 to yr=2000 - 2005

Appendix 2

Search strategies for systematic reviews, RCTs and economic evaluations

Scoping searches – systematic reviews

Database: MEDLINE (Ovid) 1966 to October week 4 2004

1 daclizumab.mp.
2 basiliximab.mp.
3 mycophenolate.mp.
4 exp TACROLIMUS/ or tacrolimus.mp.
5 zenapax.mp.
6 simulect.mp.
7 cellcept.mp.
8 myfortic.mp.
9 prograf.mp.
10 rapamycin.mp.
11 mmf.mp.
12 fk506.mp.
13 (kidney$ adj transplant$).mp.
14 (renal adj transplant$).mp.
15 exp Kidney Transplantation/ or kidney transplantation.mp.
16 or/13 - 15
17 or/1-12
18 16 and 17
19 (systematic adj review$).tw.
20 (data adj synthesis).tw.
21 (published adj studies).ab.
22 (data adj extraction).ab.
23 meta-analysis/
24 meta-analysis.ti.
25 comment.pt.
26 letter.pt.
27 editorial.pt.
28 animal/
29 human/
30 28 not (28 and 29)
31 18 not (25 or 26 or 27 or 30)
32 or/19-24
33 31 and 32

Database: Cochrane Library (Update Software) 2004 Issue 4

#1 renal next transplant*
#2 kidney next transplant*
#3 exp kidney transplantation/
#4 (#1 or #2 or #3)
#5 daclizumab
#6 basiliximab
#7 mycophenolate
#8 tacrolimus
#9 zenapax
#10 simulect
#11 cellcept
#12 myfortic
#13 prograf
#14 rapamycin
#15 mmf
#16 fk506
#17 exp tacrolimus/
#18 interleukin
#19 (#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18)
#20 #19 and #4

Main search strategies – clinical effectiveness

Database: MEDLINE (Ovid) 1966 to November week 3 2004

1 daclizumab.mp.
2 basiliximab.mp.
3 mycophenolate.mp.
4 exp TACROLIMUS/ or tacrolimus.mp.
5 zenapax.mp.
6 simulect.mp.
7 cellcept.mp.
8 myfortic.mp.
9 prograf.mp.
10 rapamycin.mp.
11 mmf.mp.
12 fk506.mp.
13 (kidney$ adj transplant$).mp.
14 (renal adj transplant$).mp.
15 exp Kidney Transplantation/ or kidney transplantation.mp.
16 or/13-15
17 or/1-12
18 16 and 17
19 randomized controlled trial.pt.
20 controlled clinical trial.pt.

21 randomized controlled trials.sh.
22 random allocation.sh.
23 double blind method.sh.
24 single-blind method.sh.
25 or/19 - 24
26 (animals not human).sh.
27 25 not 26
28 clinical trial.pt.
29 exp clinical trials/
30 (clin$ adj25 trial$).ti,ab.
31 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
32 placebos.sh.
33 placebo$.ti,ab.
34 random$.ti,ab.
35 research design.sh.
36 or/28 - 35
37 36 not 26
38 37 not 27
39 27 or 38
40 18 and 39
41 limit 40 to yr=2002-2004

Database: MEDLINE (Ovid) In-Process and Other Non-Indexed Citations 3 December 2004

1 daclizumab.mp.
2 basiliximab.mp.
3 mycophenolate.mp.
4 exp TACROLIMUS/ or tacrolimus.mp.
5 zenapax.mp.
6 simulect.mp.
7 cellcept.mp.
8 myfortic.mp.
9 prograf.mp.
10 rapamycin.mp.
11 mmf.mp.
12 fk506.mp.
13 (kidney$ adj transplant$).mp.
14 (renal adj transplant$).mp.
15 exp Kidney Transplantation/ or kidney transplantation.mp.
16 or/13-15
17 or/1-12
18 16 and 17
19 randomi?ed.ti,ab.
20 18 and 19

Database: EMBASE (Ovid) 1980 to 2004 week 48

1 randomized controlled trial/
2 exp clinical trial/
3 exp controlled study/
4 double blind procedure/
5 randomization/
6 placebo/
7 single blind procedure/
8 (control$ adj (trial$ or stud$ or evaluation$ or experiment$)).mp.
9 ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).mp.
10 (placebo$ or matched communities or matched schools or matched populations).mp.
11 (comparison group$ or control group$).mp.
12 (clinical trial$ or random$).mp.
13 (quasiexperimental or quasi experimental or pseudo experimental).mp.
14 matched pairs.mp.
15 or/1-14
16 (kidney$ adj transplant$).mp.
17 (renal adj transplant$).mp.
18 exp KIDNEY TRANSPLANTATION/
19 or/16-18
20 daclizumab.mp. or exp DACLIZUMAB/
21 basiliximab.mp. or exp BASILIXIMAB/
22 mycophenolate.mp.
23 mycophenolate mofetil.mp. or exp Mycophenolic Acid 2 Morpholinoethyl Ester/
24 tacrolimus.mp. or exp Tsukubaenolide/
25 zenapax.mp.
26 simulect.mp.
27 cellcept.mp.
28 myfortic.mp.
29 prograf.mp.
30 rapamycin.mp. or exp RAPAMYCIN/
31 mmf.mp.
32 fk506.mp.
33 or/20-32
34 15 and 19 and 33
35 limit 34 to yr=2002-2004

Database: CINAHL (Ovid) Cumulative Index to Nursing and Allied Health Literature 1982 to November week 4 2004

1 randomized controlled trial/
2 exp clinical trial/
3 (kidney$ adj transplant$).mp.
4 (renal adj transplant$).mp.
5 exp KIDNEY TRANSPLANTATION/
6 or/3-5
7 or/1-2
8 daclizumab.mp.
9 basiliximab.mp.
10 exp MYCOPHENOLATE MOFETIL/ or mycophenolate.mp.
11 tacrolimus.mp.
12 zenapax.mp.
13 simulect.mp.
14 cellcept.mp.
15 myfortic.tw.
16 prograf.mp.
17 rapamycin.mp.
18 mmf.mp.

19 fk506.mp.
20 or/8-19
21 6 and 7 and 20
22 6 and 20

Cochrane Library (Update Software) 2004 Issue 4

#1 (renal next transplant*)
#2 (kidney* next transplant*)
#3 KIDNEY TRANSPLANTATION
#4 (#1 or #2 or #3)
#5 daclizumab
#6 basiliximab
#7 mycophenolate
#8 tacrolimus
#9 zenapax
#10 simulect
#11 cellcept
#12 myfortic
#13 prograf
#14 rapamycin
#15 mmf
#16 fk506
#17 TACROLIMUS
#18 interleukin
#19 (#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18)
#20 (#19 and #4)

Main search strategies – cost-effectiveness

Database: MEDLINE (Ovid) 1966 to November week 3 2004

Search strategy: cost
1 daclizumab.mp.
2 basiliximab.mp.
3 mycophenolate.mp.
4 exp TACROLIMUS/ or tacrolimus.mp.
5 zenapax.mp.
6 simulect.mp.
7 cellcept.mp.
8 myfortic.mp.
9 prograf.mp.
10 rapamycin.mp.
11 mmf.mp.
12 fk506.mp.
13 (kidney$ adj transplant$).mp.
14 (renal adj transplant$).mp.
15 exp Kidney Transplantation/ or kidney transplantation.mp.
16 or/13-15
17 or/1-12
18 16 and 17
19 economics/
20 exp "costs and cost analysis"/
21 cost of illness/
22 exp health care costs/
23 economic value of life/
24 exp economics medical/
25 exp economics hospital/
26 economics pharmaceutical/
27 exp "fees and charges"/
28 (econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw.
29 (expenditure$ not energy).tw.
30 (value adj1 money).tw.
31 budget$.tw.
32 or/19-31
33 18 and 32
34 limit 33 to yr=2002-2004

Database: MEDLINE(Ovid) 1966 to November week 3 2004

Search strategy: economic modelling
1 daclizumab.mp.
2 basiliximab.mp.
3 mycophenolate.mp.
4 exp TACROLIMUS/ or tacrolimus.mp.
5 zenapax.mp.
6 simulect.mp.
7 cellcept.mp.
8 myfortic.mp.
9 prograf.mp.
10 rapamycin.mp.
11 mmf.mp.
12 fk506.mp.
13 (kidney$ adj transplant$).mp.
14 (renal adj transplant$).mp.
15 exp Kidney Transplantation/ or kidney transplantation.mp.
16 or/13-15
17 or/1-12
18 16 and 17
19 decision support techniques/
20 markov.mp.
21 exp models economic/
22 decision analysis.mp.
23 cost benefit analysis/
24 or/19 - 23
25 18 and 24
26 limit 25 to yr=2002-2004

Database: MEDLINE (Ovid) 1966 to November week 3 2004

Search strategy: quality of life
1 daclizumab.mp.
2 basiliximab.mp.
3 mycophenolate.mp.
4 exp TACROLIMUS/ or tacrolimus.mp.
5 zenapax.mp.

6 simulect.mp.
7 cellcept.mp.
8 myfortic.mp.
9 prograf.mp.
10 rapamycin.mp.
11 mmf.mp.
12 fk506.mp.
13 (kidney$ adj transplant$).mp.
14 (renal adj transplant$).mp.
15 exp Kidney Transplantation/ or kidney transplantation.mp.
16 or/13-15
17 or/1-12
18 16 and 17
19 quality of life/
20 life style/
21 health status/
22 health status indicators/
23 or/19 - 22
24 18 and 23
25 limit 24 to yr=2002-2004

Database: EMBASE (Ovid) 1996 to 2004 week 48

Search strategy: cost
1 (kidney$ adj transplant$).mp.
2 (renal adj transplant$).mp.
3 exp KIDNEY TRANSPLANTATION/
4 or/1-3
5 daclizumab.mp. or exp DACLIZUMAB/
6 basiliximab.mp. or exp BASILIXIMAB/
7 mycophenolate.mp.
8 mycophenolate mofetil.mp. or exp Mycophenolic Acid 2 Morpholinoethyl Ester/
9 tacrolimus.mp. or exp Tsukubaenolide/
10 zenapax.mp.
11 simulect.mp.
12 cellcept.mp.
13 myfortic.mp.
14 prograf.mp.
15 rapamycin.mp. or exp RAPAMYCIN/
16 mmf.mp.
17 fk506.mp.
18 or/5-17
19 4 and 18
20 cost benefit analysis/
21 cost effectiveness analysis/
22 cost minimization analysis/
23 cost utility analysis/
24 economic evaluation/
25 (cost or costs or costed or costly or costing).tw.
26 (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
27 (technology adj assessment$).tw.
28 or/20-27
29 19 and 28
30 limit 29 to yr=2002 - 2004

Appendix 3

Data extraction form

Patient characteristics

First author, year, trial name

Country(ies) (and years of recruitment)

Patient numbers
[paediatric trials include breakdown of numbers by age, if reported]

Age (years) Mean (SD) [range]

Sex (proportion male %)

Body weight (kg) [paediatric studies only]

Donor (cadaveric/living/asystolic %)

Duration of dialysis (years)

First transplant (%)

Ethnic group (proportion white %)

Diagnosis
Hypertension (%)
Diabetes (%)
Glomerulonephritis (%)

Sensitisation – panel reactive antibodies

HLA matches (%)
0 (%)
1 (%)
2 (%)

Inclusion/exclusion criteria

Graft cold ischaemic time (h)

Follow-up points (e.g. 3, 6, 12 months …)

Comments

Immunosuppressive regimen

First author, year, trial name

Induction

Azathioprine (mg/kg/day)

Prednisone

Ciclosporin (mg/kg/day)

Tacrolimus (mg/kg/day)

MMF

MPS

Sirolimus

Comments

Trial quality

First author, year, trial name

Method of randomisation stated?

Method of allocation concealment stated?

Blinding undertaken (who)?

Withdrawals (%)

Analysis by intention to treat?

Jadad score

Comments

(This table is for information only – enter directly into the table above)

Question		Scoring scheme	Score
1. Was the study described as randomised (this includes the use of words such as randomly, random and randomisation)?		Yes (+1) No (0)	1
1a. The method to generate the sequence of randomisation was described and it was:	**Appropriate** (table of random numbers, computer generated, etc.)	(+1)	1
	Inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc.)	(–1)	
2. Was the study described as double blind?		Yes (+1) No (0)	1
2a. The method of double blinding was described and it was:	**Appropriate** (identical placebo, active placebo, dummy, etc.)	(+1)	1
	Inappropriate (e.g. comparison of tablet vs injection with no double dummy)	(–1)	
3. Was there a description of withdrawals and dropouts?		Yes (+1) No (0)	1
Jadad score (0–5)			5

Guidelines for assessment

1. **Randomisation**: a method to generate the sequence of randomisation will be regarded as appropriate if it allowed each study participant to have the same chance of receiving each intervention and the investigators could not predict which treatment was next. Methods of allocation using date of birth, date of admission, hospital numbers or alternation should be not regarded as appropriate.
2. **Double blinding**: a study must be regarded as double blind if the word 'double blind' is used. The method will be regarded as appropriate if it is stated that neither the person doing the assessments nor the study participant could identify the intervention being assessed, or if in the absence of such a statement the use of active placebos, or dummies is mentioned.
3. **Withdrawals and drop-outs**: participants who were included in the study but did not complete the observation period or who were not included in the analysis must be described. The number **and** the reasons for withdrawal in each group must be stated. If there were no withdrawals, it should be stated in the article. If there is no statement on withdrawals, this item must be given no points.

Outcomes at 6 months

First author, year, trial name

Patient deaths (*n*/*N*)

Graft loss (*n*/*N*)

Graft loss excluding all deaths (*n*/*N*)

Biopsy confirmed acute rejection (*n*/*N*)

Other acute rejection [define] (*n*/*N*)

Glomerular filtration rate (ml/min/m^2)

Serum creatinine (μmol/l)
or where not reported, Creatinine clearance

Adverse events
Serious infections, diabetes, hyperlipidaemia and post-transplant lymphoproliferative disease

Any infection
(and any reported severity/treatment)

Withdrawal due to any adverse event

Growth [paediatric studies only]
Height and weight

Quality of life

Drug switching
[i.e. number of patients who cross over from intervention to control drug or vice versa, or any form of switching]

Comments

Outcomes at 12 months

First author, year, trial name

Patient deaths (*n*/*N*)

Graft loss (*n*/*N*)

Graft loss excluding all deaths (*n*/*N*)

Biopsy confirmed acute rejection (*n*/*N*)

Other acute rejection [define] (*n*/*N*)

Glomerular filtration rate (ml/min/m^2)

Serum creatinine (μmol/l)
or where not reported, Creatinine clearance

Adverse events
Serious infections, diabetes, hyperlipidaemia and post-transplant lymphoproliferative disease

Any infection
(and any reported severity/treatment)

Withdrawal due to any adverse event

Growth [paediatric studies only]
Height and weight

Quality of life

Drug switching
[i.e. number of patients who cross over from intervention to control drug or vice versa, or any form of switching]

Comments

Outcomes at longest follow-up point [state]

First author, year, trial name

Patient deaths (*n*/*N*)

Graft loss (*n*/*N*)

Graft loss excluding all deaths (*n*/*N*)

Biopsy confirmed acute rejection (*n*/*N*)

Other acute rejection [define] (*n*/*N*)

Glomerular filtration rate (ml/min/m^2)

Serum creatinine (μmol/l)
or where not reported, Creatinine clearance

Adverse events
Serious infections, diabetes, hyperlipidaemia and post-transplant lymphoproliferative disease

Any infection
(and any reported severity/treatment)

Withdrawal due to any adverse event

Growth [paediatric studies only]
Height and weight

Quality of life

Drug switching
[i.e. number of patients who cross over from intervention to control drug or vice versa, or any form of switching]

Comments

Subgroup analyses

First author, year, trial name

Subgroup examined

Comments

Appendix 4

Systematic reviews handsearched for primary studies

Adu D, Cockwell P, Ives NJ, Shaw J, Wheatley K. Interleukin-2 receptor monoclonal antibodies in renal transplantation: meta-analysis of randomised trials. *BMJ* 2003;**326**:789–91.

Chapman JR. Optimizing the long-term outcome of renal transplants: opportunities created by sirolimus. *Transplant Proc* 2003;**35** (3 Suppl):67S–72S.

Filler G. Evidence-based immunosuppression after pediatric renal transplantation – a dream? *Transplant Proc* 2003;**35**:2125–7.

Keown PA, Balshaw R, Khorasheh S, Chong M, Marra C, Kalo Z, *et al*. Meta-analysis of basiliximab for immunoprophylaxis in renal transplantation. *Biodrugs* 2003;**17**:271–9.

Knoll GA, Bell RC. Tacrolimus versus cyclosporin for immunosuppression in renal transplantation: meta-analysis of randomised trials. *BMJ* 1999;**318**:1104–7.

Mulay AV, Hussain N, Fergusson D, Knoll GA. Calcineurin inhibitor withdrawal from sirolimus-based therapy in kidney transplantation: a systematic review of randomized trials. *Am J Transplant* 2005;**5**:1748–56.

Murphy GJ, Waller JR, Sandford RS, Furness PN, Nicholson ML. Randomized clinical trial of the effect of microemulsion cyclosporin and tacrolimus on renal allograft fibrosis. *Br J Surg* 2003;**90**:680–6.

Wang K, Zhang H, Li Y, Wei Q, Li H, Yang Y, *et al*. Efficacy of mycophenolate mofetil versus azathioprine after renal transplantation: a systematic review. *Transplant Proc* 2004;**36**: 2071–2.

Wang K, Zhang H, Li Y, Wei Q, Li H, Yang Y, *et al*. Safety of mycophenolate mofetil versus azathioprine in renal transplantation: a systematic review. *Transplant Proc* 2004;**36**:2068–70.

Webster AC, Lee VW, Powell J, Chapman JR, Craig JC. TOR-inhibitors (sirolimus and everolimus) for primary immunosuppression of renal transplant recipients: a meta-analysis randomised trials [abstract]. *Transplantation* 2004;**78**:29–30.

Webster AC, Playford EG, Higgins G, Chapman JR, Craig J. Interleukin 2 receptor antagonists for kidney transplant recipients. *The Cochrane Library* 2004;(4):38 A.D. (ID CD003897).

Webster AC, Playford EG, Higgins G, Chapman JR, Craig JC. IL2 receptor antagonists for renal transplant recipients: a meta-analysis of randomised trials [abstract]. *Transplant Soc Aust NZ* 2003;58.

Webster AC, Playford EG, Higgins G, Chapman JR, Craig JC. Interleukin 2 receptor antagonists for renal transplantation recipients: a meta-analysis of randomized trials. *Transplantation* 2004;**77**: 166–76.

Appendix 5

Included adult daclizumab RCTs

Note that where an outcome section (e.g. outcomes at 6 months) is missing in the following tables, data were not reported.

Patient characteristics

First author, year, Trial name	**Vincenti, 1998**
Country(ies)	US, Canada, Sweden Years of recruitment somewhere including April 1995–January 1996 DAC + (CIC + AZA + steroid) Placebo + (CIC + AZA + steroid) CIC was sandimmune or neoral
Patient numbers [paediatric trials include breakdown of numbers by age, if reported]	DAC 126 vs placebo 134 Total *n* = 260
Age (years) Mean (SD) [range]	47 ± 13 DAC vs 47 ± 13 placebo
Sex (proportion male %)	74/126 (59%) DAC vs 81/134 (60%) placebo
Body weight (kg) [paediatric studies only]	NR
Donor (cadaveric/living/asystolic %)	100% cadaveric
Duration of dialysis (years)	NR
First transplant (%)	100%
Ethnic group (proportion white %)	84/126 (67%) vs 81/134 (60%)
Diagnosis Hypertension (%) Diabetes (%) Glomerulonephritis (%)	 18/126 (14%) vs 19/134 (14%) 32/126 (25%) vs 29/134 (22%) 33/126 (26%) vs 40/134 (30%)
Sensitisation – panel reactive antibodies	'Comparable' gives for 0–10%, 11–49%, 50–100%
HLA matches (%) 0 (%) 1 (%) 2 (%)	'No significant difference' 15% DAC vs 16% placebo 39% DAC vs 46% placebo 40% DAC vs 30% placebo
Inclusion/exclusion criteria	Inclusion: 1st transplant, cadaveric only Exclusion: multiple organ transplants; positive cross-match for T-cell lymphocytes
Graft cold ischaemic time (h)	'No significant difference' 22 ± 8 vs 21 ± 9
Follow-up points (e.g. 3, 6, 12 months …)	6 months, 12 months, 3 years
Comments	

Immunosuppressive regimen

First author, year, trial name	Vincenti, 1998
Induction [not relevant here]	Daclizumab 5 doses i.v.: 1 mg/kg up to 100 mg max. within 24 h pretreatment, then at 2, 4, 6, 8 weeks post or placebo
Azathioprine (mg/kg/day)	4 mg/kg i.v. at time of transplant, then 1–2 mg/kg/day thereafter
Prednisone	NR
Ciclosporin (mg/kg/day)	12 h pre- to within 24 h post-transplant 5 mg/kg b.d. oral starting dose
Tacrolimus (mg/kg/day)	NA
MMF	NA
MPS	NA
Sirolimus	NA
Comments	After 1 year use of additional immunosuppressive medications was permitted

Trial quality

First author, year, trial name	Vincenti, 1998
Method of randomisation stated?	No
Method of allocation concealment stated?	No
Blinding undertaken (who)?	Yes, double; no other information
Withdrawals (%)	No
Analysis by intention to treat?	Yes
Jadad score	2
Comments	

Outcomes at 6 months

First author, year, trial name	**Vincenti, 1998**
Patient deaths (*n*/*N*)	NR
Graft loss (*n*/*N*)	NR
Graft loss excluding all deaths (*n*/*N*)	NR
Biopsy confirmed acute rejection (*n*/*N*)	28/126 (22%) DAC vs 47/134 (35%) placebo $p = 0.03$, OR 0.5
Other acute rejection [define] (*n*/*N*)	2 or more AR 7% DAC vs 13% placebo
Glomerular filtration rate (ml/min/m^2)	55 ± 23 DAC vs 52 ± 22 placebo
Serum creatinine (μmol/l)	150 ± 60 in both groups
Adverse events Serious infections, diabetes, hyperlipidaemia and post-transplant lymphoproliferative disease	No significant difference between the 2 groups Lymphoma 2/126 DAC vs 1/134 placebo
Any infection (and any reported severity/treatment)	Sepsis/bacteraemia 4/126 DAC vs 9/134 placebo Pneumonia 3/126 vs 4/134 Fungal infection 21/126 vs 27/134 Local infection (some patients had more than one type) 59/126 vs 70/134 Any viral infection 29/126 vs 32/134 CMV 15/126 vs 14/134 Subdivisions of each category also given Severity of episode of CMV: Mild: DAC 7, Placebo 2 Moderate: DAC 10, Placebo 11 Severe: DAC 1, Placebo 1 Local: DAC 3, Placebo 3
Withdrawal due to any adverse event	NR
Growth Height and weight	NR
Quality of life	NR
Drug switching [i.e. number of patients who cross over from intervention to control drug or vice versa, or any form of switching]	NR
Comments	Inadequately powered to show a difference in graft survival at 3 years

AR, acute rejection; OR, odds ratio.

Outcomes at 12 months

First author, year, trial name	**Vincenti, 1998**
Patient deaths (*n*/*N*)	DAC 3/ 126 vs placebo 5/134
Graft loss (*n*/*N*)	DAC 6/126 (5%) vs placebo 13/134 (10%)
Graft loss excluding all deaths (*n*/*N*)	DAC 3/126 vs placebo 8/134
Biopsy confirmed acute rejection (*n*/*N*)	BPAR episodes
Other acute rejection [define] (*n*/*N*)	NR
Glomerular filtration rate (ml/min/m^2)	NR
Serum creatinine (μmol/l)	NR
Adverse events Serious infections, diabetes, hyperlipidaemia and post-transplant lymphoproliferative disease	No significant differences between placebo and daclizumab. Malignancies – patients DAC 2 vs placebo 4
Any infection (and any reported severity/treatment)	NR
Withdrawal due to any adverse event	NR
Growth Height and weight	NR
Quality of life	NR
Drug switching [i.e. number of patients who cross over from intervention to control drug or vice versa, or any form of switching]	NR
Comments	Withdrawal/discont/cross-over DAC 85% vs 80% placebo

Outcomes at longest follow-up point (3 years)

First author, year, trial name	**Vincenti, 1998** 3 years/36 months – reported in Bumgardener *et al.*[50]
Patient deaths (*n*/*N*)	Survival 92% DAC vs 94% placebo
Graft loss (*n*/*N*)	Survival 84% placebo vs 83% DAC Loss at 3 years 23/134 (17%) placebo vs 20/126 (16%) DAC Graft loss over 3 years includes chronic rejection
Graft loss excluding all deaths (*n*/*N*)	Loss at 3 years 16/134 placebo vs 13/126 DAC Graft loss over 3 years includes chronic rejection
Biopsy confirmed acute rejection (*n*/*N*)	NR
Other acute rejection [define] (*n*/*N*)	NR
Glomerular filtration rate (ml/min/m^2)	47 ± 3.1 (n = 45) DAC vs 47 ± 2.6 (n = 56) placebo, p = NS
Serum creatinine (μmol/l)	1.8 ± 0.07 (n = 92) DAC vs 1.7 ± 0.11 (n = 97) placebo, mean ± SEM, p = NS (all in mg/dl)
Adverse events Serious infections, diabetes, hyperlipidaemia and post-transplant lymphoproliferative disease	Malignancies 7.9% vs 6.7% Lymphoma at 3 years 3/134 (2.2%) placebo vs 2/126 (1.6%) DAC
Any (other?) infection (and any reported severity/treatment)	Placebo 1/134 vs 0 aspergillosis 1/134 vs 0 coccidiomycosis Nothing for sepsis, pneumonia, infective endocarditis, no other infections reported
Withdrawal due to any adverse event	NR
Growth Height and weight	NR
Quality of life	NR
Drug switching [i.e. number of patients who cross over from intervention to control drug or vice versa, or any form of switching]	Placebo 11% vs DAC 13% converted from CIC to TAC Placebo 17% vs DAC 28% converted from AZA to MMF All
Comments	Still on steroids at 3 years placebo 108 (95% of available patient data at 3 years) vs DAC 100 (96%)

NS, not significant.

Subgroup analyses

First author, year, trial name	**Vincenti, 1998**
Subgroup examined	NR
Comments	

Appendix 6

Included paediatric and adult basiliximab RCTs

Note that where an outcome section (e.g. outcomes at 6 months) is missing in the following tables, data were not reported.

Patient characteristics

First author, year, trial name	**Bingyi, 2003** BAS + CIC + AZA + steroid Placebo + CIC + AZA + steroid	**Folkmane, 2001** I: conventional triple (AZA, CIC, steroid) – control II: MMF-based triple (MMF, CIC, steroid) III: BAS induction + (AZA, CIC, steroid)	**Grenda, 2004** BAS + TAC + AZA + steroid Nothing + TAC + AZA + steroid
Country(ies)	NR	Latvia Recruited 1997–9	15 centres, 6 European countries March 2001 – March 2004
Patient numbers [paediatric trials include breakdown of numbers by age, if reported]	Total $n = 12$ 6 patients treated with simulect vs 6 control	I = 25 control vs III = 23 BAS Total $n = 71$	Total 197, 102 patients with BAS, 95 without BAS were randomised but 93 control, 99 for BAS was used in report called full analysis set – these 5 patients either did not receive medication or transplant. Under 12 years, control $n = 42$ vs BAS $n = 46$; 12 years and over, control 51 vs BAS 53
Age (years) Mean (SD) [range]	35–59 BAS vs 36–54 control	45.1 ± 13.0 control vs 40.6 ± 13.2 MMF vs 39.8 ± 12.4 BAS Mean 43.4 ± 14.2, range 15–70 Control group significantly higher age ($p = 0.05$)	TAC/AZA/steroid/BAS, $n = 99$, 11.5 ± 4.1 [2–17] TAC/AZA/steroid, $n = 93$, 11.3 ± 4.0 [2–17]
Sex (proportion male %)	4/6 (66%) male treatment vs 5/6 (83%) male control	NR	With BAS (62.6%) vs without BAS (61.3%), control $n = 93$, BAS = 99 Gives for under 12 years and 12 years and over
Body weight (kg) [paediatric studies only]	NR	NR	TAC/AZA/steroid mean ± SD, min.–max. 36.6 ± 17.1, 12–102 TAC/AZA/steroid/BAS 38.3 ± 17.3, 36–83 Gives for under 12 years and 12 years and over
Donor (cadaveric/living/asystolic %)	Cadaveric kidney transplants	100% cadaveric	Cadaveric 77/93 (82.8%) control vs 79/99 (79.8%) BAS Others were living
Duration of dialysis (years)	NR	NR	NR
First transplant (%)	NR	NR (first or second)	87/93 (93.5%) control vs 95/99 (96.0%) BAS
Ethnic group (proportion white %)	NR	'No difference across groups'	NR

continued

Diagnosis Hypertension (%) Diabetes (%) Glomerulonephritis (%)	NR	NR	Secondary diagnosis 59/93 control vs 63/99 BAS 0/93 control vs 0/99 BAS 16/93 (17.2%) control vs 12/99 (12.1%) BAS
Sensitisation – panel reactive antibodies	NR	NR 'No difference'?	Under 50%: 88/93 control vs 94/99 BAS 50–100%: 1/0 plus some not recorded
HLA matches (%) 0 (%) 1 (%) 2 (%)	NR	NR	ABO compatible Mean total mismatch 2.2% with BAS, 2.3% without
Inclusion/exclusion criteria	NR	Inclusion: first or second cadaveric; age 15–70 years Exclusion: NR	Inclusion: male or female aged 18 years or younger regardless of race; female of childbearing age, agreed to use contraceptive; cadaveric or living donor with compatible ABO blood type; end-stage kidney disease; consent given from patients or parents Exclusion: <5 kg; panel reactive antibodies (PRA) grade ≥50% within the previous 6 months and or having a re-transplantation for immunological reasons; patients allergic or intolerant to HCO-60 or to the treatments used; any other use of systemic immunosuppressive drugs; if patients or donors are known to be HIV+; significant liver disease; patients with/history of malignancy; significant infection, severe diarrhoea, vomiting or active peptic ulcer; previously received transplant other than kidney; previous 4 weeks/concomitant investigational drug; patients with relapsing uraemic syndrome; patients unlikely to comply; patients with any substance abuse; pregnant or lactating women
Graft cold ischaemic time (h)	NR	NR	Mean ± SD 18.0 ± 8.5 (n = 80) control vs 16.5 ± 8.5 (n = 85) BAS
Follow-up points (e.g. 3, 6, 12 months …)	12 months	6 and 12 months	6 months
Comments	Serious lack of information		

Patient characteristics

First author, year, trial name	**Ponticelli, 2001** Placebo + CIC (Neoral) + AZA + steroid BAS + CIC (Neoral) + AZA + steroid	**Sheashaa, 2003** BAS + CIC + AZA + steroid CIC + AZA + steroid
Country(ies)	Europe, Mexico, South Africa, Israel. 31 centres Years of recruitment NR	One centre in Egypt June 1998 – June 1999
Patient numbers [paediatric trials include breakdown of numbers by age, if reported]	168 BAS vs 172 placebo Total $n = 340$	Adult $n = 100$, BAS $n = 50$, control $n = 50$
Age (years) Mean (SD) [range]	44.2 (13.5) BAS vs 44.2 (13.0) placebo	32.9 ± 9.9 BAS vs 32.5 ± 10.8 control
Sex (proportion male %)	65.5% (110/168) BAS vs 68.6% (118/172) placebo	44/50 (88%) BAS vs 41/50 (82%) control
Body weight (kg) [paediatric studies only]	NR	Mean 62.6 ± 13.1 BAS vs 63.7 ± 15.1 control
Donor (cadaveric/living/asystolic %)	Cadaveric % 83.9% vs 81.4% Rest were living	100% living
Duration of dialysis (years)	35.5 months (40%) vs 36.9 months (38.5%)	1.6 ± 3.2 BAS vs 1.4 ± 1.3 control
First transplant (%)	156/168 (92.9%) BAS vs 161/172 (93.6%) placebo	100%, all first transplant
Ethnic group (proportion white %)	Caucasian 86.9% vs 87.2%	NR
Diagnosis Hypertension (%) Diabetes (%) Glomerulonephritis (%)	NR	NR
Sensitisation – panel reactive antibodies	1.6% BAS vs 1.6% placebo	NR
HLA matches (%) 0 (%) 1 (%) 2 (%)	Mean mismatch 2.9 ± 1.4 vs 2.9 ± 1.4	<3 mismatches: 9/50 BAS vs 9/50 control 3 mismatches: 34/50 BAS vs 31/50 control ≥4 mismatches 7/50 BAS vs 10/50 control
Inclusion/exclusion criteria	Inclusion: male and female 18–70 years; first or second kidney transplant; negative pregnancy test; adequate contraception. Exclusion: HIV+; hepatitis; ABO incompatible; prior use of study drugs; PRA >80%; +ve T-cell cross match; asystolic donor; HLA identical; multiple organ transplant; previous induction therapy	First kidney transplant Living related donor
Graft cold ischaemic time (h)	16.3 ± 9.2 BAS vs 15.6 ± 9.0 placebo	NR
Follow-up points (e.g. 3, 6, 12 months …)	6, 12 months	6, 12, 36 months
Comments	Delayed graft function 23.85 vs 22.1% Also non-significant difference in recipients' past or coexistent medication conditions or causes of renal failure	

Immunosuppressive regimen

First author, year, trial name	Bingyi, 2003	Folkmane, 2001	Grenda, 2004
Induction [not relevant here]	Simulect (BAS) 2 doses of 20 mg each by 30-minute i.v. infusion. The first is on day 0, 2 h before transplantation, the second on day 4, after transplantation	BAS 20 mg given per dose 1st dose before transplant, 2nd dose on day 4	2 doses BAS. 10 mg in <40 kg patients, 20 mg in ≥40 kg patients i.v. The first BAS was administered on day 0 prior to reperfusion. The second dose was administered on day 4 after transplantation
Azathioprine (mg/kg/day)	75–100 mg/day	1–2 mg/kg/day oral	1–2 mg/kg/day oral or i.v. during first week, 1–2 mg/kg oral from day 8 onwards
Prednisone	3000 mg on day 0, 3000 mg on day 1, 2000 mg on day 2, 1000 mg on day 3 i.v., and oral prednisolone started on day 4 at 50 mg/day and tapered to 20 mg/day by day 28 and dosage 10 mg/day by day 56	Up to 500 mg i.v. on day of transplant Oral on day 1 = 0.5 mg/kg/day tapering to min. 5 mg/day by 12 months	On day 0, 300–600 mg/m^2 i.v. followed by oral daily doses of 60 mg/m^2 on day 1, 40 mg/m^2 from day 2 to 7, 30 mg/m^2 from day 8 to 14, 20 mg/m^2 from day 15 to 28, 10 mg/m^2 from day 29 to 42 and ≤10 mg/m^2 from day 43 on
Ciclosporin (mg/kg/day)	Neoral 5–8 mg/kg/day	Oral. Target trough 150–350 ng/ml weeks 1–4, 150–250 ng/ml rest of study (to 300 ng/ml)	NA
Tacrolimus (mg/kg/day)	NA	NA	TAC 0.3 mg/kg/day oral within 24 h, then adjusted to trough levels 10–20 ng/ml on days 0–21, 5–15 ng/ml on days 22–183
MMF	NA	1g b.d.	NA
MPS	NA	NA	NA
Sirolimus	NA	NA	NA
Comments			

Immunosuppressive regimen

First author, year, trial name	Ponticelli, 2001	Sheashaa, 2003
Induction [not relevant here]	BAS 20 mg i.v. per dose, 1 dose on day 0 and 1 dose on day 4 or placebo	BAS i.v. 20 mg per dose. 1 dose 2 h preoperatively and second on day 4 after transplantation
Azathioprine (mg/kg/day)	Fixed 1–2	Oral 1 mg/kg/day from the third day after transplantation
Prednisone	Bolus perioperatively i.v. Oral 20 mg/day tapered to min. 5 mg/day	500 mg i.v. on day 0 and 250 mg the next day, followed by oral prednisolone 1.5 mg/kg/day tapered to 0.3 mg/kg/day at the end of the first month and 0.15 mg/kg/day at the ninth month and thereafter
Ciclosporin (mg/kg/day)	Neoral 10 mg/kg/day given in 2 equal doses on day 0. Days 1–7 150–400 ng/ml, trough 150–300 ng/ml days 8–28, 100–250 ng/ml thereafter	Neoral oral 2 days before transplantation 8 mg/kg/day in 2 divided doses, readjusted according to the whole blood trough level, which was kept between 200 and 300 ng/ml during the first month, 125–150 ng/ml until the end of the sixth month and 100–125 ng/ml thereafter
Tacrolimus (mg/kg/day)	NA	NA
MMF	NA	NA
MPS	NA	NA
Sirolimus	NA	NA
Comments		

Trial quality

First author, year, trial name	Bingyi, 2003	Folkmane, 2001	Grenda, 2004
Method of randomisation stated?	No	No	Unclear
Method of allocation concealment stated?	No	No	Yes Sealed randomisation envelopes provided by Fujisawa/Astellas
Blinding undertaken (who)?	Unclear	No	No Open-label study but biopsy blindly evaluated
Withdrawals (%)	No	No	TAC/AZA/steroid/BAS 11/102 (11%) TAC/AZA/steroid 17/95 (18%) (Numbers from ITT by reviewer YA) reported were 17/93 (18.3%) control vs 11/99 (11.1%) BAS
Analysis by intention to treat?	Unclear	Yes	Yes But report uses full analysis set 93 instead of 95 for control and 99 instead of 102 for BAS
Jadad score	1	1	2: 1 for randomisation and 1 for description of withdrawals/discontinuations
Comments	Serious lack of data	Baseline characteristics not significantly different except mean age	Stratification for age but 100% was not achieved

Trial quality

First author, year, trial name	Ponticelli, 2001	Sheashaa, 2003
Method of randomisation stated?	No 'According to central list of randomisation'	No
Method of allocation concealment stated?	Treatment codes said centres were blinded 'Centres remained blinded for the treatment codes up to the end of the 12-month follow-up'	No
Blinding undertaken (who)?	Yes. Double blind but no further details on who, but both placebo and BAS were injected i.v. Abstract 606 says study personnel remained blinded until completion	
Withdrawals (%)	Yes 153 in each group completed 6 months Withdrawal 8.9% BAS vs 11% placebo and full reasons given	No
Analysis by intention to treat?	Yes	Yes
Jadad score	4	1
Comments	Funded by Novartis Stratified by 1st/2nd transplant 1:1 Randomised prior to transplantation	

Outcomes at 6 months

First author, year, trial name	Folkmane, 2001	Grenda, 2004	Ponticelli, 2001
Patient deaths (*n*/*N*)	NR	No death occurred	2/168 BAS vs 3/172 placebo
Graft loss (*n*/*N*)	NR	TAC/AZA/steroid/BAS 5/99 (5.1%); says 4 lost in BAS TAC/AZA/steroid 5/93 (5.4%)	13 including 2 died/168 BAS vs 18 including 3 died/172 placebo
Graft loss excluding all deaths (*n*/*N*)	NR	No deaths	11/168 BAS vs 15/172 placebo
Biopsy confirmed acute rejection (*n*/*N*)	8/25 (32%) control vs 5/23 (21.7%) vs 4/23 (17.3 %) BAS within 6 months 17.3% BAS vs 32% control, $p = 0.05$	19/93 (20.4%) control vs 19/99 (19.2%) BAS, $p = 0.8296$ Corticosteroid resistant BPAR 3/93 (3.2%) control vs 3/99 (3.0%) BAS	31/168 (18.5%) BAS vs 50/172 (29.1%) placebo, $p = 0.023$ at 6 months
Other acute rejection [define] (*n*/*N*)	NR	BPAR under 12 years 4/42 control vs 6/46 BAS; 12 years and over 15/51 control vs 13/53 BAS	Incidence of 1st acute rejection: 35/168 (20.8%) BAS vs 60/172 (34.9%) placebo, $p = 0.005$
Glomerular filtration rate (ml/min/m^2)	NR	Median 79.4 ml/min/1.73 m^2 control vs 77.6 ml/min/1.73 m^2 BAS Schwartz equation Mean ± SD 80.46 ± 19.65 ($n = 76$) control vs 77.24 ± 20.47 ($n = 88$) BAS	Creatinine clearance mean ± SD: 59.99 ± 24.00 BAS vs 58.40 ± 23.95 placebo (*n* not given, take ITT)
Serum creatinine (μmol/l)	NR	Median 86 μmol/l control vs 91 μmol/l BAS Mean = 92.5 ± 35.13 SD ($n = 76$) control vs 96.97 ± 34.97 SD ($n = 88$) BAS	154 ± 100 BAS vs 168 ± 132, p = NS (*n* not given, take ITT) (mean ± SD)
Adverse events Serious infections, diabetes, hyperlipidaemia and post-transplant lymphoproliferative disease	NR	UTI 19/99 (19.2%) with BAS vs 26/93 (28%) without BAS (control) Bronchitis 11/99 (11.1%) with BAS vs 4/93 (4.3%) without BAS Hypertension control 38.7% vs BAS 34.3% CMV infection (classed as SAE) 2/93 control vs 7/99 BAS PTDM 4/93 (4.3%) control vs 5/99 (5.1%) BAS PTLD 2/93 control vs 0/99 BAS	CMV infection: 29/168 (17.3%) BAS vs 25/172 (14.5%) placebo Malignant 1 BAS vs 3 placebo 'Number and severity cf in the two groups' 0 PTLD in either group All AEs 149/168 (88.7%) BAS vs 151/172 (87.8%) placebo

continued

Any infection (and any reported severity/treatment)	6 or 12 months? CMV 3/25 (12%) control vs 9/23 (39.1%); 4/23 (17.3%) BAS (5/23 for arm III)	Overall 42/93 control vs 45/99 BAS Bacterial 30/93 vs 32/99 BAS Viral 15/93 vs 15/99 or 16.1% control vs 15.2% BAS Fungal 6/93 vs 12/99	110/168 (65.5%) vs 113/172 (65.7%)
Withdrawal due to any adverse event	NR	8/93 control vs 4/99 BAS	Overall withdrawal 8.9% BAS vs 11% placebo 1 BAS vs 3 placebo due to AE
Growth Height and weight	NR	NR	NR
Quality of life	NR	NR	NR
Drug switching [i.e. number of patients who cross over from intervention to control drug or vice versa, or any form of switching]	NR		NR
Comments	All episodes of acute rejection were confirmed by biopsy	Three different acute rejections reported: resolving, corticosteroid sensitive and corticosteroid resistant	Graft survival at 6 months 93.5% BAS vs 89.5% placebo, p = NS Steroid-resistant rejection episode treatment with antibody = 9/168 BAS vs 17/172 placebo Steroid-resistant rejection episode treated with antibody/TAC/MMF = 16/168 BAS vs 24/172 placebo Mean steroid dose at 6 months 12.2 mg/day ± 11.1 SD BAS (n = 168) vs 20.4 ± 75.7 (n = 172) placebo

AE, adverse event; SAE, serious adverse event.

Outcomes at 6 months

First author, year, trial name	**Sheashaa, 2003**
Patient deaths (*n*/*N*)	NR
Graft loss (*n*/*N*)	NR
Graft loss excluding all deaths (*n*/*N*)	NR
Biopsy confirmed acute rejection (*n*/*N*)	18/50 (36%) BAS vs 31/50 (62%) control, $p = 0.009$
Other acute rejection [define] (*n*/*N*)	NR
Glomerular filtration rate (ml/min/m^2)	NR
Serum creatinine (μmol/l)	1.39 ± 0.03 mg/dl BAS vs 1.40 ± 0.39 mg/dl control
Adverse events Serious infections, diabetes, hyperlipidaemia and post-transplant lymphoproliferative disease	NR
Any infection (and any reported severity/treatment)	NR
Withdrawal due to any adverse event	NR
Growth Height and weight	NR
Quality of life	NR
Drug switching [i.e. number of patients who cross over from intervention to control drug or vice versa, or any form of switching]	NR
Comments	

Outcomes at 12 months

First author, year, trial name	Bingyi, 2003	Folkmane, 2001 Up to 12 months	Ponticelli, 2001
Patient deaths (*n*/*N*)	Unclear	NR	4/168 (2.4%) BAS vs 5/172 (2.9%) control
Graft loss (*n*/*N*)	Unclear	Loss: 3/25 control vs 2/23 BAS	16/168 (9.5%) BAS vs 20/172 (11.6%) control
Graft loss excluding all deaths (*n*/*N*)	NR	NR	
Biopsy confirmed acute rejection (*n*/*N*)	NR	NR	32/168 BAS vs 52/172 placebo, patients not episodes
Other acute rejection [define] (*n*/*N*)	Rejection episodes were confirmed by clinical diagnosis. Not stated the definition of AR 0/6 with BAS vs 2/6 without (control)	NR	NR
Glomerular filtration rate (ml/min/m^2)	NR	NR	Creatinine clearance ml/min (*n* not given): 59.49 ± 23.05 BAS vs 58.87 ± 22.65 (mean ± SD)
Serum creatinine (μmol/l)	119 ± 29 μmol/l with BAS vs 124 ± 43 μmol/l control	NR	139 ± 80 BAS vs 163 ± 156 (*n* not given) (mean ± SD)
Adverse events Serious infections, diabetes, hyperlipidaemia and post-transplant lymphoproliferative disease	No increase reported. No evidence of infections, tumour, PTLD or PTDM	NR	Malignant 3 BAS vs 6 placebo (including 1 PTLD)
Any infection (and any reported severity/treatment)	NR	NR	NR
Withdrawal due to any adverse event	NR	NR	NR
Growth Height and weight	NR	NR	NR
Quality of life	NR	NR	NR
Drug switching [i.e. number of patients who cross over from intervention to control drug or vice versa, or any form of switching]	NR	NR	NR
Comments			

Outcomes at 12 months

First author, year, trial name	**Sheashaa, 2003**
Patient deaths (*n*/*N*)	NR
Graft loss (*n*/*N*)	NR
Graft loss excluding all deaths (*n*/*N*)	NR
Biopsy confirmed acute rejection (*n*/*N*)	Number of patients with acute rejection in the first 12 months 18/50 vs 31/50, $p = 0.009$
Other acute rejection [define] (*n*/*N*)	
Glomerular filtration rate (ml/min/m^2)	Creatinine clearance 75.04 ± 14.08 ml/min BAS vs 72.0 ± 12.9 control
Serum creatinine (μmol/l)	1.43 ± 0.04 mg/dl BAS vs 1.45 ± 0.40 mg/dl control (mean ± SD)
Adverse events Serious infections, diabetes, hyperlipidaemia and post-transplant lymphoproliferative disease	NR
Any infection (and any reported severity/treatment)	NR
Withdrawal due to any adverse event	NR
Growth Height and weight	NR
Quality of life	NR
Drug switching [i.e. number of patients who cross over from intervention to control drug or vice versa, or any form of switching]	NR
Comments	Cumulative steroid dose, g (mean ± SD) during 1st 12 months 8.6 ± 2.3 BAS vs 9.9 ± 2.7 control

Outcomes at longest follow-up point [3 years]

First author, year, trial name	**Sheashaa, 2003**
Patient deaths (*n*/*N*)	0/50 BAS vs 1/50 control
Graft loss (*n*/*N*)	Survival 96% BAS vs 92% control 4% vs 8% no significant difference
Graft loss excluding all deaths (*n*/*N*)	
Biopsy confirmed acute rejection (*n*/*N*)	Number of patients with acute rejection during the 36 months follow-up 26/50 BAS vs 36/50 control, $p = 0.039$
Other acute rejection [define] (*n*/*N*)	NR
Glomerular filtration rate (ml/min/m^2)	Creatinine clearance 76.56 ± 12.93 ml/min BAS vs 72.26 ± 13.7 ml/min control (*n* not given)
Serum creatinine (μmol/l)	1.51 ± 0.45 mg/dl BAS vs 1.56 ± 0.45 mg/dl control (*n* not given)
Adverse events Serious infections, diabetes, hyperlipidaemia and post-transplant lymphoproliferative disease	CVM 3/50 BAS vs 3/50 control Herpes zoster 2/50 vs 6/50 UTI 3/50 vs 5/50 Urinary TB 1/50 vs 1/50 Malignancy, cutaneous Kaposi's sarcoma 1/50 vs 1/50 Diabetes mellitus 4/50 vs 7/50
Any (other?) infection (and any reported severity/treatment)	NR
Withdrawal due to any adverse event	NR
Growth Height and weight	NR
Quality of life	NR
Drug switching [i.e. number of patients who cross over from intervention to control drug or vice versa, or any form of switching]	NR
Comments	

Subgroup analyses

First author, year, trial name	Bingyi, 2003	Folkmane, 2001	Grenda, 2004	Ponticelli, 2001	Sheashaa, 2003
Subgroup examined	NR	NR	BPAR age <12 years with BAS 6/46 (13%) vs without 4/42 (9.5%), $p = 0.60$ BPAAR ≥ 12 years 13/53 (24.5%) vs 15/51 (29.4%), $p = 0.57$	NR	NR
Comments			BPAR with spontaneous resolving, corticosteroid sensitive, corticosteroid resistant reported		

Appendix 7

Included paediatric and adult tacrolimus RCTs

Note that where an outcome section (e.g. outcomes at 6 months) is missing in the following tables, data were not reported.

Patient characteristics

First author, year, trial name	**Campos, 2002** TAC+AZA+STER CIC+AZA+STER	**Jurewicz, 1999** TAC + AZA + steroid TAC + AZA + steroid Neoral + AZA + steroid Neoral + AZA + steroid	**Mayer, 1997** **European Tacrolimus Multicentre Renal Study Group** TAC vs CIC
Country(ies)	15 centres in Brazil	Recruited Since 1996 May 1997–May 1998	Europe, 15 centres including UK Recruited 1993–4
Patient numbers [paediatric trials include breakdown of numbers by age, if reported]	Total 166 patients, TAC arm *n* = 85, CIC microemulsion *n* = 81	179 232 51 TAC *n* = 90 115 27 CIC *n* = 89 117 24	303/145 TAC/CIC Total 448 Total 451 (303/148)
Age (years) Mean (SD) [range]	TAC 40.5 ± 10.7 (*n* = 85) vs CIC 40.9 ± 12.3 (*n* = 81)	44/48	46.6 [18–72] vs 45.8 [20–70]
Sex (proportion male, %)	TAC male 41/85 (48%) vs CIC 45/81 (56%)	NR 48.52 CIC vs 49.51 TAC	196/303 (64.7%) vs 92/145 (63.4%)
Body weight (kg) [paediatric studies only]	NR	NR	NR
Donor (cadaveric/living/asystolic %)	39/85 (46%) cadaver in TAC vs 42 (52%) CIC 46 (54) living in TAC vs 39 (48) in CIC	Cadaveric	100% cadaveric
Duration of dialysis (years)	43 ± 33.5 TAC vs 33.7 ± 32.3 CIC		NR
First transplant (%)	80/85 (94%) TAC vs 78/81 (96%) CIC	80/85	274/303 (90%) vs 130/145 (90%)
Ethnic group (proportion white %)	NR	NR	NR
Diagnosis		NR	NR
Hypertension (%)	18/85 (21%) TAC vs 16/81 (20%) CIC		15/303 vs 6/145
Diabetes (%)	2/85 (2.5%) TAC vs 4/81 (5%) CIC		121/303 vs 62/145
Glomerulonephritis (%)	30/85 (35%) TAC vs 26/81 (32%) CIC		
Sensitisation – panel reactive antibodies	NR	NR	0% 197/303 vs 98/145 1–49% 73/303 vs 40/145 50–100% 33/303 vs 7/145

continued

HLA matches (%) 0 (%) 1 (%) 2 (%)	NR	Mismatch total 2.5 ± 0.3 CIC vs 2.4 ± 0.2 TAC	 65/68 24/28 11/5
Inclusion/exclusion criteria	NR	NR	Inclusion: 18 years or above Exclusion: allergy or intolerance to ciclosporin or FK506; ABO-incompatible grafts; use of ciclosporin or FK506 in last 28 days; +T-cell cross match; HIV+; pregnancy/inadequate contraception; multiple organ transplant; significant hepatic disease
Graft cold ischaemic time (h)	NR	1165 ± 147 CIC vs 1220 ± 112 TAC	NR
Follow-up points (e.g. 3, 6, 12 months …)	12 months	1 and 3 years, 12 months	12 months
Comments	Previous transplants 5 (6%) TAC vs 3 (4%) CIC	Numbers from interim analysis	

Patient characteristics

First author, year, trial name	**Murphy, 2003** Only non-heart beating recipients got AZA as well, NOT the living donor recipients TAC + AZA + steroid CIC AZA + steroid	**Shapiro, 1991** TAC vs CIC	**Sperschneider, 2001** TAC + AZA + steroid Neoral + AZA + steroid
Country(ies)	Single centre in UK	USA, recruited 1989–91	50 centres within 7 European countries
Patient numbers [paediatric trials include breakdown of numbers by age, if reported]	Total 102 patients, TAC *n* = 52 vs CIC *n* = 50	Total *n* = 57, 28 TAC vs 29 CIC	Total 560 randomised, TAC 287 vs CIC 273, but 3 excluded as did not receive study drug or transplant: *n* = 557, 286 TAC vs 271 CIC
Age (years) Mean (SD) [range]	TAC 45 (14) vs CIC 45 (12)	36.5 ± 11.6 TAC vs 39.4 ± 9.9 CIC	42.4 ± 10.4 TAC (*n* = 286) vs 43.8 ± 10.4 CIC *n* = 271
Sex (proportion male, %)	TAC 61.5% vs CIC 70%	NR	200/286 (69.9%) TAC vs 171/271 (63.1%) CIC
Body weight (kg) [paediatric studies only]	NR	NR	NR
Donor (cadaveric/living/asystolic %)	TAC live donor (LD) 9 (17%), CAD 22 (42), Non-heart beating donor (NHBD) 21 (40) CIC LD 8 (16), CAD 21 (42), NHBD 21 (42)	NR	Cadaveric 273/286 (95.5%) TAC vs 263/271 (97.0%) CIC
Duration of dialysis (years)	NR	NR	NR
First transplant (%)	CIC 44/50 (88%) vs TAC 46/52 (88%) TAC one or more 6 (11.5%) CIC one or more 6 (12%)	100 vs 100	267/286 (93.4%) TAC vs 252/271 (93.0%) CIC
Ethnic group (proportion white %)	NR	NR	283/286 (99.0%) TAC vs 270/271 (99.6%) CIC
Diagnosis Hypertension (%) Diabetes (%) Glomerulonephritis (%)	 TAC 3 (6%) vs CIC 3 (6%) TAC 7 (13%) vs CIC 2 (4%) TAC 7 (13%) vs CIC 6 (12%)	NR	 Pretransplant 77.5% vs 75.1% Diabetic nephropathy 11/286 (3.8%) TAC vs 12/271 (4.4%) CIC, but pretransplant diabetes 4.9% TAC vs 5.8% CIC 110/286 (38.5%) TAC vs 119/271 (43.9%) CIC
Sensitisation – panel reactive antibodies	NR	NR	NR

continued

HLA matches (%) 0 (%) 1 (%) 2 (%)	TAC 7 (13) 2 (4) 8 (15)	CIC 4 (8) 4 (8) 10 (20)	NR	Mean total HLA mismatch 2.51 TAC vs 2.54 CIC
Inclusion/exclusion criteria	Inclusion: consecutive patients who underwent renal transplantation but no details reported		Inclusion: 16–60, PRA <40%; 1st transplant Exclusion: previous or concomitant liver transplant; hepatic dysfunction; cardiac disease	Included: end-stage kidney disease; age between 18 and 60 years; premenopausal to use adequate contraception; donor aged 5–60 years with compatible blood type; primary or repeated, effective birth control Excluded: immune mediated renal graft failure within 1 year; pregnant; PRA >50%; allergic/intolerant to antimetabolites, HCO-60, steroids, macrolite antibiotics, tacrolimus, cyclosporine or related; HIV+; previous non-kidney transplant; pre-existing malignancy; pre-existing uncontrolled systemic infection; disease/condition known to reduce oral absorption of study drugs; required immunosuppressive therapy for concomitant disorders; significant hepatic gastrointestinal disorders; ongoing infection
Graft cold ischaemic time (h)	TAC LD 2.2 (2.1) CAD 18.7 (7.9) NHBD 15.1 (5.6)	CIC 1.7 (1.6) 19.0 (8.0) 15.1 (5.0)	33.8 ± 8.2 TAC vs 33.2 ± 9.2 placebo	17.5 ± 6.6 TAC vs 17.6 ± 6.4 CIC
Follow-up points (e.g. 3, 6, 12 months …)	3, 6 and 12 months		12 months	6 months
Comments			Randomised within non-randomised study	6 months completed by 244 TAC vs 189 CIC

Patient characteristics

First author, year, trial name	**Trompeter, 2002; Filler, 2005** TAC + AZA + steroid CIC + AZA + steroid	**Van Duijhoven, 2002** TAC vs CIC
Country(ies)	18 centres (19), nine European countries Data collection: December 1996–June 1999	The Netherlands Years of recruitment NR
Patient numbers [paediatric trials include breakdown of numbers by age, if reported]	204; TAC = 105 vs CIC = 99 randomised but excluded 2 from each arm due to not being recorded according to Good Clinical Practice (GCP), 4 in CIC either not transplanted or no medications, leaving 196. 196 paediatric patients, 18 years or younger in both arms TAC (Prograf) 103 vs CIC micro (Neoral) 93 <13 years: 62 TAC vs 59 CIC ≥13 years: 41 TAC vs 34 CIC	11 TAC vs 12 CIC
Age (years) Mean (SD) [range]	10.5 ± 4.6 TAC vs 10.1 ± 4.5 CIC	45.4 (25–70) vs 47.8 (23–61)
Sex (proportion male %)	64/103 (62.1%) TAC vs 56/93 (60.2%) CIC	8/11 (73%) vs 9/12 (75%)
Body weight (kg) [paediatric studies only]	34.1 ± 17.6 kg TAC vs 30.9 ± 14.7 kg CIC	NR
Donor (cadaveric/living/asystolic %)	84.5% cadaveric TAC vs 83.9% CIC 16 (15.5%) living related TAC vs 15 (16.1%) CIC	Cadaveric
Duration of dialysis (years)	Patients on dialysis prior to transplantation 79 (76.7%) TAC vs 75 (80.6%) CIC	NR
First transplant (%)	91.2% TAC vs 85.6% CIC	9/11 vs 9/12
Ethnic group (proportion white %)	Caucasian 87.4% TAC vs 88.2% CIC	All white
Diagnosis Hypertension (%) Diabetes (%) Glomerulonephritis (%)	 NR NR 7 (6.8%) TAC vs 8 (8.6%) CIC	 NR 0/0 NR
Sensitisation – panel reactive antibodies	NR	NR
HLA matches (%) 0 (%) 1 (%) 2 (%)	Mean total mismatch: 2.5 TAC vs 2.7 CIC	NR

continued

Inclusion/exclusion criteria	Inclusion: males or females who were 18 years or younger; minimum body weight 10 kg; all had end-stage renal disease defined by GFR; 15 ml/min/1.73 m^2; cadaveric or living donor Exclusion: HIV positive; incompatible ABO blood group; hypersensitive or had contraindication to ciclosporin, HCO-60, steroid, macrolide antibiotics or TAC; patients with previous organ transplant other than kidney or who were to receive another organ with the kidney; if required induction therapy with immunosuppressive antibody preparation(s); relapsing and non-diarrhoeal form of haemolytic uraemia syndrome; PRA 50% or more; severe ongoing infections	Inclusion: 18 years or above; recipient of cadaveric kidney transplant Exclusion: history of diabetes mellitus
Graft cold ischaemic time (h)	NR	NR
Follow-up points (e.g. 3, 6, 12 months …)	6 months, 4 years	3 years
Comments	Congenital nephropathy 27.% vs 34.4% No antibody induction therapy was accepted	No significant difference between groups

Immunosuppressive regimen

First author, year, trial name	**Campos, 2002** TAC + AZA + steroid CIC + AZA + steroid	**Jurewicz, 1999**	**Mayer, 1997** **European Tacrolimus Multicentre Renal Study Group**
Induction [not relevant here]	15 centres in Brazil		None
Azathioprine (mg/kg/day)	Total 166 patients, TAC arm $n = 85$, CIC microemulsion $n = 81$	1.5	2 i.v. then 1–2 oral, tried to stop after 3 months
Prednisolone	TAC 40.5 ± 10.7 ($n = 85$) vs CIC 40.9 ± 12.3 ($n = 81$)	Initial 20 mg/day initial tapering to 5 mg/day at 12 weeks, then stopped altogether unless the patient had been treated for rejection	500 mg i.v.; 125 mg i.v. day 1; tapered to 20 mg/day by day 5
Ciclosporin (mg/kg/day)	TAC male 41/85 (48%) vs CIC 45/81 (56%)	Neoral 8 Trough 150–250 ng/ml in 1st month, 100–150 ng/ml thereafter	Sandimmune, initiated at 8 oral, trough 100–150 ng/ml after 3 months
Tacrolimus (mg/kg/day)		0.2, then trough 10–15 ng/ml in 1st month, 5–10 ng/ml thereafter	I.v. to 0.3 oral Trough after 3 months 5–15 ng/ml
MMF	39/85 (46%) cadaver TAC vs 42 (52%) CIC 46 (54) living TAC vs 39 (48) CIC	NA	NA
MPS	43 ± 33.5 TAC vs 33.7 ± 32.3 CIC	NA	NA
Sirolimus	TAC 80/85 (94%) vs CIC 78/81 (96%)	NA	NA
Comments			
	18/85 (21%) TAC vs 16/81 (20%) CIC 2/85 (2.5%) TAC vs 4/81 (5%) CIC 30/85 (35%) TAC vs 26/81 (32%) CIC		
	12 months		
	Previous transplants TAC 5 (6%) vs CIC 3 (4%)		

Immunosuppressive regimen

First author, year, trial name	Murphy, 2003	Shapiro, 1991 TAC + AZA + steroid CIC + AZA + steroid	Sperschneider, 2001
Induction [not relevant here]	NA	None	NA
Azathioprine (mg/kg/day)	1 mg/kg as a single daily dose	NR	Imuran. 2 mg/kg i.v. or orally on day 0 and 1–2 mg/kg orally on days 1–91; thereafter (day 92 onwards) discontinuation was optional
Prednisone	20 mg/day for the first 3 months after kidney transplant, after which the steroid dosage was tapered in a linear fashion to 10 mg on alternate days (or 5 mg/day for diabetic patients) at 6 months	Range used: 2.5–5.0 to 17.5–20.0 mg/day	500 mg on day 0 and 125 mg on day 1, followed by oral prednisone 20 mg/day on days 2–14, 15 mg/day on days 15–28, 10 mg/day on days 29–42 and 5 mg/day thereafter until the end of the study
Ciclosporin (mg/kg/day)	Neoral 15 mg/kg/day in two doses reduced by 2 mg/kg/day each week to a baseline level of 5 mg/kg/day at week 6 200–300 ng/ml trough over first 3 months then reduced to 100–200 ng/ml	NR	Neoral microemulsion 8 mg/kg/day then trough 100–400 ng/ml up to day 91, 100–200 ng/ml from day 92 onwards
Tacrolimus (mg/kg/day)	0.2 mg/kg/day adjusted to whole blood trough levels of 8–15 ng/ml over the first 3 months, then reduced to 5–10 ng/ml	0.075–0.15 mg/kg/day i.v., oral dose 0.15 mg/kg b.d.	Prograf 0.3 ng/ml then trough 10–20 ng/ml up to day 91, 5–15 ng/ml from day 92 onwards
MMF	NA	NA	NA
MPS	NA	NA	NA
Sirolimus	NA	NA	NA
Comments			

Immunosuppressive regimen

First author, year, trial name	Trompeter, 2002; Filler, 2005	Van Duijhoven, 2002
Induction [not relevant here]	NA	None
Azathioprine (mg/kg/day)	Imuran 2–4 mg/kg i.v. or orally days 0–7, then 2 mg/kg day 8 onwards	1–2 until month 3
Prednisone	A bolus of 300–600 mg/m^2 methylprednisolone on day 0. Oral prednisolone tapered from 60–80 to 15 mg/m^2 at 6 months	500 mg methylprednisolone on day 1 and 125 mg on day 1 after kidney transplant, thereafter 20 mg prednisolone tapered to 5 mg by week 6 Bolus on days 0 and 1
Ciclosporin (mg/kg/day)	Neoral, initial oral daily 300 mg/m^2, then 150–250 ng/ml for 1st 6 weeks, 100–200 ng/ml thereafter. i.v. was 1/3 of the oral dose	8 oral in 2 doses After month 3, trough 100–150 ng/ml
Tacrolimus (mg/kg/day)	Prograf, first dose either oral or nasogastric or i.v. administered within 24 h of transplantation, oral daily TAC dose 0.3 mg/kg then 10–20 ng/ml days 0–30, 5–10 ng/ml day 30 onwards or 0.06 mg/kg daily i.v. continuous infusion	0.3 mg/kg/day orally in 2 doses. Target trough initially 10–15 ng/ml after month 3
MMF	N/A	NA
MPS	N/A	NA
Sirolimus	N/A	NA
Comments	Switch to the alternative immunosuppressant had to be withdrawn from study Dose modifications or discontinuation of steroid or AZA were accepted Whole blood trough concentrations of TAC and CIC were monitored	

Trial quality

First author, year, trial name	Campos, 2002	Jurewicz, 1999	Mayer, 1997 European Tacrolimus Multicentre Renal Study Group
Method of randomisation stated?	NR	NR	NR Stratified by centre and by PRA 80% or above and/or previous transplant functional for <12 months 2 TAC vs 1 CIC
Method of allocation concealment stated?	NR	NR	NR
Blinding undertaken (who)?	Open label	Open	Open label
Withdrawals (%)	1 in each arm excluded for protocol violation	NR Loss to follow-up stated? NR	91/303 vs 23/145, $p = 0.002$ withdrawn early Withdrawn due to lack of treatment efficacy 30.8% vs 78.3% Withdrawn due to death 9.9% vs 4.3%
Analysis by intention to treat?	No. TAC N = 85, CIC N = 81 but analysis used TAC N = 84, CIC N = 80	NR	NR (but undertaken)
Jadad score	Scores 1 for being randomised	1	1
Comments		Funding stated? NR	

Trial quality

First author, year, trial name	Murphy, 2003	Shapiro, 1991	Sperschneider, 2001
Method of randomisation stated?	Randomised before operation but method NR	NR	Central randomisation for each centre
Method of allocation concealment stated?	NR	NR	No
Blinding undertaken (who)?	Open label	NR	Open
Withdrawals (%)	NR. It is reported 5 altogether CIC 4 vs TAC 1	NR	TAC 2 died + 42 (14.7%) withdrawn CIC 4 died + 80 (29.5%) withdrawn
Analysis by intention to treat?	Yes	NR	Yes
Jadad score	0	0	2
Comments			Funding stated? Fujisawa/Astellas

Trial quality

First author, year, trial name	Trompeter, 2002; Filler, 2005	Van Duijhoven, 2002
Method of randomisation stated?	Was performed centrally Preoperatively Stratified by centre and age (<13 years/≥13 years)	NR
Method of allocation concealment stated?	Sealed envelopes used	Sealed envelopes
Blinding undertaken (who)?	Open trial, open extension after 6 months	NR
Withdrawals (%)	23/103 (22.3%) TAC vs 34/93 (36.6%) CIC	21% (reasons given) 1 withdrawn from CIC for PTDM 2 withdrawn from TAC to return to dialysis for pre-existing kidney abnormalities
Analysis by intention to treat?	Yes[a]	NR
Jadad score	3	2
Comments	[a] Strictly the ITT was not applied, as there were 2 from the TAC arm and 6 from the CIC excluded from analysis after randomisation	

Outcomes at 6 months

First author, year, trial name	Jurewicz, 1999	Sperschneider, 2001	Trompeter, 2002; Filler, 2005	Van Duijhoven, 2002
Patient deaths (*n*/*N*)	NR	TAC 2 died (0.7%) vs CIC 4 died (1.5%) Survival was 284/286 (99.3%) TAC vs 267/271 (98.5%) CIC	3/103 (2.9%) TAC vs 3/93 (3.2%) CIC Deaths during initial 6 months: 1 TAC vs 1 CIC	NR
Graft loss (*n*/*N*)	NR	9 (3.1%) TAC vs 14 (5.2%) CIC 15 (5.2%) TAC vs 22/271 (8.1%) CIC Survival was 94.6% TAC vs 91.9% CIC	7.8% TAC vs 16% CIC 8/103 TAC vs 15/93 CIC Kaplan–Meir estimates for graft survival over 6 months were 92.2%	NR
Graft loss excluding all deaths (*n*/*N*)	NR	NR	NR	NR
Biopsy confirmed acute rejection (*n*/*N*)	NR	56/286 (19.6%) TAC vs 101/271 (37.3%) CIC, $p < 0.001$ Steroid-resistant BPAR 27/286 (9.4%) TAC vs 57/271 (21.0%) CIC, $p < 0.001$ All numbers are patients	17/94 (18.1%) TAC vs 37/86 (43.0%) CIC, $p = 0.001$, but with ITT 17/103 (16.5%) vs 37/93 (39.8%)	NR

continued

Other acute rejection [define] (*n*/*N*)	NR	NR	NR	2 in TAC group and 2 in CIC group were treated for acute rejection; all before 6 months
Glomerular filtration rate (ml/min/m^2)	NR	NR	66.5 ± 19.9 ml/min/1.73 m^2 TAC vs 61.2 ± 15.8 CIC, $p = 0.096$ Schwartz equation TAC $n = 91$ vs CIC $n = 86$	Creatinine clearance TAC 44.8 (13.6–106.1) vs CIC 65.1 (29.6–84.2)
Serum creatinine (μmol/l)	Creatinine clearance estimated from graph, 54 ml/min CIC vs 62 ml/min TAC	139 ± 50.2 TAC vs 147 ± 86.5 CIC	90.91 ± 34.21 TAC vs 86.09 ± 26.76 CIC	NR
Adverse events Serious infections, diabetes, hyperlipidaemia and post-transplant lymphoproliferative disease	NR	Hypercholesterolaemia 4.2% TAC vs 8.9% CIC, $p < 0.05$ Cholesterol 5.34 ± 0.94 ($n = 244$) vs 6.03 ± 1.01 ($n = 189$) in favour of TAC, $p = 0.0004$ Malignancy 2/286 TAC vs 1/271 CIC	95.1% TAC vs 100% CIC, not significant Overall infections 71/103 (68.9%) vs 60/93 (64.5%) Bacterial, viral, fungal, protozoal and unconfirmed infections were comparable and not significant New onset insulin-dependent diabetes mellitus 3/103 TAC vs 2/93 CIC 4.88 ± 2.2 mmol/l TAC dropped at 6 months vs increased levels in CIC 4.73 ± 2.2 to 5.02 ± 1.92 mmol/l, n = NR PTLD 1/103 TAC vs 2/93 CIC	1 in CIC group developed PTDM
Any infection (and any reported severity/treatment)	NR	Urinary tract infection 28.3% TAC vs 26.2% CIC Hepatitis C+ at study end 15 TAC vs 15 CIC CMV 7.0% TAC vs 6.3% CIC	NR	NR
Withdrawal due to any adverse event	NR	24 (8.4%) TAC vs 56 (20.7%) CIC	23/103 (22%) TAC vs 34/93 (36.5%) CIC 10 TAC vs 14 CIC	NR
Growth Height and weight	NR	NA	NR	NR
Quality of life	NR	NR	NR	NR
Drug switching [i.e. number of patients who cross over from intervention to control drug or vice versa, or any form of switching]	NR	Switch of cornerstone immunosuppressant 1/286 (0.3%) TAC vs 27/271 (10.0%) CIC, $p < 0.001$ MMF added 8/286 (2.8%) TAC vs 6/271 (2.2%) CIC	0/103 (0%) TAC vs 5/93 (5.4%) CIC, $p = 0.023$	NR
Comments			Corticosteroid-resistant BPAR was 5.8% TAC v 21.5% CIC	Creatinine clearance (ml/min) for $n = 11$ and 12: 44.8 TAC vs 65.1 CIC

Outcomes at 12 months

First author, year, trial name	Campos, 2002	Jurewicz, 1999	Mayer 1997 European Tacrolimus Multicentre Renal Study Group
Patient deaths (*n*/*N*)	Survival 92% TAC vs 97% CIC	NR	Survival 282/303 (93.0%) TAC vs 140/145 (96.5%) CIC, $p = 0.140$ Kaplan–Meir estimates Deaths 21/303 TAC vs 5/145 CIC
Graft loss (*n*/*N*)	Survival 82% TAC vs 86% CIC 19.5% TAC vs 25% CIC, $p = 0.351$ (log-rank test)	Survival 92% CIC vs 100% TAC	Survival 250/303 (82.5%) TAC vs 125/145 (86.2%) CIC, $p = 0.380$ All loss 53/303 TAC vs 20/145 CIC
Graft loss excluding all deaths (*n*/*N*)	NR	NR	Survival 265/303 (87.4%) TAC vs 127/145 (87.6%) CIC, $p = 0.967$ Loss excluding deaths 38/303 TAC vs 18/145 CIC
Biopsy confirmed acute rejection (*n*/*N*)	BPAR episode 29/84 (34%) TAC vs 31/80 (39) CIC; this is actually number of patients with BPAR episodes	23% TAC vs 42% CIC, $p = 0.046$ Histology confirmed but unsure of timepoint – biopsies done at 3, 6, 12 months 35% CIC vs 22% TAC, $p < 0.05$; unsure whether this is at 12 months	78/303 (25.9%) TAC vs 66/145 (45.7.%) CIC, $p < 0.001$
Other acute rejection [define] (*n*/*N*)	Clinically diagnosed 35/84 (42%) TAC vs 35/80 (44%) CIC steroid resistant reported	NR	Corticosteroid-resistant acute rejections 11.3% TAC vs 21.6% CIC, $p = 0.001$ Kaplan–Meir estimates
Glomerular filtration rate (ml/min/m^2)	NR	Estimate from graph, 65 ml/min TAC vs 54 ml/min CIC agree	NR
Serum creatinine (μmol/l)	NR	129 TAC vs 153 CIC, $p = 0.001$ Creatinine clearance estimated from graph 53 ml/min CIC vs 65 ml/min TAC, $p < 0.05$	NR
Adverse events Serious infections, diabetes, hyperlipidaemia and post-transplant lymphoproliferative disease	Infections total TAC 215 (100%) episodes vs 207 (100%) CIC (not significant). Bacterial, viral, fungal, protozoal also reported PTDM 10 TAC (5 became insulin free) vs 3 CIC (1 became free), $p = 0.03$ Diabetes 10/85 (12%) TAC vs 3/81 (4%) CIC, $p = 0.03$	PTDM 19.9% TAC vs 4.0% CIC	(Events that achieve $p \leq 0.05$) T > C: creatinine concentration, hypergylcaemia, PTDM, tremor, diarrhoea, angina, fungal infections, angina pectoris C > T: acne, gingivitis, hirsutism, arrhythmia C = T: need for dialysis, myocardial infarction hypertension, Malignancies 3/303 TAC vs 2/145 CIC Lymphomas 3/303 TAC vs 1/145 CIC Diabetes mellitus at 12 months 5.5% TAC vs 2.2% CIC, $p = 0.189$

continued

Any infection (and any reported severity/treatment)	Severity NR	CMV on paper 1648	Overall incidence 75.6% TAC vs 75.2% CIC Deep/systemic fungal 5/303 TAC vs 0/145 CIC, $p = 0.282$ CMV 13.5% TAC vs 16.6% CIC *P. carinii* 2.0% TAC vs 0% CIC *Aspergillus* 1.3% TAC vs 0% CIC Epstein–Barr virus 0.7% TAC vs 0.7% CIC
Withdrawal due to any adverse event	NR	NR	50/303 (16.5%) TAC vs 4/145 (2.8%) CIC, $p < 0.001$
Growth Height and weight	NR	NR	NR
Quality of life	NR	NR	NR
Drug switching [i.e. number of patients who cross over from intervention to control drug or vice versa, or any form of switching]	12 crossed over from CIC to TAC vs 3 from TAC to CIC, $p = 0.003$	At what follow-up point is this 2.3% TAC vs 11.6% CIC Conversion AZA to MMF 9.1% TAC vs 16.3% CIC	TAC to CIC: 9 deaths
Comments			Treatment withdrawals, discontinuations or cross-overs 91/303 (30.0%) TAC vs 23/145 (15.9%) CIC, $p = 0.002$ Actuarial survival rates Creatinine clearance 73.7 TAC vs 61.5 ml/min/1.73 m^2 CIC

Outcomes at 12 months

First author, year, trial name	Murphy, 2003	Shapiro, 1991	Trompeter, 2002; Filler, 2005	Van Duijhoven, 2002
Patient deaths (*n*/*N*)	TAC 2/52 (4%) vs CIC 0/50 (0%)	Survival 27 (96%) TAC vs 26 (89%) CIC, $p = 0.611$	3.9% TAC vs 3.4% CIC	NR
Graft loss (*n*/*N*)		Survival 23 (82%) TAC vs 23 (79%) CIC, $p = 0.470$ Actuarial graft survival was 77% CIC vs 74% FK506	10/103 (10%) TAC vs 17/93 (18.3%) CIC, $p = 0.06$	NR
Graft loss excluding all deaths (*n*/*N*)	TAC 2/52 (4%) vs CIC 5/50 (10)		NR	NR
Biopsy confirmed acute rejection (*n*/*N*)	Table 3 does not say BPAR but protocol stated biopsy at 1 year; TAC 18/52 (35%) vs CIC 18/50 (36%)	NR	NR	NR
Other acute rejection [define] (*n*/*N*)		57% CIC vs 59% FK506	Possibly BPAR but poorly defined; 38/103 (36.9%) TAC vs 55/93 (59.1%) CIC, $p = 0.003$	NR
Glomerular filtration rate (ml/min/m^2)	TAC 47 (18) vs CIC 47 (14)	NR	62.5 ± 20.1 TAC ($n = 88$) vs 56.4 ± 20.8 CIC ($n = 77$), $p = 0.034$ 64.9 ± 20.7 or 22.0 ml/min/1.73 m^2 TAC ($n = 84$) vs 57.8 ± 21.9 ml/min/1.73 m^2 CIC ($n = 77$)	Creatinine clearance (ml/min) 60.2 (11.5–86.2) TAC vs 64.9 (29.5–84.5) CIC
Serum creatinine (μmol/l)	TAC 157 (61) mmol/l vs CIC 170 (90) mmol/l, $p = 0.564$	1.9 ± 1.7 mg/dl TAC vs 1.9 ± 1.7 mg/dl CIC	NR	NR
Adverse events Serious infections, diabetes, hyperlipidaemia and post-transplant lymphoproliferative disease	PTDM 4 patients TAC vs 2 patients CIC PTDM (1 year), p = not significant HbA1c (1 year), p = not significant LDL and cholesterol, $p = 0.021$		NR	
Any infection (and any reported severity/ treatment)	NR	CMV 15% CIC vs 17% FK506	NR	NR
Withdrawal due to any adverse event	NR	NR	NR	NR
Growth Height and weight	NR	NR	NR	NR

continued

Quality of life	NR	NR	NR	NR
Drug switching [i.e. number of patients who cross over from intervention to control drug or vice versa, or any form of switching]	NR	NR	NR	NR
Comments				
or cross-overs NR			Corticosteroid-resistant acute reactions TAC 7.8% vs CIC 25.8%, $p = 0.001$	

Outcomes at longest follow-up point (2, 3 and 4 years)

First author, year, trial name	**Jurewicz, 1999** 3 years	**Trompeter, 2002; Filler, 2005** 2 and 3 years	**Trompeter, 2002; Filler, 2005** 4 years	**Van Duijhoven, 2002** 3 years
Patient deaths (*n*/*N*)	Cumulative death TAC 4.4% vs CIC 7.9%	TAC 6% vs CIC 8%, $p = 0.86$ TAC 3 vs CIC 4 within 2 years Kaplan–Meier estimates for patient survival over 24 months TAC 97.1% vs CIC 95.4%	TAC 5/103 vs CIC 4/93 Kaplan–Meier estimates for probability of patient survival over 4 years TAC 94% vs CIC 92%	NR
Graft loss (*n*/*N*)	Survival (including death with functioning graft) TAC 88% vs CIC 76% 24-month survival TAC 96% vs CIC 88% Graft survival 6 years TAC 81% vs CIC 60% but graph shows 85% vs 66%	TAC 11/103 vs CIC 20/93, statistically significant using log-rank test At 2 years graft survival TAC 10/103 vs CIC 19/93 Graft survival TAC 90.3% vs CIC 79.6%	ID 2155 graft loss at 4 years TAC 11/103 vs CIC 20/93 Kaplan–Meier estimates for probability of graft survival over 4 years TAC 86% vs CIC 69% At 4 years when censoring for patient death graft survival was TAC 95.4% vs CIC 79.2%, $p = 0.0035$	NR
Graft loss excluding all deaths (*n*/*N*)	Cumulative graft loss TAC 4.4% vs CIC 9.0%	NR	Death with a functioning graft TAC $n = 2$ vs CIC $n = 3$	NR
Biopsy confirmed acute rejection (*n*/*N*)	NR	NR	NR	NR
Other acute rejection [define] (*n*/*N*)	NR	In the 2nd year TAC 7/77 patients vs CIC 9/71 had acute rejection; in the 3rd year TAC 2/70 vs CIC 6/57	In the 4th year TAC 2/57 vs CIC 6/42 had acute rejection	NR
Glomerular filtration rate (ml/min/m^2)	NR	Two-year data reported differently in two publications, i.e. TAC 64.9 ± 19.8 ml/min/1.73 m^2 or 64.5 ± 22.6 ($n = 71$, $n = 75$) vs CIC 51.7 ± 20.3 or 51.9 ± 19.7 ($n = 66$) or ID 2155 ($n = 70$), $p = 0.0005$ At 3 years TAC 66.7 ± 26.4 ($n = 81$) vs CIC 53.0 ± 23.3 ($n = 53$), $p = 0.0022$	TAC 71.5 ± 22.9 ($n = 51$) vs CIC 53.0 ± 21.6 ($n = 44$), $p = 0.0001$	Creatinine clearance TAC 64 (38.9–97.9) vs CIC 66.9 (9.5–94.2)
Serum creatinine (μmol/l)	2 years: TAC 129 vs CIC 157, $p = 0.046$ 5 years: TAC 1.4 mg/dl vs CIC 1.7 mg/dl, $p = 0.0014$ 2 years: creatinine clearance estimated from graph TAC 65 ml/min vs CIC 49 ml/min, $p < 0.05$	NR	NR	NR

continued

Adverse events Serious infections, diabetes, hyperlipidaemia and post-transplant lymphoproliferative disease	NR	Cholesterol: TAC 4.25 ± 0.90 mmol/l vs CIC 4.97 ± 1.27 mmol/l Diabetes mellitus: no difference between arms PTLD: TAC 3/103 vs CIC 3/93	PTLD TAC 3 vs CIC 3 all diagnosed by 3 years PTDM TAC 3 vs CIC 3	PTDM 18.5% TAC vs 10.8% CIC, p = not significant, over follow-up period 18–46 months
Any infection (and any reported severity/ treatment)	NR	NR	NR	NR
Withdrawal due to any adverse event	NR	NR	NR	NR
Growth Height and weight	NR	NR	NR	NR
Quality of life	NR	NR	NR	NR
Drug switching [i.e. number of patients who cross-over from intervention to control drug or vice versa, or any form of switching]	NR	NR	NR	NR
Comments		GFR reported to be a useful surrogate marker for long-term outcome	TAC, steroid withdrawal data available on 57 patients, 50/57 still on, 7 stopped; CIC, data available on 51 patients, 44/51 still on, 7 stopped	

Subgroup analyses

First author, year, trial name	Campos, 2002	Jurewicz, 1999	Mayer, 1997 European Tacrolimus Multicentre Renal Study Group
Subgroup examined	NR NR	NR Multivariate analysis based on GFR measurements at 6 months and 1, 3 and 5 years for delayed graft function, acute rejection, CMV disease, CIC/TAC	NR High-risk vs low-risk patients at 1 year TAC vs CIC: no significant differences in outcomes in either high- or low-risk patients High- vs low-risk patients: no significant difference in TAC treatment effect or trough level
Comments	NR	NR	High-risk: PRA grade >80% and/or previous transplant functional >1 year Numbers of patients small and therefore likely to be underpowered

Subgroup analyses

First author, year, trial name	Murphy, 2003	Shapiro, 1991	Sperschneider, 2001	Trompeter, 2002; Filler, 2005	Van Duijhoven, 2002
Subgroup examined	NR NR	NR NR	NR NR	NR NR	NR NR
Comments	NR	NR	NR	NR	NR

Appendix 8

Included adult mycophenolate mofetil RCTs

Note that where an outcome section (e.g. outcomes at 6 months) is missing in the following tables, data were not reported.

Patient characteristics

First author, year, trial name	**Baltar, 2002**	**Folkmane, 2001** I: conventional triple (AZA, CIC, steroid) – control II: MMF-based triple (MMF, CIC, steroid) III: BAS induction + (AZA, CIC, steroid)	**Miladpour, 2002** MMF + CIC + steroid AZA + CIC + steroid
Country(ies)	Spain (NR)	Latvia Recruited in 1997–9	Iran Recruited in 1997–2000
Patient numbers [paediatric trials include breakdown of numbers by age, if reported]	26	I = 25; II = 23; III = 23 Total *n* = 71	80: 40 MMF, 40 AZA
Age (years) Mean (SD) [range]	Median 50.5 (40.5–61 years, NR if range)	I: 45.1 ± 13.0; II: 40.6 ± 13.2; III: 39.8 ± 12.4 Mean 43.4 ± 14.2, range 15–70 Control group significantly higher age ($p = 0.05$)	MMF 39 (20–68) AZA 37 (19–63)
Sex (proportion male %)	69%	NR	MMF *n* = 21/40 (53%) AZA *n* = 18/40 (45%)
Body weight (kg) [paediatric studies only]	NR	NA	NR
Donor (cadaveric/living/asystolic %)	100% cadaver	100% cadaveric	NR
Duration of dialysis (years)	7 months (4–13)	NR	NR
First transplant (%)	100%	NR (first or second)	NR but some had a previous transplant
Ethnic group (proportion white %)	100% hispanic (presumed but NR)	'No difference across groups'	NR
Diagnosis Hypertension (%) Diabetes (%) Glomerulonephritis (%)	 NR 7.7 26.9	NR	2 groups 'similar'
Sensitisation – panel reactive antibodies	NR	NR 'No difference'?	2 groups 'similar'
HLA matches (%) 0 (%) 1 (%) 2 (%)	NR	NR	NR

continued

Inclusion/exclusion criteria	Consecutive primary transplant patients	Inclusion: first or second cadaveric; age 15–70 years Exclusion: NR	NR
Graft cold ischaemic time (h)	NR	NR	NR
Follow-up points (e.g. 3, 6, 12 months …)	15, 30, 90, 180, 365 days	12 months	6 months
Comments	Main outcome health-related quality of life indices		Baseline characteristics were similar with respect to primary causes, previous transplant, age, gender, and panel reactive antibodies

Patient characteristics

First author, year, trial name	**MMF Acute Renal Rejection Study Group [MMF AAR], 1998, 2001** MMF + CIC + steroid AZA + CIC + steroid	**Sadek, 2002** Arm 1 = MMF + CIC + steroid after 3 months swap to AZA for 9 months Arm 2 = MMF + CIC + steroid for 12 months Arm 3 = AZA + CIC + steroid for 12 months	**Tricontinental MMF Renal Transplantation Study Group, 1996** MMF 2 g + CIC + steroid MMF 3 g + CIC + steroid AZA + CIC + steroid (used placebo to blind)	**Tuncer, 2002**
Country(ies)	15 centres USA and Canada 1991–4 Randomised, double-blind for 12 months plus open label for 2 years	Belgium, Brazil, Canada, Italy, Norway, Spain, Switzerland, UK; 28 centres Recruited years NR	Europe, Canada, Australia; 21 centres Study covered August 1992–September 1994 (all completed 1 year)	Turkey Recruited February 95–August 1999
Patient numbers [paediatric trials include breakdown of numbers by age, if reported]	221: MMF 113; AZA 108	Total 447: arm 1 158; arm 2 162; arm 3 157	503, but 497 received drug MMF 3 g =164, 162 got drug MMF 2 g = 173, 171 got drug AZA = 166, 164 got drug Study originally designed as 1 year, some elected not to continue to 3 years MMF 3 g = 18 MMF 2 g = 23 AZA = 19 250/497 completed 3 years on study MMF 3 g = 83 MMF 2 g = 85 AZA = 83	Total *n* = 76; MMF 38; AZA 38

continued

Age (years) Mean (SD) [range]	MMF 43.1 ± 11.6; AZA 43.7 ± 11.6	44.7 ± 12.2; 43.9 ± 12.8; 43.9 ± 13.0	MMF 3 g 46 ± 13 MMF 2 g 46 ± 13 AZA 47 ± 13	MMF 34.8 ± 2.3; AZA 41.4 ± 3.0, $p = 0.091$
Sex (proportion male %)	63.7% MMF; 59.3% AZA	64.6; 71.0; 59.9	MMF 3 g 98/66 male/female (60% male) MMF 2 g 93/79 (54%) AZA 111/55 (67%)	MMF 71%; AZA 74%
Body weight (kg) [paediatric studies only]	NR	NR	NA	NR
Donor (cadaveric/living/asystolic %)	Cadaveric or living non-related	86, 86, 87 cadaveric/living but no asystolic	100% cadaveric	MMF 6 cadaveric, 32 living AZA 9 cadaveric, 29 living
Duration of dialysis (years)	NR	34.4 ± 39.5, 29.6 ± 34.0, 30.8 ± 34.4	NR	NR
First transplant (%)	94/108 AZA; 103/113 MMF	100%	1st or 2nd: 443/503 = 1st Previous renal transplant MMF 3 g = 18; MMF 2 g = 24; AZA = 18 First renal transplant: MMF 2 g 82; MMF 3 g 76; AZA 82	100%
Ethnic group (proportion white %)	67.3% white MMF; 68.5% white AZA	89.9, 91.4, 90.4	NR	NR
Diagnosis			Hypertension NR: 3 groups balanced for prognostic variables	
Hypertension (%)	11% MMF vs 12% AZA	NR		MMF 10/28; AZA 16/22
Diabetes (%)	24% MMF vs 25% AZA	NR		MMF 2/36; AZA 1/37
Glomerulonephritis (%)	25% MMF vs 14% AZA	28.5, 34.0, 33.1	Diabetes: MMF 3 g = 10/164; MMF 2 g = 19/173; AZA = 21/166 Glomerulonephritis: MMF 3 g = 54/164; MMF 2 g = 55/173; AZA = 54/166	NR
Sensitisation – panel reactive antibodies	<20% in 90% AZA patients, 89% MMF	NR	Pre-transplant ≥20% MMF 3 g 6 MMF 2 g 20 AZA 14 Imbalanced statistically, $p = 0.0038$	NR
HLA matches (%)		NR	NR	MMF 2.5 ± 0.1 mismatches AZA 2.7 ± 0.1 mismatches
0 (%)	0 mismatches in 5 AZA vs 3 MMF			
1 (%)	1 mismatch in 4 AZA vs 6 MMF			
2 (%)	2 in 6 vs 9 MMF			

continued

Inclusion/exclusion criteria	Inclusion (note patients already had BPAR before the start of the intervention, not sure if other studies have similar type of population): >18 years; BPAR ≥7 days but ≤6 months; established renal function; serum creatinine <5 mg/dl; adequate contraception Exclusion: antilymphocyte antibody in previous 24 h; no dialysis in previous 5 days; pregnancy; nursing; unwilling to use adequate contraceptive therapy; >1 dose i.v. steroids for presumptive or biopsy-proven rejection at any time before study entry; severe infections; HTLV-1; HIV; hepatitis B; thrombocytopenia; severe leukopenia or anaemia; active peptic ulcer disease; severe diarrhoea; malignancy; other investigational drugs	Inclusion: either sex; between 18 and 70 years; first transplant; negative pregnancy test Exclusion: asystolic donors; previous transplant; induction with anti-thymocyte globulin (ATG), anti-lymphocytic globulin (ALG) or anti-CD3 monoclonal antibody (OKT3); +ve T-cell match; ABO incompatible; HIV+ve; gout; malignancy; other study drugs within 30 days; insufficient contraceptives	Inclusion: age ≥18 years; 1st or 2nd transplant Exclusion: malignancies; unable to take oral medication; pregnant women/nursing; inadequate contraceptives; serum +ve for HIV or hepatitis B; peptic ulcer active; sever diarrhoea; gastrointestinal disorders; systemic infection requiring antibiotics	1st graft
Graft cold ischaemic time (h)	NR in detail	NR	MMF 3 g 20 ± 7 MMF 2 g 21 ± 9 AZA 20 ± 7	NR
Follow-up points (e.g. 3, 6, 12 months …)	2 phases: 6–12 months and 3 years	12 months	12 months treatment then offered 2 year extension	1–5 years
Comments			Delayed graft function: MMF 3 g 30; MMF 2 g 36; AZA 22	

Immunosuppressive regimen

First author, year, trial name	Baltar, 2002	Folkmane, 2001	Miladpour, 2002
Induction [not relevant here]	NR	BAS 2 × 20 mg 1st before kidney transplant, 2nd on day 4	None
Azathioprine (mg/kg/day)	1 arm dose NR	1–2 mg/kg/day oral	100–150 mg/day
Prednisone	Both arms dose NR	Up to 500 mg i.v. on day of kidney transplant Oral day 1, 0.5 mg/kg/day tapered to 0 until 12 months if no contraindications (to minimum 5 mg/day by 12 months)	Used but NR
Ciclosporin (mg/kg/day)	Both arms	Oral. Target trough 150–350 ng/ml weeks 1–4, 150–250 ng/ml rest of study (to 300 ng/ml)	Used but NR
Tacrolimus (mg/kg/day)	No	None	None
MMF	1 arm dose NR	1 g b.d.	1 g b.d.
MPS	NR	None	None
Sirolimus	NR	None	None
Comments	Trial of AZT vs MMF in patients also on ciclosporin and prednisolone to see effects on health-related quality of life including EQ-5D		

Immunosuppressive regimen

First author, year, trial name	MMF AAR, 1998	Sadek, 2002	Tricontinental MMF Renal Transplantation Study Group, 1996	Tuncer, 2002
Induction [not relevant here]	None	None	None	None
Azathioprine (mg/kg/day)	AZA 1–2 mg/kg/day	AZA 1–2 mg/kg o.d. or b.d. depending on local practice	AZA 100–150 mg o.d.	1.5 mg/kg/day
Prednisone	I.v. 5 mg/kg/day then 5-day oral taper of 100 mg q.d.s. 80 mg q.d.s. 60, 40, 20 mg	Min. 10 mg/day for at least 6 months then reduced Given o.d. or b.d. depending on local practice	1 g i.v. pre-transplant, then up to 500 mg 12 h later. Oral prednisone started at 30 mg/day, tapered to 10 mg/day by day 84, then 10 mg/day to 6 months then gradual withdrawal if stable	Yes, no dosage reported
Ciclosporin (mg/kg/day)	Sandimmune in dose established at each centre	Started at 10, trough 250–400 ng/ml, 200–300 mg/ml then 2–6 months 150–250 ng/ml, 7–12 months 100–200 ng/ml	Ciclosporin started time of transplant/day 1 at 8–10 mg/kg/day oral then maintain within levels of target range at each centre to 3.7–4.0 mg/kg at 6 months	Yes
Tacrolimus (mg/kg/day)	None	None	None	None
MMF	1.5 g p.o. b.d. initially	2 g/day	MMF 3 g, 1.5 g b.d. MMF 2 g, 1 g b.d.	2 g/day
MPS	None	None	None	None
Sirolimus	None	None	None	None
Comments				

q.d.s., four times a day.

Trial quality

First author, year, trial name	Baltar, 2002	Folkmane, 2001	Miladpour, 2002
Method of randomisation stated?	NR	Method not stated	NR
Method of allocation concealment stated?	NR	NR	NR
Blinding undertaken (who)?	NR	No	NR
Withdrawals (%)	2 patients between 3rd and 6th months on neither AZT or MMF because of CMV infection (one from each)	NR	1 graft loss in AZA
Analysis by intention to treat?	Not for all outcomes – sometimes 24 patients reported	No	NR
Jadad score	1	0	1
Comments		Baseline characteristics not significantly different except mean age	Full paper had very limited information. Poor quality

Trial quality

First author, year, trial name	MMF AAR, 1998	Sadek, 2002	Tricontinental MMF Renal Transplantation Study Group, 1996	Tuncer, 2002
Method of randomisation stated?	Not described Stratified by centre and then first or second graft	Sequential numbers	No Stratified according to 1st/2nd transplant, within each centre, randomised equally	Method NR
Method of allocation concealment stated?	Not described	Stratified by donor type Almedica drug labelling system	Blinded double capsule format with placebo	NR
Blinding undertaken (who)?	Double blind, open label after 1 year	Open label	Double blinding of investigators and patients continued throughout 3 years of study of patients	Non-blind trial
Withdrawals (%)	Poorly described – possibly 8 and 1 Premature withdrawal 42.6% AZA vs 33.6% MMF 12 months 51/108 (47.2%) AZA vs 40/113 (35.4%) MMF 36 months	Withdrawal/discontinuation 54/158 (34.2%); 52/162 (32.1%); 72/157 (45.9%)	Fully described. 6 did not get study drug – 4 in AZA, 2 in MMF 2 g (3 acute tabular necrosis, 2 consent withdrawn, 1 inability to take oral medication) 138/503 (27%) during 6 months 42 in MMF 3 g 46 in MMF 2 g 50 in AZA Also fully described for 3 years	NR
Analysis by intention to treat?	Yes	Yes	Yes for 6 months, no for 12 months	No
Jadad score	3	3	3	1
Comments				

Outcomes at 6 months

First author, year, trial name	Baltar, 2002	Folkmane, 2001	Miladpour, 2002
Patient deaths (*n*/*N*)	0/12 AZA, 0/14 MMF	NR	NR
Graft loss (*n*/*N*)	NR	NR	AZA 1 patient
Graft loss excluding all deaths (*n*/*N*)	NR	NR	NR
Biopsy confirmed acute rejection (*n*/*N*)	NR	8/25 (32%); 5/23 (21.7%); 4/23 (17.3%) within 6 months 17.3% BAS vs 32% control, $p = 0.05$	NR
Other acute rejection [define] (*n*/*N*) No definition of acute rejection	5/11 AZA, 1/14 MMF	NR	'Acute rejection episodes' MMF 4/40, AZA 10/40, $p = 0.05$
Glomerular filtration rate (ml/min/m^2)	NR	NR	NR
Serum creatinine (μmol/l)	NR	NR	MMF 1.3 (0.8–2.3) mg/dl, AZA 1.3 (0.8–2.0) mg/dl
Adverse events Serious infections, diabetes, hyperlipidaemia and post-transplant lymphoproliferative disease	1/11 AZA and 1/14 MMF CMV illness (more infected on test)	NR	CMV disease: MMF 3/40 (7.5%), AZA 0/40 (0.0%) MMF > AZA diarrhoea, gastrointestinal bleeding, CMV disease AZA > MMF leukopenia, thrombocytopenia, including liver enzymes, jaundice
Any infection (and any reported severity/treatment)	1/11 AZA and 1/14 MMF CMV illness (more infected on test)	6 or 12 months CMV 3/25 (12%); 9/23 (39.1%); 4/23 (17.3%) (5/23 for arm III)	NR
Withdrawal due to any adverse event	1/11 AZA and 1/14 MMF CMV illness (more infected on test)	NR	NR
Growth Height and weight	NR	NR	NR
Quality of life	Health-related quality of life down in AZA 9/11 and MMF 7/13	NR	NR
Drug switching [i.e. number of patients who cross over from intervention to control drug or vice versa, or any form of switching]	NR	NR	NR
Comments		All episodes of acute rejection were confirmed by biopsy	

Outcomes at 6 months

First author, year, trial name	MMF ARR, 1998	Tricontinental MMF Renal Transplantation Study Group, 1996
Patient deaths (*n*/*N*)	NR	MMF 3 g = 3/164 MMF 2 g = 1/173 AZA = 2/166
Graft loss (*n*/*N*)	Loss or death: 4/108 (3.7%) AZA vs 2/113 (1.8%) MMF	Graft loss or death MMF 3 g = 6/164 MMF 2 g = 8/173 AZA = 7/166
Graft loss excluding all deaths (*n*/*N*)	NR	MMF 3 g = 3/164 MMF 2 g = 7/173 AZA = 5/166
Biopsy confirmed acute rejection (*n*/*N*)	NR	MMF 3 g = 26/164 (15.9%) MMF 2 g = 34/173 (19.7%) AZA = 59/166 (35.5%)
Other acute rejection [define] (*n*/*N*) No definition of acute rejection	NR	Clinical or BPAR MMF 3 g = 44/164 (26.8%) MMF 2 g = 55/173 (31.8%) AZA = 80/166 (48.2%)
Glomerular filtration rate (ml/min/m^2)	Creatinine clearance: 56.8 ml/min MMF vs 52.8 ml/min AZA	NR
Serum creatinine (μmol/l)	2.08 mg/dl MMF vs 1.92 mg/dl AZA, estimated from graph; graph also has ± SEM but difficult to estimate	MMF 3 g = 1.44 ± 0.08 mg/dl MMF 2 g = 1.59 ± 0.08 mg/dl AZA = 1.59 ± 0.08 mg/dl
Adverse events Serious infections, diabetes, hyperlipidaemia and post-transplant lymphoproliferative disease	NR	NR
Any infection (and any reported severity/treatment)	NR	NR
Withdrawal due to any adverse event	NR	25; 23; 23 patients Discontinuation of study drug due to adverse event: MMF 3 g 15/164 (9.1%); MMF 2 g 14/173 (8.0%); AZA 7/166 (4.2%)
Growth Height and weight	NR	NR

continued

Quality of life	NR	NR
Drug switching [i.e. number of patients who cross over from intervention to control drug or vice versa, or any form of switching]	NR	NR
Comments	Steroid dosing at 6 months 13.2 mg/day ± 0.6 SEM AZA vs 12.9 mg/day ± 0.6 SEM MMF	Discontinuation of study drug before acute rejection, graft loss, death: 25/164 (15.2%); 24/173 (13.9%); 17/166 (10.2%)

Outcomes at 12 months

First author, year, trial name	Baltar, 2002	Folkmane, 2001	MMF AAR, 1998
Patient deaths (*n*/*N*)	0	NR	3/113 MMF vs 2/108 AZA Survival Kaplan–Meier curve reported
Graft loss (*n*/*N*)	NR	Loss 3/25; 2/23; 2/23	16/108 (14.8%) AZA vs 10/113 (8.9%) MMF
Graft loss excluding all deaths (*n*/*N*)	NR	NR	NR
Biopsy confirmed acute rejection (*n*/*N*)	NR	NR	NR
Other acute rejection [define] (*n*/*N*)	NR	NR	NR
Glomerular filtration rate (ml/min/m^2)	NR	NR	Creatinine clearance 62.5 ml/min MMF vs 59.9 ml/min AZA
Serum creatinine (mg/dl)	1.5 ± 0.8	NR	1.75 mg/dl MMF vs 1.78 mg/dl AZA, estimated from graph; graph also has ± SEM but difficult to estimate
Adverse events Serious infections, diabetes, hyperlipidaemia and post-transplant lymphoproliferative disease	NR	NR	AZA / MMF CMV syndrome/viraemia 16/108 / 23/113 CMV tissue invasive 16/108 / 20/113 Herpes simplex 14/108 / 15/113 Herpes zoster 6/108 / 8/113 *P. carinii* pneumonia 1/108 / 1/113 *Candida* (urinary tract) 2/108 / 2/113 Lymphoma or lymphoproliferative disease 3/108 / 2/113
Any infection (and any reported severity/treatment)	1 CMV illness in each arm	NR	NR
Withdrawal due to any adverse event	NR	NR	20/113 (17.7%) MMF vs 11/108 (10.2%) AZA 13/108 (12.0%) AZA vs 21/113 (18.6%) MMF
Growth Height and weight	NR	NR	NR
Quality of life	EQ-5D 0.87 ± 0.19	NR	NR
Drug switching [i.e. number of patients who cross over from intervention to control drug or vice versa, or any form of switching]	NR	NR	NR
Comments			Steroid dosing at 12 months 10.5 mg/day ± 0.5 SEM AZA vs 10.3 mg/day ± 0.5 SEM MMF

Outcomes at 12 months

First author, year, trial name	Sadek, 2002	Tricontinental MMF Renal Transplantation Study Group, 1996	Tuncer, 2000
Patient deaths (*n*/*N*)	5/158 (3.2%); 8/162 (4.9%); 7/157 (4.5%)	Survival MMF 3 g 157 (95.7%) MMF 2 g 165 (96.5%) AZA 155 (95.7%) Total deaths MMF 3 g = 7 but out of 164 MMF 2 g = 6 but out of 171 AZA = 7 but out of 162	AZA 3/38, MMF 0/38
Graft loss (*n*/*N*)	Or death 17/158 (10.8%); 22/162 (13.6%); 20/157 (12.7%)	Survival MMF 3 g 146 (89.0%) MMF 2 g 151 (88.3%) AZA 140 (86.4%) Graft loss or death (events **are** mutually exclusive) MMF 3 g 18/164 MMF 2 g 20/171 AZA 22/162	AZA 4/38, MMF 1/38
Graft loss excluding all deaths (*n*/*N*)	14/158 (8.9%); 16/162 (9.9%); 16/157 (10.2%)	Graft loss (subgroups of events are not mutually exclusive) MMF 3 g 13/164 MMF 2 g 15/171 AZA 18/162	NR
Biopsy confirmed acute rejection (*n*/*N*)	27/158 (17.1%); 27/162 (16.7%); 43/157 (27.4%)	NR	NR
Other acute rejection [define] (*n*/*N*)	Steroid resistant rejection (1st) 10/158 (6.3%); 11/162 (6.8%); 23/157 (14.7%)	MMF 3 g 26 (15.9%) MMF 2 g 34 (19.7%) AZA 59* (35.5%)	NR
Glomerular filtration rate (ml/min/m^2)	NR	NR	NR
Serum creatinine (mg/dl)	145.5 ± 68.1 SD; 150.5 ± 95.7; 130.2 ± 37.2 Median 133.6; 129.8; 127.4	MMF 3 g = 1.42 ± 0.07 mg/dl MMF 2 g = 1.64 ± 0.07 mg/dl AZA = 1.60 ± 0.07	NR
Adverse events Serious infections, diabetes, hyperlipidaemia and post-transplant lymphoproliferative disease	Increased blood pressure 25.9; 21.6; 22.3% Leukopenia 19.6; 18.5; 18.5% Anaemia 18.4; 17.3; 15.9% Renal dysfunction 13.9; 21.6; 13.4% Nausea 16.5; 14.2; 14.6%	MMF > AZA abdominal pain, vomiting, diarrhoea, infections, PTLD AZA > MMF nausea, thrombocytopenia, hyperkalaemia, hyperglycaemia, hyperbilirubinaemia, malaise, deep thrombophlebitis	NR

continued

	Vomiting 9.5; 17.3; 12.1% Diarrhoea 12.7; 17.3; 8.3% Infection 69; 75.3; 65.6%	Vary by MMF dose: anaemia, leukopenia Malignancies 14/164 (9%); 18/171 (11%); 12/162 (7%) PTLD 2/164 (1%); 2/171 (1%); 1/162 (<1%)		
Any infection (and any reported severity/treatment)	Any infections 1–12 months 109/158 (69.0%); 122/162 (75.3%); 103/157 (65.6%) Serious infection 32/158 (20.3%); 37/162 (22.8%); 31/157 (19.7%) Bacterial, viral, CMV and fungal also given	UTI Systemic infection Opportunistic infection CMV viraemia/syndrome CMV tissue invasion Herpes simplex Herpes zoster *Candida* *P. carinii* pneumonia Aspergillus/mucor MMF 3 g 164; MMF 2 g 171; AZA 162 Incidence of reported events for all patients	42; 41; 35% 19; 15; 15% 46; 46; 44% 11; 12; 11% 11; 7; 6% 25; 21; 24% 8; 7; 7% 12; 12; 12% 0; 0; 2% <1; <1; <1%	NR
Withdrawal due to any adverse event	9/158 (5.7%); 12/162 (7.4%); 19/157 (12.1%)	NR		NR
Growth Height and weight	NR	NR		NR
Quality of life	NR	NR		NR
Drug switching [i.e. number of patients who cross over from intervention to control drug or vice versa, or any form of switching]	NR	NR		NR
Comments		28; 28; 33% withdrawn prematurely		

Outcomes at >12 months

First author, year, trial name	MMF AAR, 1998	Tricontinental MMF Renal Transplantation Study Group, 1996 3 years $n = 250$ but ITT	Tuncer, 2002 3 years; 5 years; Kaplan–Meier estimates
Patient deaths (*n*/*N*)	12/113 MMF vs 12/108 AZA	Kaplan–Meier estimate for deaths at 3 years (ITT) MMF 3 g 9.1%; MMF 2 g 4.7%; AZA 8.6% Survival MMF 3 g 90.9% MMF 2 g 95.3%, 163/171 AZA 91.4%, 150/164	Patients survival 1, 3 and 5 years First year AZA 97% vs MMF 100% Third year 89% vs 93% Fifth year 89% vs 93% NS Kaplan–Meier for 1, 3, 5 years also reported
Graft loss (*n*/*N*)	Loss or death 26/108 (24.1%) AZA vs 22/113 (19.6%) MMF Loss from rejection 12/113 (10.6%) MMF vs 15/108 (13.9%) AZA	Survival: patients alive with functioning graft ITT MMF 3 g 84.8%; MMF 2 g 81.9%, 140/171; AZA 80.2%, 132/164 On study +90 days (censoring at 90 days after termination from study), MMF 3 g 86.4%; MMF 2 g 84.0%; AZA 82.7% Kaplan–Meier estimate for graft loss or death at 3 years (ITT) MMF 3 g 15.2%; MMF 2 g 18.1%; AZA 19.8%	5/38 MMF vs 11/38 AZA, $p = 0.091$
Graft loss excluding all deaths (*n*/*N*)	Excluding death with function 6/113 (5.3%) MMF vs 12/108 (11.1%) AZA	Kaplan–Meier estimate for graft loss excluding death at 3 years (ITT) MMF 3 g 8.5%; MMF 2 g 14.6%; AZA 15.4%	NR
Biopsy confirmed acute rejection (*n*/*N*)	NR	Biopsy proven 26.1%	NR
Other acute rejection [define] (*n*/*N*)	Subsequent presumptive or BPAR 71/108 (65.7%) AZA vs 44/113 (38.9%) MMF	No biopsy proven rejection 5.7%	Acute rejection episodes 7/38 MMF vs 13/38 AZA, $p = 0.118$ Time is NR
Glomerular filtration rate (ml/min/m^2)	GFR 59.7 ± 4.0 ml/min MMF vs 58.6 ± 3.5 ml/min AZA Creatinine clearance 74 ± 4.2 ml/min MMF vs 69.3 ± 4.8 ml/min AZA	NR	NR
Serum creatinine (μmol/l)	NR	Renal function confounded by patients who withdrew due to graft loss during study, leaving only functional grafts to provide renal function data mg/dl ± SEM at 3 years: ITT MMF 3 g 1.56 ± 0.10 vs MMF 2 g 1.78 ± 0.10 vs AZA 1.70 ± 0.10 On study MMF 3 g 1.44 ± 0.09 vs MMF 2 g 1.68 ± 0.09 vs AZA 1.45 ± 0.10	NR

continued

Adverse events Serious infections, diabetes, hyperlipidaemia and post-transplant lymphoproliferative disease	At 1 year cumulative incidence of CMV viraemia/syndrome/tissue invasive 24.4% AZA vs 32.2% MMF At 3 years 25.7% AZA vs 36.9% MMF At 1 year *Candida* infection 17.8% AZA vs 22.5% MMF At 3 years 22.3% AZA vs 32.7% MMF Lymphoma/lymphoproliferative disease 3 in each group at 3 years	MMF > AZA abdominal pain, vomiting, diarrohea, infections, PTLD AZA > MMF thrombocytopenia, hyperkalaemia, hyperglycaemia, hyperbilirubinaemia, malaise, deep thrombophlebitis Vary by MMF dose: nausea, anaemia, leukopenia Lymphoma/lymphoproliferative disorders 3/164 (1.8%) MMF 3 g vs 2/171 (1.2%) MMF 2 g vs 1/162 (0.6%) AZA	NR
Any infection (and any reported severity/treatment)	NR	MMF 3 g *n* = 164; MMF 2 g 171; AZA 162 CMV viraemia/syndrome 13.4% 12.9% 12.3% CMV tissue invasion 11.0 7.0 6.8 Herpes simplex 26.8 22.2 24.1 Herpes zoster cutaneous 11.6 8.2 9.3 Pneumocystis, aspergillus/mucor, *Candida*, fungaemia all below 1.9%	NR
Withdrawal due to any adverse event	13/108 (12.0%) AZA vs 21/113 (18.6%) MMF	34/164 (20.7%) MMF 3 g vs 31/171 (18.1%) MMF 2 g vs 27/162 (16.7%) AZA	NR
Growth Height and weight	NR	NR	NR
Quality of life	NR	NR	NR
Drug switching [i.e. number of patients who cross over from intervention to control drug or vice versa, or any form of switching]	NR	NR	NR
Comments	Mean ± SEM mg/day steroid dose 24 months excluding patients in rejection 9.3 ± 0.4 AZA (*n* = 66) vs 8.4 ± 0.4 MMF (*n* = 83) 36 months 8.3 ± 0.4 AZA (*n* = 58) vs 8.1 ± 0.4 MMF (*n* = 73)	Features in published pooled analysis with previous two studies Also available are weighted pairwise differences and CIs for deaths, loss, loss excluding death for Kaplan–Meier on study and ITT	AZA/MMF Kaplan–Meier estimates 1-year graft survival 89/97% 3-year graft survival 72/93% 5-year graft survival 69/86% 1-year patient survival 97/100% 3-year patient survival 89/93% 5-year patient survival 89/93% Results not statistically significant. Insufficient power

Subgroup analysis

First author, year, trial name	Baltar, 2002	Folkmane, 2001	Miladpour, 2002	MMF AAR, 1998	Sadek, 2002	Tricontinental, MMF Renal Transplantation Study Group 1996	Tuncer, 2002
Subgroup examined	NR	NR	NR	NR	NR	NR	NR
Comments							

Appendix 9

Included adult mycophenolate sodium RCTs

Note that where an outcome section (e.g. outcomes at 6 months) is missing in the following tables, data were not reported.

Patient characteristics

First author, year, trial name	**Salavadori *et al.*, 2003** MPS 1.4 g/day + CIC + steroid MMF 2 g/day + CIC + steroid
Country(ies)	Europe and North America, 30 centres
Patient numbers [paediatric trials include breakdown of numbers by age, if reported]	MPS 213, MMF 210
Age (years) Mean (SD) [range]	MPS 47 (12), MMF 47 (12)
Sex (proportion male %)	MPS 64, MMF 68
Body weight (kg) [paediatric studies only]	
Donor (cadaveric/living/asystolic %)	Cadaveric donor MPS 85, MMF 82
Duration of dialysis (years)	NR
First transplant (%)	100%
Ethnic group (proportion white %)	MPS 88, MMF 89
Diagnosis Hypertension (%) Diabetes (%) Glomerulonephritis (%)	NR
Sensitisation – panel reactive antibodies	NR
HLA matches (%) 0–3 (%) 4–6 (%)	 MPS 62, MMF 60 MPS 37, MMF 38
Inclusion/exclusion criteria	Inclusion: first transplant Exclusion: asystolic donors; previous transplant; +ve T-cell match; ABO incompatible; HIV+ve; gout; malignancy; other study drugs within 4 weeks
Graft cold ischaemic time (h)	MPS 17 (9), MMF 16 (9)
Follow-up points (e.g. 3, 6, 12 months …)	6 and 12 months
Comments	

Immunosuppressive regimen

First author, year, trial name	**Salvadori et *al*., 2003**
Induction [not relevant here]	Used for treatment of acute rejection episodes
Azathioprine (mg/kg/day)	None
Prednisone	Tapered according to local practice but not less than 5 mg/day for at least 6 months
Ciclosporin (mg/kg/day)	Started at 10, trough 200–400 ng/ml 1–7 days, 200–300 weeks 1–4, 150–250 ng/ml 2–6 months, 100–200 ng/ml 7–12 months
Tacrolimus (mg/kg/day)	None
MMF	2 g/day (1 g b.d.)
MPS	1.44 g/day (720 mg b.d.)
Sirolimus	None
Comments	

Trial quality

First author, year, trial name	**Salvadori et *al*., 2003**
Method of randomisation stated?	Computer-generated
Method of allocation concealment stated?	No
Blinding undertaken (who)?	Patients, clinicians and investigators
Withdrawals (%)	Withdrawal/discontinuation MPS 62/213, MMF 52/210
Analysis by intention to treat?	Yes
Jadad score	4
Comments	

Outcomes at 6 months

First author, year, trial name	**Salavadori et *al*., 2003**
Patient deaths (*n*/*N*)	NR
Graft loss (*n*/*N*)	NR
Graft loss excluding all deaths (*n*/*N*)	NR
Biopsy confirmed acute rejection (*n*/*N*)	NR
Other acute rejection [define] (*n*/*N*)	NR
Glomerular filtration rate (ml/min/m^2)	NR
Serum creatinine (μmol/l)	NR
Adverse events Serious infections, diabetes, hyperlipidaemia and post-transplant lymphoproliferative disease	NR
Any infection (and any reported severity/treatment)	NR
Withdrawal due to any adverse event	NR
Growth Height and weight	NR
Quality of life	NR
Drug switching [i.e. number of patients who cross over from intervention to control drug or vice versa, or any form of switching]	NR
Comments	

Outcomes at 12 months

First author, year, trial name	**Salvadori *et al.*, 2003**
Patient deaths (*n*/*N*)	NR
Graft loss or death (*n*/*N*)	MPS 11/213 (5.2%), MMF 14/ 210 (6.7%)
Graft loss excluding all deaths (*n*/*N*)	NR
Biopsy confirmed acute rejection (*n*/*N*)	MPS 48/213 (22.5%), MMF 51/210 (24.3%)
Other acute rejection [define] (*n*/*N*)	NR
Glomerular filtration rate (ml/min/m^2)	NR
Serum creatinine (μmol/l)	NR
Adverse events Serious infections, diabetes, hyperlipidaemia and post-transplant lymphoproliferative disease	PTDM MPS 2/213, MMF 1/210 PTLD NR Hyperlipidaemia NR
Any infection (and any reported severity/treatment)	CMV MPS 46/213 (21.6%), MMF 43/210 (20.5%)
Withdrawal due to any adverse event	NR
Growth Height and weight	NR
Quality of life	NR
Drug switching [i.e. number of patients who cross over from intervention to control drug or vice versa, or any form of switching]	Did not report switching of MPS to MMF to other drugs
Comments	

Subgroup analyses

First author, year, trial name	**Salvadori *et al.*, 2003**
Subgroup examined	NR
Comments	

Appendix 10

Included paediatric and adult sirolimus RCTs

Note that where an outcome section (e.g. outcomes at 6 months) is missing in the following tables, data were not reported.

Patient characteristics

First author, year, trial name	**WYETH Study 0468E1-217-US [unpublished study report]** Sirolimus + CIC or TAC + steroid vs CIC or TAC + steroid ± AZA or MMF	**Kahan, 2000** SIR 2 mg/day + CIC + steroid SIR 5 mg/day + CIC + steroid AZA + CIC + steroid			**Machado, 2004** SIR + CIC + steroid AZA + CIC + steroid
Country(ies) (and years of recruitment)	Multicentre USA, Canada, Mexico [50 centres] Recruitment May 1999–June 2004	USA, 38 centres Conducted 1996–2000			Brazil June 1999–February 2000
Patient numbers [paediatric trials include breakdown of numbers by age, if reported]	SIR group $n = 65$ Control group $n = 37$ All aged ≤20 years	USA, 38 centres Conducted 1996–2000			Total 70 patients SIR $n = 35$ vs AZA $n = 35$
Age (years) Mean (SD) [range]	12.8 (SE 0.2) vs 15.4 (SE 0.7), $p = 0.0006$	SIR 2 mg/day, 44.9 (13.6)	SIR 5 mg/day, 46.8 (13.0)	AZA 45.6 (13.0)	35.8 ± 10.5 SIR vs 32.7 ± 10.4 AZA
Sex (proportion male %)	65 vs 65	208 (73%), $p < 0.001$; significantly more women than men were assigned SIR 5 mg/day and AZA	170 (62%)	91 (57%)	66% (23/35) SIR vs 66% (23/35) AZA
Body weight (kg) [paediatric studies only]	45.5 (SE 2.5) vs 54.0 (SE 3.1), $p = 0.001$	NR	NR	NR	NR
Donor (cadaveric/living/asystolic %)	Cadaver 26% SIR vs 24% control	Cadaveric 180 (63%)	167 (61%)	119 (74%)	100% living
Duration of dialysis (years)	NR	NR	NR	NR	NR
First transplant (%)	First or second	100%	NR	NR	100% all first
Ethnic group (proportion white %)	85/86	White 160 (56%) Black 63 (22%)	154 (56%) 62 (23%)	92 (57%) 41 (25%)	71% (25/35) white SIR vs 63% (22/35) AZA
Diagnosis					
Hypertension (%)	NR	72 (25%)	77 (28%)	47 (29%)	3 (9%) SIR vs 5 (14%) AZA
Diabetes (%)	NR	59 (21%)	53 (19%)	32 (20%)	5 (14%) SIR vs 1 (3%) AZA
Glomerulonephritis (%) [chronic]	6 SIR vs 1 control	64 (23%)	50 (18%)	18 (11%)	11 (31%) SIR vs 15 (43%) AZA

continued

Sensitisation – panel reactive antibodies	NR	% PRA 2.4 (SD 9.8)	3.2 (11.9)	3.7 (13.1)	<5 33/35 (94%) SIR vs 30/35 (86%) AZA ≥5 2/35 (6%) SIR vs 5/35 (14%) AZA
HLA matches (%)		3.4 (SE 0.2) mismatch	3.5 (0.1)	3.7 (0.3)	HLA mismatches: 2.7 ± 0.60 SIR vs 2.7 ± 0.5 AZA
0 (%)	2/9				
1 (%)	3/3				
2 (%)	36/34				
Inclusion/exclusion criteria	Inclusion: high risk paediatric/adolescent with ≥1 acute rejection episodes and/or biopsy proven CAN; ≤20 years old; acute rejection episode that responded to treatment and occurred ≥30 days before enrolment plus stable renal function at the time of enrolment; contraceptive use; total white cell count ≥4000/mm^3; platelet count ≥100,000/mm^3; fasting triglycerides ≤500 mg/dl; fasting cholesterol ≤350 mg/dl Exclusion: pregnancy; multi-organ transplant; lack of biopsy at entry; active infection; history of malignancy; investigational product within 4 weeks; use of immunosuppressive agents; current use of cytochrome P450 inducers/inhibitors, unless discontinued before administration of SIR; current use of terfenadine, cisapride, astemizole or pimozide unless discontinued before admin of SIR; chest radiograph abnormality; hypersensitivity to sirolimus	Inclusion: end-stage renal disease; aged 13 years and over; weight >40 kg; women with negative pregnancy test; white cell count ≥4 × 10^9/l; platelets ≥100 × 10^9/l; triglycerides ≤5.65 mmol/l (5.5 US); cholesterol ≤9.1 mmol/l; solitary renal transplant Exclusion: systemic infection; angina; myocardial infarction in previous 6 months; continuing treatment for life-threatening arrhythmia; history of malignancy; previous trial drug in 4 weeks; previous use of immunosuppression; concomitant treatment with cytochrome P450 inducers or inhibitors or terferadine, cisapride, astemizole, pimozide; use of antibiotic induction treatment; continuing gastrointestinal disorders likely to interfere with drug absorption; abnormal chest X-ray; known hypersensitivity to macrolide antibiotics, azathioprine, 6-mercaptopurine			Inclusion: end-stage renal disease; aged 13 years of age or older; weight 40 kg or more; first haplotype living related kidney transplant; negative T-cell crossmatch; negative pregnancy test for women; for women to have a medically approved birth control; white total blood cell count ≥4.0 × 10^9/l; platelet count ≥100.0 × 10^9/l; fasting cholesterol ≤350 mg/dl (≤9.1 mmol/l) and/or fasting triglycerides ≤500 mg/dl (≤5.65 mmol/l) Exclusion: systematic infection; clinically significant cardiac abnormalities; malignancies within the last 10 years; treatment with an investigational agent within 4 weeks of administration of SIR; prior immunosuppressive agent/P450 inducers/inhibitors; abnormal chest radiography; known hypersensitivity to macrolides; those requiring induction therapy
Graft cold ischaemic time (h)	20.8/20.7	NR	NR	NR	NR
Follow-up points (e.g. 3, 6, 12 months …)	Up to 36 months	12 months	Age of donor 44.5 ± 11.1 SIR vs 42.9 ± 10.0 AZA Follow-up time 12 months		
Comments		Clinical end-point: composite of graft loss; death, loss to follow-up; first occurrence of BPAR within 6 months (efficacy failure); Bonferroni 0.025 ITT For US trial, transplant had to be judged as functional before trial entry to avoid need for induction therapy (prohibited)			Age of donor 44.5 ± 11.1 SIR vs 42.9 ± 10.0 AZA Follow-up time 12 months

Patient characteristics

First author, year, trial name	**Johnson, 2001** **Rapamune Maintenance Regime (RMR)** Initial 3 months post-transplant: SIR 2 mg/day + CIC + steroid Randomised at 3 months SIR 2 mg/day + CIC + steroid SIR 2 mg/day + steroid	**Groth, 1999** SIR 16–24 mg/m^2/day initial followed 8–12 mg/m^2/day CIC 10 mg/kg/day
Country(ies)	Europe, Canada, Australia, 57 centres Enrolled May 1998–June 1999	Europe 11 centres
Patient numbers [paediatric trials include breakdown of numbers by age, if reported]	Total 525 SIR 2 mg/day + CIC + steroid – 215 SIR 2 mg/day + steroid – 215	Total 83 SIR 41 CIC 42
Age (years) Mean (SD) [range]	45.8 SIR + CIC + steroid/44.6 SIR + steroid	48/42
Sex (proportion male %)	66.5/61.9	29/25
Body weight (kg) [paediatric studies only]	NA	NA
Donor (cadaveric/living/asystolic %)	Cadaveric 87.9/88.4	100
Duration of dialysis (years)	NR	NR
First transplant (%)	91.6/90.2 or second only	100
Ethnic group (proportion white %)	93.5/95.3	98/88
Diagnosis Hypertension (%) Diabetes (%) Glomerulonephritis (%)	 7.0/5.1 6.5/7.9 22.8/20.5	 NR NR NR
Sensitisation – panel reactive antibodies	NR	NR
HLA matches (%) 0 (%) 1 (%) 2 (%)	HLA mismatches 2.9/3.0	15/12 17/17 27/21

continued

Inclusion/exclusion criteria	Inclusion: end-stage renal disease; aged 13 years and over, weight ≥40 kg; women with negative pregnancy test; white cell count ≥4 × 10^9/l; platelets ≥100 × 10^9/l; triglyceride ≤5.65 mmol/l (5.5 US); (fasting triglycerides ≤4.6 mmol/l); cholesterol ≤9.1 mmol/l (fasting cholesterol ≤7.8 mmol/l); solitary renal transplant Exclusion: systemic or localised major infection; chronic ventricular arrhythmia; history of malignancy; previous trial drug in 4 weeks; previous use of immunosuppression; concomitant treatment with strong cytochrome P450 inducers or inhibitors or terferadine, cisapride, astemizole, pimozide; use of antibiotic induction treatment; continuing gastrointestinal disorders likely to interfere with drug absorption; abnormal chest X-ray; known hypersensitivity to macrolide antibiotics, azathioprine, 6-mercaptopurine Exclusion for randomisation: Banff 3 acute rejection; vascular rejection in preceding 4 weeks; dialysis dependency; serum creatinine >400 μmol/l; inadequate renal function to support CIC elimination	Inclusion: 18 and 60 years of age and receive a primary cadaveric donor kidney that was functional within 24 h after transplantation. Protocol deviations were approved that permitted the enrollment of 6 patients over 60 years of age, and 10 patients were enrolled who subsequently had acute tubular necrosis. Exclusion: Evidence of systemic infection, an unstable disease state (i.e. unstable hypertension or diabetes mellitus), clinically significant cardiac abnormality, history of malignancy, or an active gastrointestinal disorder, which might interfere with drug absorption. Pregnant women were excluded, as were patients having pretransplant sera containing panel-reactive antibodies ≥ 70%.
Graft cold ischaemic time (h)		18.9/17.4
Follow-up points (e.g. 3, 6, 12 months …)	17.8/16.4	12 months
Comments	1, 2 and 4 years	

Immunosuppressive regimen

First author, year, trial name	0468E1-217-US	Kahan, 2000	Machado, 2004	Johnson, 2001	Groth, 1999
Induction [not relevant here]	None	None	NA	None	None
Azathioprine (mg/kg/day)	Details not given	1st dose within 24–48 h 2–3 mg/kg daily	Initial dose 1.5–2 mg/kg/day	None	Initial dose 2 mg/kg/day
Prednisone	Trough level <20 mg/m^2/day	500 mg loading dose then tapering to 30 mg daily by 6th day, 10 mg daily by 6 months and 5–10 mg daily thereafter	Methylprednisolone 1 g before graft revascularisation and then 0.5 mg/kg/day prednisolone, max. 30 mg/day for 30 days, tapered to 20 mg/day by month 2 and 10 mg/day between months 3 and 6	Local standard practice and were then tapered by month 6 to 5–10 mg/day	500 mg loading dose then tapering to 30 mg/daily by 7th day, 10 mg/daily by month 6
Ciclosporin (mg/kg/day)	Trough level 100–300 ng/ml	Dose adjusted according to trough concentrations Neoral Microemulsion 9–12 within 48 h; 200–350 ng/ml 1st month; 200–300 ng/ml 2nd month; 150–250 ng/ml thereafter	8–10 mg/kg twice daily within 24 h of graft revascularisation, then adjusted trough 200–400 ng/ml during 1st month, 200–300 ng/ml month 2, 150–250 ng/ml thereafter microemulsion CIC reduced more rapidly and earlier post-transplant if in SIR group	Dose adjusted according to trough concentrations Neoral Microemulsion 9–12 within 48 h, 200–400 ng/ml 1st month, 150–300 ng/ml 2nd month to randomisation, 150–250 ng/ml thereafter	Initial dose of 10 mg/kg/day, with dosage then adjusted to maintain whole blood trough levels of 200–400 ng/ml for 2 months, and 100–200 ng/ml thereafter
Tacrolimus (mg/kg/day)	Trough level 5–15 ng/ml	NA	NA	None	None
MMF	Details not given	NA	NA	None	None
MPS	None	NA	NA	None	None
Sirolimus	Trough level 5–15 ng/ml	Single loading dose of either 6 or 15 mg then 2 or 5 mg daily oral solution	6 mg SIR loading dose orally followed by 2 mg fixed daily dose	2 mg/day then adjusted to maintain trough level above 5 ng/ml	Initial loading dose of 16–24 mg/m^2/day, followed by 8–12 mg/m^2/day until day 7–10, then adjusted to achieve steady-state whole blood trough levels of approximately 30 ng/ml for 2 months, and 15 ng/ml thereafter
Comments				Triple therapy arm: SIR as above once randomised with CIC troughs 75–200 ng/ml Dual therapy arm: SIR trough 20–30 ng/ml and CIC gradually reduced and eliminated over 4–6 weeks	

Trial quality

First author, year, trial name	0468E1-217-US	Kahan, 2000	Machado, 2004	Johnson, 2001	Groth, 1999
Method of randomisation stated?		Yes (computer generated, US stratified by black recipients and treatment centre)	NR	Yes (computer generated)	Yes (computer generated)
Method of allocation concealment stated?		Yes, telephone	NR	Yes, telephone	Yes, telephone
Blinding undertaken (who)?	[**Confidential information removed**]	Yes, patients, physicians, medical personnel of Wyeth all blinded Appropriate placebos matched to AZA and SIR	No, open-label	No, open label	No, open label
Withdrawals (%)		2%	NR	NR	NR
Analysis by intention to treat?		Yes	Yes, Table 4	Yes	Yes
Jadad score		4	1	3	3

Outcomes at 6 months

First author, year, trial name	**0468E1-217-US**	**Kahan, 2000** SIR 2 mg/day	**Kahan, 2000** SIR 5 mg/day	**Kahan, 2000** AZA
Patient deaths (*n*/*N*)		NR	NR	NR
Graft loss (*n*/*N*)		NR	NR	NR
Graft loss excluding all deaths (*n*/*N*)		NR	NR	NR
Biopsy confirmed acute rejection (*n*/*N*)		48/284 (16.9)	33/274 (12.0)	48/161 (29.8)
Other acute rejection [define] (*n*/*N*)		NR	NR	NR
Glomerular filtration rate (ml/min/m^2)		NR	NR	NR
Serum creatinine (μmol/l)		154.2 (3.7)	157.6 (4.6)	129.4 (5.5)
Adverse events Serious infections, diabetes, hyperlipidaemia and post-transplant lymphoproliferative disease	[**Confidential information removed**]	62.29 (1.22)	59.15 (1.51)	68.78 (2.13)
Any infection (and any reported severity/treatment)		NR	Hypercholesterolaemia *n* = 281; 269; 159: 30%; 35%; 21%	Hyperlipidaemia *n* = 281; 269; 159: 30%; 38%; 18%
Withdrawal due to any adverse event		NR	NR	NR
Growth Height and weight		19/284 (6.7%)	29/274 (10.6%)	15/161 (9.3%)
Quality of life		NR	NR	NR
Drug switching [i.e. number of patients who cross over from intervention to control drug or vice versa, or any form of switching]		NR	NR	NR
Comments				

Outcomes at 6 months

First author, year, trial name	Johnson, 2001 RMR study	Groth, 1999
Patient deaths (*n*/*N*)	NR	0/41 vs 1/42
Graft loss (*n*/*N*)	NR	40/41 vs 38/42
Graft loss excluding all deaths (*n*/*N*)	NR	NR
Biopsy confirmed acute rejection (*n*/*N*)	NR	17/41 vs 16/42
Other acute rejection [define] (*n*/*N*)	NR	NR
Glomerular filtration rate (ml/min/m^2)	NR	NR
Serum creatinine (μmol/l)	NR	69.5 vs 58.7
Adverse events Serious infections, diabetes, hyperlipidaemia and post-transplant lymphoproliferative disease	NR	Hyperglycaemia: 8/41 vs 3/42 PTDM: 1/41 vs 1/42 PTLD: NR
Any infection (and any reported severity/treatment)	NR	CMV 6/41 vs 5/42
Withdrawal due to any adverse event	NR	NR
Growth Height and weight	NR	NR
Quality of life	NR	NR
Drug switching [i.e. number of patients who cross over from intervention to control drug or vice versa, or any form of switching]	NR	NR
Comments	Mean steroid dose 10.5 mg/day triple vs 10.0 mg/day dual	

Outcomes at 12 months

First author, year, trial name	0468E1-217-US	Kahan, 2000 SIR 2 mg/day; SIR 5 mg/day; AZA	Machado, 2004	Johnson, 2001 RMR study SIR + CIC vs SIR alone
Patient deaths (*n*/*N*)		15/284; 19/274; 5/161	1/35 (2.9) SIR vs 1/35 (2.9) AZA	6/215 vs 4/215
Graft loss (*n*/*N*)		16/284; 20/274; 9/161 Graft survival from Kaplan–Meier 94.3%; 92.7%; 94.4%	1/35 (2.9) SIR vs 1/35(2.9) AZA	9/215 vs 6/215
Graft loss excluding all deaths (*n*/*N*)		9/284; 12/274; 7/161	NR	NR
Biopsy confirmed acute rejection (*n*/*N*)		62/284 (21.8%); 40/274 (14.6%); 50/161 (31.1%)	5/35 (14.3) SIR vs 7/35 (20) AZA, $p = 0.752$ 4/35 (11.4%) SIR vs 5/35 (14.3%) AZA	9/215 vs 21/215
Other acute rejection [define] (*n*/*N*)		NR	NR	NR
Glomerular filtration rate (ml/min/1.72 m^2)		NR	Creatinine clearance for ITT: 59.7 ± 19.9 SIR vs 68.1 ± 24.6 AZA, $p = 0.136$	56.6 ± 1.3 ($n = 215$) vs 62.7 ± 1.5 ($n = 215$) mean ± SE
Serum creatinine (μmol/l)	[**Confidential information removed**]	160.0 (4.9); 171.1 (6.0); 133.1 (5.1)	For ITT: 1.8 ± 0.6 (33 mg/dl) SIR vs 1.6 ± 0.6 (33) AZA, $p = 0.226$	158.1 ± 4.2 ($n = 215$) vs 141.6 ± 5.3 ($n = 215$) mean ± SE
Adverse events Serious infections, diabetes, hyperlipidaemia and post-transplant lymphoproliferative disease		61.95 (1.36); 55.48 (1.62); 67.51 (1.83)	Any infection: 32/35 (91%) SIR vs 27/35 (77%) AZA Bacterial, viral and herpes subgroups given Diabetes 2 (6%) SIR vs 2 (6%) AZA Hyperlipidaemia 17 (49%) SIR vs 6 (17%) AZA, $p = 0.01$ No malignancies during follow-up period	NR
Any infection (and any reported severity/treatment)		Hypercholesterolaemia $n = 281$; 269; 159: 33%; 37%; 24% Hyperlipidaemia $n = 281$; 269; 159: 34%; 42%; 24% PTDM NR Lymphoma 0.4%; 2 0.7%; 1 0.6%	NR	Generalised CMV 2.3% vs 2.8%, both $n = 215$ PTDM-insulin dependent 1.4% triple vs 2.8% dual PTDM 3.3% vs 4.0% PTLD 6/215 vs 3/215 Serum cholesterol (mmol/l)

continued

		PTLD NR		6.0 vs 6.3 Hypercholesterolaemia 16.3% vs 24.7% Serum triglyceride (mmol/l) 2.2 vs 2.5 Hypertriglyceridaemia 25.1% vs 31.2%
Withdrawal due to any adverse event	[**Confidential information removed**]	*n* = 281; 269; 159 Bacterial Sepsis 24 (8.5%); 22 (8.0%); 6 (3.7%) UTI 54 (19.1%); 60 (22.1%); 45 (28.5%) Pneumonia 8 (2.8%); 16 (5.8%); 3 (1.9%) *P. carinii* pneumonia 2 (0.7%); 1 (0.4%); 0 Systemic CMV 9 (3.2%); 8 (2.9%); 9 (5.6%) Tissue invasion CMV 3 (0.7%); 3 (1.1%); 2 (1.2%) Herpes zoster 9 (3.2%); 12 (4.4%); 8 (5.0%) Herpes simplex 13 (4.6%); 28 (10.2%); 7 (4.4%) EBV 0; 1 0.4%; 0	NR	All infections CMV
Growth Height and weight		NR	NR	30/215 vs 37/215
Quality of life		NR	Results were also reported for with and without acute rejection	NA
Drug switching [i.e. number of patients who cross over from intervention to control drug or vice versa, or any form of switching]		NR	NR	NR
Comments				Mean steroid dose 8.1 mg/day triple vs 9.3 mg/day dual

Outcomes at longest follow-up point

First author, year, trial name	0468E1-217-US	Kahan, 2000 2-years	Johnson, 2001 RMR study SIR + CIC vs SIR alone 2 years (Oberbauer)
		Survival estimated from Kaplan–Meier curves (cumulative): SIR 2 mg/day 95%; SIR 5 mg/day 93%; AZA 97%	13/215 vs 10/215
Patient deaths (*n*/*N*)		Survival estimated from Kaplan–Meier curves (cumulative): SIR 2 mg/day 96%; SIR 5 mg/day 92%; AZA 93%	19/215 vs 14/215
Graft loss (*n*/*N*)			
Graft loss excluding all deaths (*n*/*N*)		Sir 2 mg/day 23.6%/284; Sir 5 mg/day 17.5%/274; AZA 32.3%/161 cumulative %	11/215 vs 21/215
Biopsy confirmed acute rejection (*n*/*N*)		NR	NR
Other acute rejection [define] (*n*/*N*)		NR	NR
Glomerular filtration rate (ml/min/1.72m^2) [18 months]	[**Confidential information removed**]	Mean mg/dl 1.5 (*n* = 61) AZA; 1.8 (*n* = 100) SIR 2 mg/day; 2.1 (*n* = 94) SIR 5 mg/day	172 (SE 4.8) vs 143 (SE 5), *n* = 187 for both; includes values from discontinued patients (values for 6 and 12 months did not?)
Serum creatinine (μmol/l)		AZA 66.9 (*n* = 61); SIR 2 mg/day 62.4 (*n* = 100): SIR 5 mg/day 54.6 (*n* = 94)	NR
Adverse events Serious infections, diabetes, hyperlipidaemia and post-transplant lymphoproliferative disease		Lymphoma/PTLD 1/161 AZA; 2/284 SIR 2 mg/day; 3/274 SIR 5 mg/day Hypercholesterolaemia AZA 44/160; SIR 2 mg/day 99/281; SIR 5 mg/day 106/269 Hyperlipidaemia AZA 41/160; SIR 2 mg/day 98/281; SIR 5 mg/day 115/269 Diabetes mellitus AZA 13/160; SIR 2 mg/day 20/281; SIR 5 mg/day 29/269	PTDM NR PTLD 3/215 vs 1/215 Hyperlipidaemia NR
Any infection (and any reported severity/treatment) CMV		% using ITT population (*n* NR) AZA; SIR 2 mg/day; SIR 5 mg/day Bacterial sepsis 6.2%; 8.8%; 8.8% UTI/pyelonephritis 32.91%; 22.5%; 25.9% Pneumonia 5.6%; 7.7%; 9.5% *P. carinii* pneumonia 0%; 0.7%; 0.4%	All infections NR CMV NR

continued

		Systemic CMV 4.3%; 3.9%; 3.3% Tissue invasion CMV 3.1%; 1.4%; 1.8% Herpes zoster 6.8%; 3.2%; 6.2% Herpes simplex 5.0%; 5.3%; 4.4% EBV 0%; 0%; 0.7%	
Withdrawal due to any adverse event	[**Confidential information removed**]	% of patients at 24 months discontinuing treatment due to adverse events: 21 (13.0%) AZA; 33 (11.6%) SIR 2 mg/day; 57 (20.8) SIR 5 mg/day	52/215 vs 50/215
Growth Height and weight		NR	NR
Quality of life		NR	NR
Drug switching [i.e. number of patients who cross over from intervention to control drug or vice versa, or any form of switching]		NR	NR
Comments			

Subgroup analyses

First author, year, trial name	0468E1-217-US	Kahan, 2000	Machado, 2004	Johnson, 2001 RMR study	Groth, 1999
Subgroup examined	[**Confidential information removed**]	Living vs cadaver Ethnic origin (black or other groups) Antibody treatment at 6 months HLA mismatches at 6 months All for BPAR BPAR lower in living-donor recipients at 6 and 12 months in the SIR 2 mg/day group (each $p < 0.001$) than AZA	NR	NR	NR
Comments					

Appendix 11

Ongoing and recently completed RCTs

Location	Trial	Status
United Bristol Healthcare NHS Trust	MREC 00/04/049 Paediatric tacrolimus triple regimen with/without monoclonal antibody after kidney transplantation	Completed August 2003 Publication ID N0264146203 Source: NRR 2004 Issue 4
University Hospital Birmingham NHS Trust	Mycophenolate mofetil (MMF) in the management of chronic allograft nephropathy: a prospective randomised analysis of renal biopsy and clinical outcomes	Ongoing, end date April 2005 Publication ID N0265105792 Source: NRR 2004 Issue 4
St James' University Hospital Leeds	(ECSEL) A phase 04, randomised open-label, controlled, single-centre study of induction with basiliximab, mycophenolate mofetil and tacrolimus with rapid steroid withdrawal and randomisation to either continuation with mycophenolate mofetil and tacrolimus	Ongoing, end date April 2007 Publication ID N0285150656 Source: NRR 2004 Issue 4
Bradford Teaching Hospitals NHS Foundation Trust/St James' University Hospital Leeds	ECSEL: a randomised prospective trial of MMF and tacrolimus induction with rapid steroid withdrawal and early switch to sirolimus in renal transplantation	Ongoing, end date April 2007 Publication ID N0050149628 Source: NRR 2004 Issue 4
Sponsored by National Institute of Allergy and Infectious Diseases (NIAID)	Steroid withdrawal in paediatric kidney transplant recipients	Ongoing Study ID Numbers: DAIT SW01; SW01 Identifier: NCT00023244 Source: ClinicalTrials.gov
Sponsored by National Institute of Allergy and Infectious Diseases (NIAID)	Paediatric kidney transplant without calcineurin inhibitors	Ongoing Study ID Numbers: DAIT CN01; CN01 Identifier: NCT00023231 Source: ClinicalTrials.gov
Sponsored by Hoffmann-La Roche	A study to evaluate a fixed dose of CellCept compared to adjusted dose of CellCept in patients following a single organ kidney transplant in combination with full dose and reduced dose of calcineurin inhibitors	Ongoing Study ID Number: ML17225 Identifier: NCT00087581 Source: ClinicalTrials.gov
Sponsored by Fujisawa/Astellas Healthcare Inc.	Comparative study of modified release (MR) tacrolimus/MMF in *de novo* kidney transplant recipients	Ongoing Study ID Number: 02-0-158 Identifier: NCT00064701 Source: ClinicalTrials.gov
Sponsored by National Institute of Allergy and Infectious Diseases (NIAID)	A study to compare treatment with sirolimus versus standard treatment in patients who have received a kidney transplant	Ongoing Study ID Numbers: DAIT 0468E1-217-US; SRL1 Identifier: NCT00005113 Source: ClinicalTrials.gov
Sponsored by Wyeth-Ayerst Research	End-stage renal disease – high-risk transplant recipients	Ongoing Study ID Number: 0468H1-101164 Identifier: NCT00044720 Source: ClinicalTrials.gov
Sponsored by National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)	Sirolimus and thymoglobulin to prevent kidney transplant rejection	Ongoing Study ID Numbers: 000196; 00-DK-0196 Identifier: NCT00006178 Source: ClinicalTrials.gov

Appendix 12

Wyeth economic model (reproduced from adult TAR report)

Model critique

The main criticisms of the model are as follows.

1. Clarity over structure and process of model
   The description of the model is generally poor. An assumption is made without any discussion or justification that a percentage of sirolimus patients have graft function decline. From the spreadsheet model it becomes clear that 50% of sirolimus patients are assumed to have the same decline in renal function as those on ciclosporin and that 27% of patients starting on sirolimus switch within 1 year to ciclosporin, with a further 5% switching in subsequent years. No rationale is provided for these assumptions.

2. Reliance on creatinine as a proxy for long-term outcomes
   As discussed above, this is based on a single, albeit large and peer-reviewed, study. The debate between creatinine and acute rejection as predictors of graft survival is controversial and continuing.

3. Extrapolation of creatinine at 36 months
   Considerable effort is put into extrapolating creatinine levels at 36 months, using both the trial data for 12 and 24 months and the University of Wales Hospital data. The reason for this only becomes clear when these data provide the basis of the longer term projections of patient and graft survival.

4. Extrapolation to 10 and 20 years
   The derivation of 10- and 20-year graft and patient survival rates based on models linking creatinine to graft and patient survival at 1, 2 and 3 years is not fully described in the submission. The model extrapolates the 3-year survival curves to 10 years but the assumptions involved are not explained. Both death.xls and graft GF.xls (GF = graft failure) rely on curves for 1, 2 and 3 years, with each using extrapolations of the 3-year curve to obtain values for up to 10 years. A single curve is provided for acute rejection over time. It is only from reading the Wyeth submission technical appendix '12.8.2 Renal Submission – Manual' that it becomes clear that graft failure for the period beyond 3 years is based on the creatinine levels curve for year 3. How this is done is not explained. An indication of the method is provided in an apparently unpublished paper by McEwan and colleagues analysing the University of Wales Hospital database, which includes several figures provided in the Wyeth submission (Figures 7.1 and 7.3 in the submission are from the McEwan paper without acknowledgement). The latter paper states that these are conventional Kaplan–Meier curves. The same paper appears to be the source of the time from first transplant (but this is not mentioned in the submission).

5. Costs
   The reliance for cost data on the Cardiff database, although welcome in some ways, poses problems in that these costs relate to older regimens, and include a wide range of costs of treating co-morbidities. Unfortunately, these cannot readily be linked to specific adverse outcomes and therefore are not comparable to most of the other models.

6. Small differences in outcomes leading to unstable ICERs.

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Dr Ross Taylor,
Senior Lecturer, Department of General Practice and Primary Care, University of Aberdeen

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Consumer member, HTA – Expert Advisory Network

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We look forward to hearing from you.

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@hta.ac.uk
http://www.hta.ac.uk

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