NICE National Institute for Health and Care Excellence

Immunosuppressive therapy for renal transplantation in children and adolescents

Issued: April 2006

NICE technology appraisal guidance 99

guidance.nice.org.uk/ta99

© NICE 2006

Contents

1 Guidance 4

2 Clinical need and practice 6

Induction therapy 9

Initial therapy 9

Maintenance therapy 10

Acute rejection therapy 10

3 The technologies 11

Basiliximab 11

Daclizumab 11

Tacrolimus 12

Mycophenolate mofetil 13

Mycophenolate sodium 13

Sirolimus 14

4 Evidence and interpretation 15

4.1 Clinical effectiveness 15

4.2 Cost effectiveness 21

4.3 Consideration of the evidence 24

5 Recommendations for further research 32

6 Implications for the NHS 33

7 Implementation and audit 34

8 Related guidance 36

9 Review of guidance 37

Appendix A. Appraisal Committee members and NICE project team 38

A. Appraisal Committee members 38

B. NICE Project Team 41

© NICE 2006. All rights reserved. Last modified April 2006

Appendix B. Sources of evidence considered by the Committee 42

Appendix C. Detail on criteria for audit of the use of immunosuppressive therapy for renal transplantation in children and adolescents 46

Possible objectives for an audit 46

Possible patients to be included in the audit 46

Measures that could be used as a basis for an audit 46

Calculation of compliance 50

Changes after publication 51

About this guidance 52

© NICE 2006. All rights reserved. Last modified April 2006

1 Guidance

This guidance considers the use of basiliximab, daclizumab, tacrolimus, mycophenolate (mofetil and sodium) and sirolimus in relation to a standard triple therapy regimen of ciclosporin, azathioprine and a corticosteroid following renal transplantation in children and adolescents.

1.1 Basiliximab or daclizumab, used as part of a ciclosporin-based immunosuppressive regimen, are recommended as options for induction therapy in the prophylaxis of acute organ rejection in children and adolescents undergoing renal transplantation, irrespective of immunological risk. The induction therapy (basiliximab or daclizumab) with the lowest acquisition cost should be used, unless it is contraindicated.

1.2 Tacrolimus is recommended as an alternative option to ciclosporin when a calcineurin inhibitor is indicated as part of an initial or a maintenance immunosuppressive regimen for renal transplantation in children and adolescents. The initial choice of tacrolimus or ciclosporin should be based on the relative importance of their side-effect profiles for the individual patient

1.3 Mycophenolate mofetil (MMF) is recommended as an option as part of an immunosuppressive regimen for child and adolescent renal transplant recipients only when:

- there is proven intolerance to calcineurin inhibitors, particularly nephrotoxicity which could lead to **risk** of chronic allograft dysfunction, or
- there is a very high risk of nephrotoxicity necessitating the minimisation or avoidance of a calcineurin inhibitor until the period of high risk has passed.

1.4 The use of MMF in corticosteroid reduction or withdrawal strategies for child and adolescent renal transplant recipients is recommended only within the context of randomised clinical trials.

1.5 Mycophenolate sodium (MPS) is currently not recommended for use as part of an immunosuppressive regimen in child or adolescent renal transplant recipients.

© NICE 2006. All rights reserved. Last modified April 2006

1.6 Sirolimus is not recommended for children or adolescents undergoing renal transplantation except when proven intolerance to calcineurin inhibitors (including nephrotoxicity) necessitates the complete withdrawal of these treatments.

1.7 As a consequence of following this guidance, some medicines may be prescribed outside the terms of their UK marketing authorisation. Healthcare professionals prescribing these medicines should ensure that children and adolescents receiving renal transplants and/or their legal guardians are aware of this, and that they consent to the use of these medicines in these circumstances.

© NICE 2006. All rights reserved. Last modified April 2006

2 Clinical need and practice

2.1 It is well documented that transplantation offers more efficient renal replacement therapy than dialysis, with the added benefits of better health-related quality-of-life and better social rehabilitation. Improved well-being for a child has implications not only for the child, but also for the parents, siblings and members of the extended family.

2.2 Over the past three decades, renal transplantation has become established as the treatment of choice for many patients with end-stage renal failure. The only alternative is dialysis. The establishment of transplantation has been made possible by the introduction of immunosuppressants. Currently, there is no standard immunosuppression regimen for children or adolescents undergoing renal transplantation, but most children in the UK receive triple therapy with a calcineurin inhibitor (ciclosporin or tacrolimus), a DNA proliferation inhibitor (usually azathioprine), and a corticosteroid.

2.3 In 2003 about 13,000 patients in England and about 900 in Wales were receiving immunosuppressive treatment after renal transplantation. A Renal Registry Report states that approximately 1800 people in England and Wales underwent renal transplantation between April 2003 and March 2004. Of these, approximately 130 (7%) were under 18 years of age.

2.4 Renal transplants can be unsuccessful for a number of reasons, including technical failure, recurrence of the original renal disease in the allograft, chronic allograft dysfunction (formerly called chronic rejection – that is, long-term deterioration of the graft), acute rejection, and death of the recipient with a functioning graft.

2.5 Chronic allograft dysfunction is arguably the most common cause of late graft loss. It is usually a gradual process, although both the time of onset and the rate of progression vary. Chronic allograft dysfunction can develop as early as within a few months of the transplant or it can emerge after several years. The course is generally unremitting, ultimately leading to total loss of graft function and necessitating retransplantation or a return to dialysis.

© NICE 2006. All rights reserved. Last modified April 2006

2.6 Episodes of acute rejection are most frequently observed during the first few weeks after transplantation, but they can occur at any time if the level of immunosuppression becomes inadequate. The response, which may be cell- or antibody-mediated, leads to injury to, or destruction of, the functioning cellular structures of the transplanted organ. Occasionally, the response can be more aggressive and include a vascular component. Clinically, acute rejection tends to occur as an acute episode heralded by a reduction in graft function (seen as changes in urine biochemistry and a reduction in urine output) and clinical features, such as fluid retention and, occasionally, graft tenderness or fever.

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

2.8 Organ transplantation is not considered fully successful for children and adolescents unless they grow and develop as normal after transplantation. Growth retardation often occurs in children with chronic renal insufficiency, and the use of corticosteroids in children may also retard growth.

2.9 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 aged 1 year or older have been reported in North America. Longer-term graft survival appears to vary with age: those aged 10 years and under appear to have the best 5-year graft survival (70–90%), while 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 concordance with immunosuppressive regimens.

2.10 Concordance with medication is a major problem in children and adolescents with renal transplants, the problem being greatest among adolescents. Poor

© NICE 2006. All rights reserved. Last modified April 2006

concordance is more likely to occur with medication that is complex to administer or is associated with side effects. Therefore, regimens that have minimal side effects are particularly important in these groups.

2.11 People who undergo renal transplantation need to receive lifelong (or, at least, long-term) treatment with immunosuppressive drugs. When selecting these treatments, the risk of immunologically mediated graft failure for any donor–recipient pair needs to be balanced against the medication's side effects for the recipient. The ultimate aim of treatment is to prolong patient and graft survival without exposing the patient to risks of excessive immunosuppression or nephrotoxicity.

2.12 Complications of immunosuppression include increased risk of developing infections, including viral infections such as cytomegalovirus (CMV), herpes simplex and herpes zoster, and Epstein–Barr virus, as well as opportunistic protozoal, fungal and bacterial infections. Because immunosuppression is usually at its highest level in the first 6 months after transplantation, this is also the peak period for infections in patients. Although modern immunosuppressive agents have activity directed principally towards the components of the rejection response, recipients are at a much higher risk of infections than the general population throughout their post-transplant life.

2.13 Suppression of the immune system is also associated with an increase in the risk of developing cancers, especially lymphoproliferative disorders.

2.14 The risk of premature death as a result of cardiovascular disease is well documented in renal transplant recipients. This is largely because of previous damage incurred during chronic renal failure. Dyslipidaemia is common in patients with end-stage renal failure, and some immunosuppressive drugs are thought to be associated with adverse lipid profiles. Hypertension and weight gain are also among the side effects of immunosuppressive drugs.

2.15 De novo post-transplant diabetes mellitus (PTDM) is another side effect of treatment. Some patients are at increased risk of this complication (for example, because of ethnic background, obesity or family history).

© NICE 2006. All rights reserved. Last modified April 2006

2.16 Nephrotoxicity is a particular complication of some immunosuppressive regimens, notably the calcineurin inhibitors, and may increase the risk of chronic graft dysfunction.

2.17 Other treatment side effects, depending on the medication used, include hirsutism, alopecia, tremors, mood swings and gastrointestinal intolerance. Some side effects are temporary and resolve with dose reduction. Others may require a change in treatment.

2.18 Most treatment centres attempt to categorise donor–recipient pairs according to the degree of perceived immunological risk and offer corresponding differing intensities of immunosuppression. Risk factors for acute rejection episodes include poor human leukocyte antigen (HLA) matching, high levels of antibody sensitisation, prolonged graft cold ischaemia times and previous renal transplantation. Most centres adopt different strategies for patients with delayed graft function, for those who receive kidneys from non-heart-beating donors, and for those who receive kidneys from live donors.

2.19 Immunosuppressive treatment following renal transplantation can be categorised as follows.

Induction therapy

2.20 Induction therapy is a course of intensive immunosuppression for about 2 weeks immediately after transplantation (although it is often started in the immediate preoperative period). The aim is to 'switch off' the immune system after transplantation to reduce the likelihood of accelerated rejection and acute rejection. It has also been used to reduce exposure to calcineurin inhibitors in the early stages after transplantation when the graft may be particularly vulnerable to their nephrotoxic effects. Basiliximab and daclizumab are the two relevant induction therapies for the purposes of this guidance.

Initial therapy

2.21 Initial therapy is the treatment given to all recipients (except if the donor is an identical twin) for 0–3 months after transplantation. Initial therapy is usually

© NICE 2006. All rights reserved. Last modified April 2006

'triple therapy', in which a calcineurin inhibitor (traditionally ciclosporin) is used as the 'primary agent' in combination with a corticosteroid (prednisolone) and azathioprine. Occasionally, dual therapy (a calcineurin inhibitor plus a corticosteroid) is used.

Maintenance therapy

2.22 Maintenance therapy is the treatment that transplant recipients receive in the long term, throughout the duration of allograft survival. Often, maintenance therapy is identical to initial therapy, except that the dosage is reduced because the transplanted kidney becomes immunologically more stable with increasing time. However, it is also not uncommon for agents used in maintenance therapy to be altered in response to the development of acute rejection, severe infections or nephrotoxicity. Poor tolerability leading to non-adherence to treatment is another possible reason for changing drugs.

Acute rejection therapy

2.23 Maintenance therapies are sometimes adjusted either temporarily or permanently following acute rejection, particularly following multiple rejection episodes. However, short courses of high-dose corticosteroids are the standard treatment for episodes of acute rejection. In most cases, corticosteroids treat the problem quickly and effectively, although it is not unusual for two courses of corticosteroids to be needed. If acute rejection does not resolve after treatment with corticosteroids, it is defined as 'corticosteroid-resistant acute rejection'. Corticosteroid-resistant acute rejection may be treated with the polyclonal antibodies ALG or ATG or the monoclonal antibody muromonab-CD3, or by switching the calcineurin inhibitor to high-dose tacrolimus.

© NICE 2006. All rights reserved. Last modified April 2006

3 The technologies

Basiliximab

3.1 Basiliximab (Novartis) is a monoclonal antibody with specificity for CD25. It has UK marketing authorisation as an induction therapy for the prophylaxis of acute organ rejection in de novo allogeneic renal transplantation in adult and paediatric renal transplant recipients. The marketing authorisation states that it should be used concomitantly with ciclosporin microemulsion and corticosteroid-based immunosuppression in patients with panel-reactive antibodies less than 80%, or in combination with a triple maintenance immunosuppressive regimen containing ciclosporin microemulsion, corticosteroids and either azathioprine or MMF. For children and adolescents weighing less than 35 kg, 10 mg should be given within 2 hours before transplantation surgery and 10 mg should be given 4 days after surgery (by intravenous injection or infusion). In paediatric patients weighing 35 kg or more, the recommended dose is 20 mg within 2 hours before surgery and 20 mg 4 days after surgery.

3.2 For children and adolescents weighing less than 35 kg, two 10-mg doses of basiliximab cost approximately £1520 (excluding VAT; *British National Formulary*, 50th edition). However, costs may vary in different settings because of negotiated procurement discounts.

Daclizumab

3.3 Daclizumab (Roche Products) is also a monoclonal antibody with specificity for CD25. It has UK marketing authorisation as an induction therapy for the prophylaxis of acute organ rejection in de novo allogeneic renal transplantation in adult and paediatric patients. The marketing authorisation states that it should be used concomitantly with an immunosuppressive regimen including ciclosporin and corticosteroids in patients who are not highly immunised. The recommended dose for daclizumab in adults and children is 1 mg/kg (by intravenous infusion). Initially it should be given at least 24 hours before transplantation. Further doses are given at intervals of 14 days, for a total of five doses.

© NICE 2006. All rights reserved. Last modified April 2006

3.4 One dose of daclizumab costs about £310 for a person weighing 35 kg (excluding VAT; *British National Formulary*, 50th edition). A five-dose course therefore costs about £1550 (excluding VAT). However, costs may vary in different settings because of negotiated procurement discounts.

Tacrolimus

3.5 Tacrolimus (Astellas Pharma) is a calcineurin inhibitor. It has UK marketing authorisation for initial and maintenance immunosuppression in adult and paediatric renal transplant recipients and for renal transplant rejection resistant to conventional immunosuppressive regimens. It may be given intravenously or orally. According to the marketing authorisation, tacrolimus therapy in children should start at 300 micrograms/kg/day (in two divided doses); it is subsequently adjusted according to whole-blood or plasma trough concentrations, with paediatric patients needing maintenance doses 1.5 to 2 times higher than adults to achieve similar blood levels. It is routinely administered with other immunosuppressive agents (but not ciclosporin) in the initial postoperative period. The dose may vary depending on the immunosuppression regimen. Dosing should be adjusted according to the needs of the individual patient.

3.6 Tacrolimus also has UK marketing authorisation for the treatment of acute rejection episodes in adults and children. Rejection episodes can be treated with increased doses of tacrolimus. It is routinely administered with other immunosuppressive agents (but not ciclosporin) in the initial postoperative period. The dose may vary depending on the immunosuppression regimen.

3.7 Initial tacrolimus doses of 300 micrograms/kg/day for a person weighing 35 kg cost about £13.90 per day (excluding VAT; *British National Formulary*, 50th edition). However, costs may vary in different settings because of negotiated procurement discounts. Daily maintenance doses are adjusted according to the individual patient.

© NICE 2006. All rights reserved. Last modified April 2006

Mycophenolate mofetil

3.8 Mycophenolate mofetil (MMF; Roche Products) is a prodrug of mycophenolic acid, prepared as the mofetil compound to increase bioavailability. Mycophenolic acid is a DNA proliferation inhibitor that acts by inhibiting the purine biosynthetic pathway. MMF has UK marketing authorisation for initial and maintenance therapy, and is indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal transplants. It should not be used concomitantly with azathioprine. The recommended dose in paediatric renal transplant recipients (aged 2–18 years) is dependent on the dose form and body surface area of the patient. Capsules, tablets and the suspension for oral administration are recommended at a dosage of 600 mg/m^2 twice daily (up to a maximum of 2 g/day). There are no data for the use of the powder for infusion in children.

3.9 Based on body surface area (600 mg/m^2), children and adolescents are likely to receive 1.5 mg/day (maximum of 2 g daily dose) of MMF, which costs about £5.25 (excluding VAT; *British National Formulary*, 50th edition). Therefore, treatment for 1 year costs about £1900. However, costs may vary in different settings because of negotiated procurement discounts.

Mycophenolate sodium

3.10 Mycophenolate sodium (MPS; Novartis) is the enteric-coated salt form of mycophenolicacid, the active component of the prodrug MMF, and a DNA proliferation inhibitor. It is indicated in combination with ciclosporin microemulsion and corticosteroids for the prophylaxis of acute transplant rejection in adult patients receiving allogeneic renal transplants. It should not be used concomitantly with azathioprine. The Summary of Product Characteristics states that insufficient data are available to support the efficacy and safety of MPS in children and adolescents.

3.11 The recommended dose for adults is 720 mg administered twice daily. This equates to a daily cost of about £8.20 and an annual cost of about £3000 (excluding VAT; *British National Formulary*, 50th edition). However, costs may vary in different settings because of negotiated procurement discounts.

© NICE 2006. All rights reserved. Last modified April 2006

Sirolimus

3.12 Sirolimus (Wyeth Pharmaceuticals) is a non-calcineurin-inhibiting immunosuppressant. Sirolimus has UK marketing authorisation for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk who have received a renal transplant. It is recommended that sirolimus is used initially in combination with ciclosporin microemulsion and corticosteroids for 2–3 months. The marketing authorisation states that sirolimus may be continued as maintenance therapy with corticosteroids only if ciclosporin can be progressively discontinued. According to this authorisation, the usual dosage regimen for sirolimus is a 6-mg oral loading dose, given as soon as possible after transplantation, followed by 2 mg once daily. The sirolimus dose should then be individualised to obtain whole-blood trough levels of 4–12 ng/ml (measured by chromatographic assay). Sirolimus therapy should be optimised with a tapering regimen of corticosteroids and ciclosporin microemulsion. In patients for whom ciclosporin withdrawal is either unsuccessful or cannot be attempted, the combination of ciclosporin and sirolimus should not be maintained for more than 3 months after transplantation. The Summary of Product Characteristics states that insufficient data are available to support the efficacy and safety of sirolimus in children and adolescents.

3.13 A 4-mg dose of sirolimus costs £12/day (excluding VAT; *British National Formulary*, 50th edition). Using a 6-mg dose immediately post surgery, followed by 2 mg/day for the first 2–3 months in combination with ciclosporin and then an average of 4 mg/day thereafter, equates to a cost of about £4000/year (excluding VAT). However, costs may vary in different settings because of negotiated procurement discounts.

© NICE 2006. All rights reserved. Last modified April 2006

4 Evidence and interpretation

The Appraisal Committee (appendix A) considered evidence from a number of sources (appendix B).

4.1 Clinical effectiveness

Only a small amount of evidence on clinical effectiveness was identified from randomised controlled trials (RCTs) involving paediatric renal transplant recipients. Therefore, the assessment included results from RCTs in adult renal transplant recipients and results from non-randomised comparative studies in paediatric renal transplant recipients.

Basiliximab

4.1.1 One unpublished randomised, placebo-controlled trial in paediatric renal transplant recipients was identified. Basiliximab induction therapy (10–20 mg) versus no induction therapy was added to concomitant triple therapy of tacrolimus, azathioprine and a corticosteroid in 197 children and adolescents up to 18 years of age. Efficacy and safety were assessed at 6 months. Details of the study were provided, but the results were marked 'academic in confidence'.

4.1.2 Four randomised, placebo-controlled trials in adults were also identified (total n = 500). Basiliximab induction therapy (20 mg) versus placebo or no therapy was added to concomitant triple therapy of ciclosporin, azathioprine and a corticosteroid. Only one trial reported outcomes beyond 1 year.

4.1.3 A meta-analysis of the results from the RCTs showed a statistically significant advantage in favour of basiliximab in terms of fewer biopsy-proven acute rejection episodes at 6 months' follow-up (relative risk [RR] 0.61, 95% confidence interval [CI] 0.46 to 0.80). However, the meta-analysis showed no statistically significant advantage of basiliximab in terms of graft or patient survival within the limited follow-up period.

4.1.4 There were no statistically significant differences between treatment arms in terms of the incidence of CMV infection (at 6 months), PTDM, liver disease or

© NICE 2006. All rights reserved. Last modified April 2006

withdrawals (at 6 months). Drug switching because of adverse events was not reported.

4.1.5 Six retrospective, comparative non-randomised studies in paediatric renal transplant recipients were identified. However, only three of these studies compared basiliximab (10 or 20 mg) with no induction therapy.

4.1.6 None of the three studies (total n = 152) showed a statistically significant difference in the incidence of biopsy-proven acute rejection or graft loss between the basiliximab and control groups at 12 months. Mortality was zero for both treatment groups in all three studies. Little information on side effects was reported, although one of the studies reported that, at 12 months, a higher proportion of patients receiving basiliximab had withdrawn from treatment compared with patients not receiving induction therapy.

Daclizumab

4.1.7 No RCTs that included children or adolescents were identified.

4.1.8 One placebo-controlled, randomised trial in adult renal transplant recipients was identified (n = 260). Daclizumab induction therapy (1 mg/kg) versus placebo was added to concomitant triple therapy of ciclosporin, azathioprine and a corticosteroid.

4.1.9 The results indicated a statistically significant advantage in favour of daclizumab in terms of fewer biopsy-proven acute rejection episodes at 6 months' follow-up (RR 0.63, 95% CI 0.42 to 0.94). However, no statistically significant advantage of daclizumab in terms of graft or patient survival was shown.

4.1.10 There was no statistically significant difference in the incidence of CMV infection at 6 months between those receiving daclizumab and those receiving placebo. The rates of hyperlipidaemia, PTDM, lymphoproliferative disease and withdrawals because of adverse events were not reported.

4.1.11 No comparative non-randomised studies of daclizumab in paediatric renal transplant recipients could be identified. The manufacturer's submission

© NICE 2006. All rights reserved. Last modified April 2006

included one non-comparative, non-randomised study. Details of the study were provided, but the results were marked 'academic in confidence'.

Tacrolimus

4.1.12 One paediatric RCT (n = 204) was identified. It compared a triple therapy combination of tacrolimus (0.3 mg/kg), azathioprine and a corticosteroid with a triple therapy combination of ciclosporin (microemulsion), azathioprine and a corticosteroid. One third of patients withdrew from the trial within 6 months.

4.1.13 The results showed a statistically significant advantage in favour of the tacrolimus-based regimen in terms of fewer biopsy-proven acute rejection episodes (RR 0.42, 95% CI 0.26 to 0.69) at 6 months. However, no statistically significant advantage of tacrolimus in terms of graft or patient survival was demonstrated at 6 months.

4.1.14 At 1 year, the proportions of graft losses in the tacrolimus and ciclosporin treatment groups were not statistically different (p = 0.08). However, statistically significant differences in favour of tacrolimus were reported at 4-year follow-up (11/103 [11%] graft losses with tacrolimus compared with 20/93 [22%] with ciclosporin; p = 0.03). An indicator of graft function, the glomerular filtration rate (GFR), was statistically significantly higher at 1 year in those receiving tacrolimus than in those receiving ciclosporin: the mean GFR with tacrolimus was 62.5 ml/min, whereas the mean GFR with ciclosporin was 56.4 ml/min (p = 0.003).

4.1.15 No statistically significant differences in side effects were recorded at 6 months between the tacrolimus- and ciclosporin-based regimens, as abstracted by the Assessment Group. However, the Assessment Group did not look specifically at cosmetic side effects, such as excessive hair growth. A statistically significantly smaller proportion of the tacrolimus-treated group than the ciclosporin-treated group withdrew from the trial because of adverse events (RR 0.61, 95% CI 0.39 to 0.96).

4.1.16 Nine RCTs in adult renal transplant recipients were identified (total n = 1664). These compared a triple therapy combination of tacrolimus, azathioprine and a corticosteroid with a triple therapy combination of ciclosporin, azathioprine and

© NICE 2006. All rights reserved. Last modified April 2006

a corticosteroid. The dose of tacrolimus used across the studies ranged from 0.1 to 0.3 mg/kg. Follow-up ranged from 6 months to 6 years.

4.1.17 A meta-analysis of the results from the RCTs showed a statistically significant advantage in favour of the tacrolimus-based regimen in terms of fewer biopsy-proven acute rejection episodes at 1-year follow-up (RR 0.61, 95% CI 0.53 to 0.71). However, the meta-analysis showed no statistically significant advantage of tacrolimus in terms of graft or patient survival.

4.1.18 Two RCTs had follow-up periods of 3 years or more. However, no statistically significant differences in all-cause mortality, graft loss or graft function were reported in either trial at long-term follow-up.

4.1.19 The RCTs in adult renal transplant recipients showed that the incidence of treatment side effects (excluding data on cosmetic side effects, which were not available) and rates of withdrawal because of adverse events were similar for both treatment groups with the exception of PTDM, the incidence of which was statistically significantly higher with tacrolimus (RR 2.38, 95% CI 1.32 to 4.31), and hyperlipidaemia, which occurred at a lower incidence with tacrolimus (RR 0.47, 95% CI 0.24 to 0.93). A statistically significantly lower level of drug switching because of adverse events was associated with tacrolimus compared with ciclosporin (RR 0.10, 95% CI 0.04 to 0.27).

4.1.20 Two comparative, non-randomised studies of ciclosporin and tacrolimus were identified in paediatric renal transplant recipients (total n = 1010). One study reported a statistically significant advantage of tacrolimus over ciclosporin in terms of improved graft function at 1-year and 2-year follow-up (mean creatinine clearance rates at year 2 of 96.7 ml/min and 73.2 ml/min [per 1.73 m^2 body surface area] respectively; $p < 0.0001$). No other statistically significant differences were reported in either study for any other outcomes.

Mycophenolate mofetil

4.1.21 No RCTs comparing MMF-based treatment regimens with azathioprine-based regimens in paediatric renal transplant recipients were identified.

© NICE 2006. All rights reserved. Last modified April 2006

4.1.22 Seven RCTs in adult renal transplant recipients were identified (total n = 1273). These compared a triple therapy combination of MMF (2–3 g), ciclosporin and a corticosteroid with a triple therapy combination of azathioprine, ciclosporin and a corticosteroid.

4.1.23 A meta-analysis showed a statistically significant advantage in favour of MMF over azathioprine in terms of fewer biopsy-proven acute rejection episodes at 1-year follow-up (RR 0.60, 95% CI 0.47 to 0.76). However, the meta-analysis showed no statistically significant advantage of the MMF-based regimen in terms of graft or patient survival at the same point of follow-up.

4.1.24 No statistically significant differences between the MMF- and azathioprine-based regimens were observed at 1-year follow-up in terms of the rates of post-transplant lymphoproliferative disease and withdrawals because of adverse events. The incidence of PTDM and hyperlipidaemia was not reported, but CMV infection rates were higher with MMF treatment (RR 1.43, 95% CI 1.02 to 2.01).

4.1.25 Four comparative non-randomised studies in paediatric renal transplant recipients were available to the Appraisal Committee. These compared MMF-based with azathioprine-based regimens, but few results allowing direct comparison of the two treatment regimens were reported. Two of the studies did not report details of the rates of biopsy-proven acute rejection. One study reported that no patient receiving MMF (n = 7) had biopsy-proven acute rejection, while three patients in the azathioprine group (n=7) had biopsy-proven acute rejection. Another study, with historical control design, reported biopsy-proven acute rejection rates at 1 year of 39% in the MMF-treated group (n = 86) and 59% in the azathioprine-treated group (n = 54), with 3-year rates of 44% and 59% respectively.

4.1.26 The Appraisal Committee considered evidence from two non-randomised studies of MMF in corticosteroid-reduction/withdrawal strategies for paediatric patients. One was a retrospective case–control study in 40 paediatric patients receiving MMF and ciclosporin with a mean follow-up of 46 months. No episodes of biopsy-proven rejection occurred in the group in which corticosteroids were withdrawn, and the standardised body mass index

© NICE 2006. All rights reserved. Last modified April 2006

decreased by 49% in this group. Another observational study reported results using a corticosteroid-avoidance immunosuppressive regimen that included daclizumab, tacrolimus and MMF in paediatric patients. Patient and graft survival rates were reported to be equivalent to those in historical controls. The corticosteroid-free group experienced anaemia, which was normalised by 6 months following treatment with erythropoietin.

Mycophenolate sodium

4.1.27 No RCTs comparing MPS-based treatment regimens with azathioprine-based regimens in paediatric renal transplant recipients were identified.

4.1.28 Only one RCT in adult renal transplant recipients was identified (n = 423). This compared a triple therapy combination of MPS (1.4 g/day), ciclosporin and a corticosteroid with a regimen of MMF plus ciclosporin and a corticosteroid. The trial was powered to detect equivalence in outcomes. No statistically significant differences between the treatment groups were reported at 1-year follow-up in terms of biopsy-proven acute rejection episodes, graft loss, side effects, or rates of withdrawal because of adverse events. Rates of drug switching and changes in health-related quality of life were not reported.

4.1.29 No non-randomised comparative studies comparing MPS with azathioprine in paediatric renal transplant recipients were identified.

Sirolimus

4.1.30 Two unpublished RCTs in paediatric renal transplant recipients were identified. One was ongoing and no data were available. Details of the other study were provided, but the results were marked 'academic in confidence'. In addition, two published RCTs in adult renal transplant recipients were identified that also included some paediatric recipients (total n = 15/1295).

4.1.31 Four further RCTs of the use of sirolimus in adult renal transplant recipients were identified. Two trials compared sirolimus (2 or 5 mg/day) with azathioprine (in triple therapy regimens also containing ciclosporin and a corticosteroid). One trial compared sirolimus (16–24 mg/m^2/day followed by 8–12 mg/m^2/day) with ciclosporin (in triple therapy regimens that also

© NICE 2006. All rights reserved. Last modified April 2006

contained azathioprine and a corticosteroid). The fourth RCT assessed the impact of a 3-month period of sirolimus treatment plus ciclosporin and a corticosteroid, and then randomised patients to continue sirolimus and a corticosteroid while either continuing or stopping ciclosporin. In a meta-analysis of the two studies comparing sirolimus with azathioprine, the number of biopsy-proven acute rejection episodes was statistically significantly lower in those receiving the sirolimus regimen at 1-year follow-up (RR 0.60, 95% CI 0.45 to 0.80). In another meta-analysis, serum creatinine was statistically significantly lower at 1-year follow-up in patients for whom ciclosporin had been removed from the regimen at 3 months compared with those in whom sirolimus and ciclosporin had been continued. No other statistically significant differences were reported in favour of ciclosporin withdrawal in any of the four RCTs in terms of biopsy-proven acute rejection, graft loss, patient survival or graft function.

4.1.32 No non-randomised comparative studies in paediatric renal transplant recipients were identified.

4.2 Cost effectiveness

4.2.1 No published economic evaluations of any of the drugs pertinent to this appraisal in paediatric or adolescent patients met the inclusion criteria for this review. Three economic evaluations were submitted by the manufacturers. All of these, as well as the evaluation performed by the Assessment Group, were based on an adaptation to the Birmingham Sensitivity Analysis (BSA) model that was constructed previously by the Assessment Group for the appraisal of immunosuppressive treatments in adult renal transplant recipients (see section 8). The Assessment Group's paediatric version of the original adult model is referred to as the BSAp model.

4.2.2 Key features of the BSAp model include the following.

- It is a Markov model containing three health states: functioning graft; graft failed/ dialysis; and death.
- An NHS perspective was adopted for costs and benefits.

© NICE 2006. All rights reserved. Last modified April 2006

- Costs and quality-adjusted life years (QALYs) were discounted at 6% and 1.5%, respectively.
- Patient and graft survival was predicted using acute rejection rates at 1-year follow-up and extrapolated over 10 years.
- If relevant child/adolescent RCTs were not available, acute rejection rates were based on RCTs in adults.
- The BSAp model used utility values of 0.5 for dialysis and 0.75 for a functioning graft.
- In the base case, the cost of dialysis was assumed to be just over £21,000/year (reflecting the costs of treating adult patients).
- The cost of treating each episode of acute rejection was put at £4600, based on amalgamating the various estimates given in the manufacturers' submissions for the appraisal of these treatments in adults.
- The costs and disutility associated with side effects were linked to withdrawals because of adverse events from the trials, but were only included where evidence suggested that there was a difference in withdrawals between treatment regimens.
- A programming error in the original BSA model was corrected in this BSAp version.

Basiliximab

4.2.3 Both the manufacturer and the Assessment Group estimated that triple therapy regimens that included basiliximab (induction therapy) were more effective and less costly compared with triple therapy regimens that did not include basiliximab. In the absence of paediatric trial data, acute rejection rates for ciclosporin-based regimens were estimated using adult RCTs. Cost-effectiveness estimates for tacrolimus-based regimens were based on a single relevant paediatric RCT (which was marked confidential).

Daclizumab

4.2.4 Both the manufacturer and the Assessment Group estimated that triple therapy regimens that included daclizumab (induction therapy) were more effective and less costly compared with triple therapy regimens that did not include

© NICE 2006. All rights reserved. Last modified April 2006

daclizumab. Both cost-effectiveness estimates were based on the acute rejection rates from adult RCTs in the absence of suitable paediatric RCT evidence.

Tacrolimus

4.2.5 Both the manufacturer's and the Assessment Group's economic evaluations compared tacrolimus-based with ciclosporin-based triple therapy regimens, and incorporated rejection rates reported by an RCT in paediatric patients.

4.2.6 The manufacturer estimated the cost effectiveness of a tacrolimus-based triple therapy regimen compared with a ciclosporin-based triple therapy regimen to be about £18,000 for an age group of below 13 years and about £31,000 for an age group of 13–18 years. These estimates include the costs and effects of switching treatments (because of side effects), but the probabilities of these events occurring were based on expert opinion. When no difference in switching rates between ciclosporin- and tacrolimus-based regimens was assumed, the cost effectiveness of tacrolimus decreased considerably.

4.2.7 The Assessment Group estimated the cost effectiveness of tacrolimus to be approximately £145,000 per QALY gained (excluding the consideration of the impact of side effects). However, changing the hazard ratio associated with acute rejection episodes and the risk of graft loss to 1.96 (from 1.41) and increasing the cost of dialysis to £50,000 (from £21,000) further reduced the cost per QALY gained to approximately £34,000.

Mycophenolate mofetil

4.2.8 The manufacturer's economic evaluation suggested that MMF was less costly and more effective than azathioprine in a ciclosporin-based regimen. Rates of acute rejection (clinical as opposed to biopsy-confirmed) were based on a single non-randomised comparative study undertaken in children.

4.2.9 The Assessment Group estimated the cost effectiveness of MMF compared to azathioprine in a ciclosporin-based regimen to be approximately £195,000 per QALY gained. This estimate was based on acute rejection rates derived from the meta-analysis of MMF RCTs in adult patients and on a hazard ratio

© NICE 2006. All rights reserved. Last modified April 2006

associated with acute rejection episodes and the risk of graft loss of 1.41. When this hazard ratio was increased to 1.96 (in line with the estimate used in the adult appraisal) and the cost of paediatric dialysis was increased to £50,000, the cost per QALY gained changed to approximately £60,000.

Mycophenolate sodium

4.2.10 Neither the manufacturer nor the Assessment Group undertook a specific economic evaluation of MPS. However, the manufacturer claimed that because MPS and MMF are clinically equivalent, the cost effectiveness of the two treatments is also similar.

Sirolimus

4.2.11 The manufacturer referred to an economic evaluation from the appraisal of immunosuppressive treatments in adult renal transplant recipients (NICE Technology Appraisal Guidance no. 85). The evaluation assessed the cost effectiveness of a sirolimus regimen that involved ciclosporin withdrawal and a corticosteroid compared with a standard calcineurin inhibitor-based treatment regimen. No RCT evidence was available for these treatment regimens; therefore treatment effects were estimated by incorporating the results from a number of other studies. The results from this analysis were used to suggest that sirolimus was a more effective and less costly treatment option.

4.2.12 The Assessment Group did not perform an economic evaluation of sirolimus because there was deemed to be insufficient clinical evidence.

4.3 Consideration of the evidence

4.3.1 The Committee reviewed the data available on the clinical and cost effectiveness of basiliximab, daclizumab, tacrolimus, MMF, MPS and sirolimus for renal transplantation in children and adolescents, having considered evidence on the nature of the condition and the value placed on the benefits of immunosuppressive therapy by people who have undergone renal transplantation, those who represent them, and clinical experts. It was also mindful of the need to take account of the effective use of NHS resources.

© NICE 2006. All rights reserved. Last modified April 2006

4.3.2 The Committee recognised the paucity of RCTs in children and adolescents undergoing renal transplantation. In addition, the Committee had been directed by NICE's Guidance Executive (in accordance with the appeal determination following the appraisal of these agents in adults) to consider all the evidence available on the clinical and cost effectiveness of immunosuppressive regimens in children and adolescents. The Committee therefore took into account observational evidence on the use of immunosuppressive regimens in children and adolescent transplant recipients, and considered RCT and other evidence relating to adults wherever necessary.

4.3.3 The Committee was also aware that the Department of Health and the Welsh Assembly Government had indicated that the Institute should consider the use of immunosuppressant drugs in renal transplant recipients as they are used in current practice, which may include use outside the terms of the UK marketing authorisation.

4.3.4 The Committee was persuaded of important differences in the management of renal transplantation between adults and children/adolescents: in particular, that there were significant differences in the relative importance to the patient of treatment side effects. The Committee heard from the experts that the actual or perceived potential for cosmetic side effects was a major contributor to lack of concordance with the immunosuppressant regimen that was prescribed, and thus a major cause of renal graft failure. Therefore, this should be taken into consideration in assessing the balance of costs and benefits of the various drugs.

4.3.5 The Committee additionally heard from the experts that the annual cost of renal replacement therapy and support for children and adolescents was much higher than that for adults. This extra cost for younger patients was related to a number of reasons and specific requirements for this patient group, including:

- increased numbers of clinical staff and other personnel required to support particularly young patients (for example, higher ratio of nursing staff, reduced numbers of patients per nephrologist, need for other support staff such as play therapists for children and psychological support for adolescents)
- increased equipment costs for dialysers and other devices for young children

© NICE 2006. All rights reserved. Last modified April 2006

- higher costs associated with the treatment of acute rejection episodes.

Further details of the costs of renal replacement therapy and support in children and adolescents were obtained from two paediatric centres in the UK, which showed that these costs are approximately £50,000–£60,000/year.

The Committee also noted that all submitted economic evaluations were based on the model constructed by the Assessment Group for the appraisal of immunosuppressive regimens for adults. This model based the annual cost of dialysis for children and adolescents on the cost used in the adult model (approximately £21,000/year). The annual cost for children and adolescents is therefore likely to have been significantly underestimated.

4.3.6 On the basis of these considerations, the Committee carefully reviewed the economic model constructed for this appraisal by the Assessment Group. It noted that the Assessment Group had assumed a hazard ratio for the association between acute rejection episodes and long-term graft survival of 1.41 based on data from a single study in paediatric patients, compared with that used in the appraisal of immunosuppression in adult renal transplant recipients of 1.96. The Committee noted the concerns expressed by consultees regarding the paediatric study: in particular, that the study involved only transplants from living, related donors, and that the results may not be applicable to the paediatric population undergoing renal transplantation in the UK. The Committee also heard from the experts that there was no plausible clinical reason to believe that this hazard ratio should be different for children and adolescents compared with adults. For these reasons, the Committee accepted a hazard ratio of 1.96 as the appropriate value to be incorporated into the economic analysis for this appraisal.

4.3.7 Therefore, all incremental cost-effectiveness ratios (ICERs) reported by the Assessment Group and quoted in the remainder of this considerations section are based on a cost of dialysis of £50,000–£60,000/year and a hazard ratio associated with acute rejection episodes and graft loss of 1.96. The Committee also considered the higher costs of an acute rejection episode (other than those associated with the requirement for dialysis); however, these costs were not adjusted because insufficient evidence was available to the Committee to make any change.

© NICE 2006. All rights reserved. Last modified April 2006

Basiliximab and daclizumab

4.3.8 The Committee noted the single RCT undertaken in paediatric patients and the confidential nature of this information. The Committee also noted that no RCTs had been undertaken of either basiliximab or daclizumab in combination with ciclosporin-based regimens in paediatric patients. In the absence of this information, the Committee considered the evidence relating to adults, which suggested that the use of induction therapies reduced acute rejection rates and costs to the NHS compared with no induction therapy. The Committee also heard from the experts that there was no evidence to suggest that acute rejection rates should be different for paediatric compared with adult populations. The Committee accepted the evidence of the treatments in combination with ciclosporin in adults, and concluded that there was no reason that this should be different in children and adolescents. It therefore considered the submitted estimates of cost effectiveness to be reasonable estimates.

4.3.9 The Committee noted that, as was the case for the appraisal of immunosuppressive regimens in adults, experts reported that basiliximab and daclizumab are more commonly used for patients with higher levels of immunological risk, although neither has UK marketing authorisation for patients at high immunological risk. The Committee was persuaded of a need for additional options for immunosuppression for this group, and the experts stated that there was no reason to anticipate that these agents would be less safe or less effective in the high-risk group.

4.3.10 The Committee noted the RCT evidence of basiliximab in combination with tacrolimus, and the confidential nature of this information. In light of this evidence, the Committee concluded that the use of basiliximab or daclizumab should be recommended as options for children and adolescents undergoing renal transplantation only as part of ciclosporin-based regimens, irrespective of the patient's immunological risk.

Tacrolimus

4.3.11 The Committee considered that the evidence from the single RCT of tacrolimus-based immunosuppressive regimens in paediatric patients

© NICE 2006. All rights reserved. Last modified April 2006

demonstrated that it reduced acute rejection rates compared with ciclosporin-based regimens.

4.3.12 The Committee also noted the discrepancies between the manufacturer's and the Assessment Group's estimates of cost effectiveness. It was persuaded that much of the difference could be explained by differing assumptions regarding the costs and effects of treatment side effects. The Committee heard from the experts that in younger patients (particularly adolescents), the relatively greater incidence of cosmetic side effects associated with the use of ciclosporin compared with tacrolimus was an important issue. The Committee noted that the Assessment Group's cost-effectiveness estimate was approximately £34,000 per QALY gained, but this estimate is without any consideration of treatment side effects or the increased cost of an acute rejection episode. Taking these factors into consideration, the ICERs were likely to be less than those quoted in both the models reviewed.

4.3.13 The Committee also took note of the comments made by the clinical experts regarding the different side-effect profiles of the two calcineurin inhibitors and the importance of minimising the risk of cosmetic and clinical side effects in paediatric patients, because such effects were a common cause of non-concordance with medication and consequent graft rejection and loss. The Committee was therefore persuaded that both calcineurin inhibitors should be available as optional treatments, and the decision about which to use should be based, in part, on the relevance of the respective side effects to the patient. The Committee therefore concluded that tacrolimus should be recommended for children and adolescents as an optional alternative to ciclosporin.

4.3.14 The Committee noted that episodes of acute rejection are sometimes treated by switching the calcineurin inhibitor from ciclosporin to tacrolimus, and that this use of tacrolimus is specified separately in its licensed indications. However, because this essentially constitutes a change to the initial or maintenance therapy, the Committee understood that the recommendations already included its use for this indication (see section 1.2).

© NICE 2006. All rights reserved. Last modified April 2006

Mycophenolate mofetil

4.3.15 The Committee noted that there were no RCTs of MMF in paediatric or adolescent patients and discussed in detail the results of the review of non-randomised studies. The Committee considered that the meta-analysis of MMF in adult patients was likely to be important in informing their estimation of differential acute rejection rates in paediatric or adolescent patients.

4.3.16 The Committee noted that the meta-analysis of adult RCTs indicated that MMF reduced the number of acute rejection episodes compared with azathioprine. It also noted that the ICER produced by the Assessment Group that incorporated this value was approximately £60,000 per QALY for MMF compared with azathioprine. The Committee noted that the manufacturer's economic evaluation suggested that MMF was less costly and more effective than azathioprine. It considered that this analysis included estimates of acute rejection rates taken from a single non-randomised, comparative study and that the historical control design of this study may have led to bias in the selection of patients. The Committee concluded that the meta-analysis of adult RCTs was the most acceptable evidence to inform the acute rejection rates used in the economic analysis. Therefore, the Committee concluded that the assessment of cost effectiveness conducted by the Assessment Group was the most appropriate analysis on which to base its recommendations.

4.3.17 The Committee was also persuaded that, as is the case for adults, MMF has a potentially clinically significant role in situations where there is a very high risk of calcineurin inhibitor nephrotoxicity, because it allows the use of these drugs to be minimised or avoided. Such situations include delayed graft function, or if kidneys are at particular risk of developing delayed graft function (for example, kidneys from non-heart-beating donors or if there is known prolonged warm or cold ischaemia time). The Committee considered that, in such circumstances, minimisation of exposure to nephrotoxic drugs was desirable, and the use of MMF therapy to cover this period of increased risk from calcineurin inhibitor nephrotoxicity was likely to be cost effective in terms of reducing the high risk of graft failure at this time. However, the Committee considered that this therapeutic approach should be maintained only until this period of high risk has passed.

© NICE 2006. All rights reserved. Last modified April 2006

4.3.18 The Committee further considered the evidence presented on MMF for the appraisal of immunosuppressive regimens in adults. In particular, it considered the situation where a patient's renal function decreases gradually after transplantation, as indicated by progressively rising creatinine levels (that is, where chronic allograft dysfunction is evident), and reduction of the dose of calcineurin inhibitor is desirable to avoid further loss of kidney function. Under these circumstances, substitution of calcineurin inhibitors with MMF was likely to be both clinically and cost effective. The Committee considered that the same would be true for children and adolescents.

4.3.19 The Committee discussed with the clinical experts a possible additional role for MMF for children and adults in terms of preventing graft loss specifically when it is considered important to escalate immunosuppressive therapy (for example, after acute rejection episodes). However, the Committee was unable to provide specific guidance on this indication because of the lack of any direct evidence.

4.3.20 The Committee was persuaded that, in general, reducing or withdrawing corticosteroids given as part of immunosuppressive regimens was important because of the known potential contribution of these agents to poor growth and metabolic complications in children. The Committee considered the evidence from non-randomised studies provided by the manufacturer of MMF relating to the reduction of corticosteroids in immunosuppressive regimens (containing daclizumab, tacrolimus and MMF). The Committee considered the evidence available for the effect of MMF in the reduction/withdrawal of corticosteroids and noted that there were no RCTs supporting the use of MMF specifically in this indication. The Committee concluded that, on the basis of the evidence presented, there was insufficient evidence to recommend MMF as part of treatment regimens for the reduction/withdrawal of corticosteroids, except within well-designed randomised clinical trials.

Mycophenolate sodium

4.3.21 In the absence of any RCT evidence to support the use of MPS in children and adolescents, the Committee paid particular attention to the claims from the manufacturer that MPS and MMF were equivalent products. However, the Committee concluded that the absence of information relating to appropriate

© NICE 2006. All rights reserved. Last modified April 2006

dose size and frequency in paediatric patients meant that the clinical and cost effectiveness of MPS was, at best, highly uncertain. Moreover, the Committee understood that issues of drug absorption and appropriate dosing schedules are particularly important for children and adolescent patients. The Committee could not, therefore, conclude that MPS was clinically or cost effective on the evidence available.

Sirolimus

4.3.22 As with the appraisal of the immunosuppressive regimens in adults, the Committee noted that there were no clinical studies directly comparing the sirolimus regimen that currently has UK marketing authorisation (sirolimus with corticosteroids in combination with ciclosporin tapered to discontinuation) with standard calcineurin-inhibitor-based therapies. Indeed, in the two studies of the licensed regimen, sirolimus was also used in the comparator arms. The Committee did not accept that this licensed regimen was clinically more effective than standard ciclosporin-based immunosuppression on the basis of the available evidence.

4.3.23 The Committee also concluded that, given the lack of other treatment options and the high risk and cost of returning to dialysis, in circumstances of proven intolerance to calcineurin inhibitors necessitating their complete withdrawal, sirolimus in combination with corticosteroids should be considered as an option.

© NICE 2006. All rights reserved. Last modified April 2006

5 Recommendations for further research

5.1 Researchers conducting trials in nephrology should include children and adolescents wherever practicable, and collect detailed information on treatment side effects.

5.2 Further research into the effectiveness of alternative immunosuppressive regimens as part of corticosteroid reduction and withdrawal strategies is recommended.

© NICE 2006. All rights reserved. Last modified April 2006

6 Implications for the NHS

No costing report or template has been produced for this appraisal, because analysis showed that the guidance is unlikely to result in a significant change to the use of resources. See the NICE website for further information about the analysis.

© NICE 2006. All rights reserved. Last modified April 2006

7 Implementation and audit

7.1 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within 3 months of this guidance being published. This means that, if a patient has had renal transplantation and the doctor responsible for their care thinks that immunosuppressive therapy is the right treatment, it should be available for use, in line with NICE's recommendations.

7.2 Clinicians with responsibility for children or adolescents undergoing renal transplantation should review their current practice and policies to take account of the guidance set out in section 1.

7.3 Local guidelines, protocols or care pathways that refer to the care of children or adolescents undergoing renal transplantation should incorporate the guidance.

7.4 To measure compliance locally with the guidance, the following criteria could be used. Further details on suggestions for audit are presented in appendix C.

7.4.1 Basiliximab or daclizumab, used as part of a ciclosporin-based immunosuppressive regimen, are considered as options for induction therapy in the prophylaxis of acute organ rejection in a child or adolescent undergoing renal transplantation, irrespective of immunological risk.

7.4.2 When basiliximab or daclizumab is used for induction therapy in the prophylaxis of acute organ rejection in a child or adolescent undergoing renal transplantation, the induction therapy (basiliximab or daclizumab) with the lowest acquisition cost is used, unless it is contraindicated.

7.4.3 Tacrolimus is considered as an alternative option to ciclosporin when a calcineurin inhibitor is indicated as part of an initial or a maintenance immunosuppressive regimen for a child or adolescent renal transplant recipient. The initial choice of tacrolimus or ciclosporin is based on the relative importance of the side-effect profiles for the individual child or adolescent.

© NICE 2006. All rights reserved. Last modified April 2006

7.4.4 MMF is considered for a child or adolescent renal transplant recipient as an option as part of an immunosuppressive regimen only when either of the following is present:

- the child or adolescent has proven intolerance to calcineurin inhibitors, particularly nephrotoxicity leading to risk of chronic allograft dysfunction, or
- there is a very high risk of nephrotoxicity necessitating minimisation or avoidance of the calcineurin inhibitor until the period of high risk has passed.

7.4.5 MMF is used in a corticosteroid reduction or withdrawal strategy for a child or adolescent renal transplant recipient only in a randomised clinical trial.

7.4.6 MPS is not used as part of an immunosuppressive regimen in a child or adolescent renal transplant recipient.

7.4.7 Sirolimus is not used for a child or adolescent renal transplant recipient except when the child or adolescent has proven intolerance to calcineurin inhibitors (including nephrotoxicity) necessitating complete withdrawal of these treatments.

7.4.8 If any of these medicines (basiliximab, daclizumab, tacrolimus, MMF, MPS or sirolimus) is prescribed outside the terms of its UK marketing authorisation, the responsible healthcare professional ensures that the child or adolescent receiving a transplant and/or the parent or guardian is aware of this and consents to its use in the circumstances.

7.5 Local clinical audits could also include measures of the timing and dosages of drug therapy used for children and adolescents undergoing renal transplantation and/or concordance of child and adolescent renal transplant recipients with the drug regimen.

© NICE 2006. All rights reserved. Last modified April 2006

8 Related guidance

8.1 All issued guidance and details of appraisals and guidelines in progress are available on the NICE website.

- Guidance on the use of home compared with hospital haemodialysis for patients with end-stage renal failure. *NICE Technology Appraisal Guidance* No. 48 (2002).
- Guidance on the use of immunosuppressive therapy for renal transplantation in adults. *NICE Technology Appraisal Guidance* No. 85 (2004).

© NICE 2006. All rights reserved. Last modified April 2006

9 Review of guidance

9.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider any new evidence on the technology, in the form of an updated Assessment Report, and decide whether the technology should be referred to the Appraisal Committee for review.

9.2 The guidance on this technology will be considered for review in March 2009.

Andrew Dillon
Chief Executive
April 2006

© NICE 2006. All rights reserved. Last modified April 2006

Appendix A. Appraisal Committee members and NICE project team

A. Appraisal Committee members

The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets twice a month except in December, when there are no meetings. The Committee membership is split into two branches, with the chair, vice chair and a number of other members attending meetings of both branches. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Jane Adam
Radiologist, St George's Hospital, London

Professor AE Ades
MRC Senior Scientist, MRC Health Services Research Collaboration, Department of Social Medicine, University of Bristol

Dr Tom Aslan
General Practitioner, Stockwell, London

Professor David Barnett (Chair)
Professor of Clinical Pharmacology, University of Leicester

Mrs Elizabeth Brain
Independent Patient Advocate

© NICE 2006. All rights reserved. Last modified April 2006

Dr Karl Claxton
Health Economist, University of York

Mrs Fiona Duncan
Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool

Professor Christopher Eccleston
Director Pain Management Unit, University of Bath

Dr Paul Ewings
Statistician, Taunton and Somerset NHS Trust, Taunton

Professor Terry Feest
Professor of Clinical Nephrology, Southmead Hospital, Bristol

Ms Alison Forbes
Health Consultant Associate, Eden Insight

Professor John Geddes
Professor of Epidemiological Psychiatry, University of Oxford

Mr John Goulston
Director of Finance, Barts and the London NHS Trust

Ms Linda Hands
Consultant Surgeon, John Radcliffe Hospital, Oxford

Dr Elizabeth Haxby
Lead Clinician in Clinical Risk Management, Royal Brompton Hospital, London

Dr Rowan Hillson
Consultant Physician, Diabeticare, The Hillingdon Hospital, Uxbridge, Middlesex

Dr Catherine Jackson
Clinical Senior Lecturer in Primary Care Medicine, University of Dundee

© NICE 2006. All rights reserved. Last modified April 2006

Professor Richard Lilford
Professor of Clinical Epidemiology, Department of Public Health and Epidemiology, University of Birmingham

Dr Simon Mitchell
Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester

Ms Judith Paget
Chief Executive, Caerphilly Local Health Board, Wales

Dr Katherine Payne
Health Economist, North West Genetics Knowledge Park, The University of Manchester

Dr Ann Richardson
Independent Patient Advocate

Mrs Kathryn Roberts
Nurse Practitioner, Hattersley Group Practice, Cheshire

Professor Philip Routledge
Professor of Clinical Pharmacology, College of Medicine, University of Wales, Cardiff

Dr Stephen Saltissi
Consultant Cardiologist, Royal Liverpool University Hospital

Mr Mike Spencer
General Manager, Clinical Support Services, Cardiff and Vale NHS Trust

Dr Debbie Stephenson
Head of HTA Strategy, Eli Lilly and Company

Professor Andrew Stevens (Vice Chair)
Professor of Public Health, University of Birmingham

© NICE 2006. All rights reserved. Last modified April 2006

Dr Cathryn Thomas
General Practitioner, Sutton Coldfield; Associate Professor, Department of Primary Care and General Practice, University of Birmingham

Dr Norman Vetter
Reader, Department of Epidemiology, Statistics and Public Health, College of Medicine, University of Wales, Cardiff

Professor Mary Watkins
Professor of Nursing, University of Plymouth

Dr Paul Watson
Medical Director, Essex Strategic Health Authority

Dr David Winfield
Consultant Haematologist, Royal Hallamshire Hospital, Sheffield

B. NICE Project Team

Each appraisal of a technology is assigned to a Health Technology Analyst and a Technology Appraisal Project Manager within the Institute.

Louise Longworth
Technical Lead, NICE project team

Janet Robertson
Technical Advisor, NICE project team

Alana Miller
Project Manager, NICE project team

© NICE 2006. All rights reserved. Last modified April 2006

Appendix B. Sources of evidence considered by the Committee

A. The assessment report for this appraisal was prepared by the West Midlands Health Technology Assessment Collaboration.

Yao G, Adi Y, Taylor R, et al. 'The clinical and cost effectiveness of immunosuppressive therapy for renal transplantation in children', August 2005

B. The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope, assessment report and appraisal consultation document. Consultee organisations are provided with the opportunity to appeal against the final appraisal determination:

I) Manufacturers/sponsors:

- Fujisawa Ltd (tacrolimus)
- Novartis Pharmaceuticals UK Ltd (basiliximab and mycophenolate sodium)
- Roche Products Ltd (daclizumab and mycophenolate mofetil)
- Wyeth Pharmaceuticals (sirolimus)

II) Professional/specialist and patient/carer groups:

- Action for Sick Children
- Association of Renal Industries
- British Association for Paediatric Nephrology
- British Association of Paediatric Surgeons
- British Kidney Patient Association
- British Renal Society
- British Transplantation Society

© NICE 2006. All rights reserved. Last modified April 2006

- Department of Health
- Kidney Alliance
- National Kidney Research Fund
- Northamptonshire Heartlands PCT
- Renal Pharmacists Group
- Royal College of Nursing
- Royal College of Paediatrics and Child Health
- Royal College of Pathologists
- Royal College of Surgeons
- Royal Pharmaceutical Society
- Transplant Support Network
- UK Renal Transplant Nurses Association
- UK Transplant Co-ordinators Association
- Welsh Assembly Government
- Welsh Association of Renal Physicians
- Welsh Kidney Patients Association

III) Commentator organisations (without the right of appeal):

- Alpharma Ltd (azathioprine)
- Ashbourne Pharmaceuticals Ltd (azathioprine)
- Aventis (polyclonal antibody)
- Board of Community Health Councils in Wales
- British National Formulary

© NICE 2006. All rights reserved. Last modified April 2006

- GlaxoSmithKline (azathioprine)
- Imtix-Sangstat (polyclonal antibody)
- IVAX Pharmaceuticals UK Ltd (azathioprine)
- Janssen (Muromonab CD3)
- National Coordinating Centre for Health Technology Assessment
- National Public Health Service for Wales
- NHS Confederation
- NHS Purchasing and Supplies Agency
- NHS Quality Improvement Scotland
- Novartis Pharmaceuticals UK Ltd (ciclosporin)
- UK Transplant Support Service Authority (NHS Special Health Authority)
- West Midlands Health Technology Assessment Collaboration

C. The following individuals were selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on immunosuppressive therapy for renal transplantation for children and adolescents by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the appraisal consultation document:

- Mr Christopher G Koffman, Consultant Surgeon, Head of Transplantation, Guy's and St Thomas NHS Trust, nominated by the Department of Health – clinical expert
- Dr Heather Maxwell, Consultant Paediatric Nephrologist, British Association for Paediatric Nephrology, nominated by NHS Quality Improvement Scotland – clinical expert
- Ms Grainne Walsh, CNS Paediatric Nephrology Transplantation, Guy's and St Thomas' Hospital, nominated by the Royal College of Nursing – clinical expert

© NICE 2006. All rights reserved. Last modified April 2006

- Ms Helen Lewis – nominated by the National Kidney Federation – patient expert
- Kenneth and Nadine Smith – nominated by the National Kidney Federation – patient experts

© NICE 2006. All rights reserved. Last modified April 2006

Appendix C. Detail on criteria for audit of the use of immunosuppressive therapy for renal transplantation in children and adolescents

Possible objectives for an audit

An audit could be carried out to ensure the appropriateness of the immunosuppressive regimen used for child and adolescent renal transplant recipients, particularly the use of basiliximab, daclizumab, tacrolimus, MMF, MPS or sirolimus.

Possible patients to be included in the audit

An audit could be carried out on child and adolescent renal transplant recipients in a suitable time period for audit, for example, 6 months. The audit could focus on groups of children or adolescents at different stages of transplantation, for example, immediately pre- and postoperative, 2–6 months postoperative, or longer-term postoperative.

Measures that could be used as a basis for an audit

The measures that could be used in an audit of immunosuppressive regimens for renal transplantation are as follows. The measures are applicable to different groups of children and adolescents, as described above.

Criterion	Standard	Exception	Definition of terms

© NICE 2006. All rights reserved. Last modified April 2006

1. Basiliximab or daclizumab are considered as options for induction therapy in the prophylaxis of acute organ rejection in a child or adolescent	100% of children or adolescents undergoing renal transplantation	None	The drugs are used as part of a ciclosporin-based immunosuppressive regimen. The consideration of the drugs as options for induction therapy is irrespective of immunological risk. Clinicians will need to agree locally on how consideration of options for therapy is documented, for audit purposes.
2. If a child or adolescent undergoing renal transplantation is treated with basiliximab or daclizumab as induction therapy, the therapy with the lowest acquisition cost is used	100% of children or adolescents who are treated with basiliximab or daclizumab	The therapy with the lowest acquisition cost is contraindicated	Clinicians will need to agree locally on how the lowest acquisition cost is determined and how contraindications are documented, for audit purposes. See the summaries of product characteristics for contraindications.
3. Tacrolimus is considered as an alternative option to ciclosporin when a calcineurin inhibitor is indicated as part of an initial or a maintenance immunosuppressive regimen for a child or adolescent	100% of children or adolescents for whom a calcineurin inhibitor is indicated as part of an initial or a maintenance immunosuppressive regimen	None	The initial choice of tacrolimus or ciclosporin is based on the relative importance of their side-effect profiles for the individual child or adolescent. Clinicians will need to agree locally on how consideration of options for therapy is documented, for audit purposes.

© NICE 2006. All rights reserved. Last modified April 2006

4. MMF is considered for a child or adolescent as an option as part of an immunosuppressive regimen only in the following situations: a. the child or adolescent has proven intolerance to calcineurin inhibitors **or** b. there is very high risk of nephrotoxicity	100% of children or adolescents who are placed on MMF	None	Clinicians will need to agree locally on how the situations described in 4a and 4b and consideration of options for therapy are documented, for audit purposes. 'Proven intolerance to calcineurin inhibitors' includes nephrotoxicity which could lead to risk of chronic allograft dysfunction. 'Very high risk of nephrotoxicity' necessitates minimisation or avoidance of the calcineurin inhibitor until the period of high risk has passed.
5. MMF is used in a corticosteroid reduction or withdrawal strategy for a child or adolescent renal transplant recipient	0% of children or adolescents who have a renal transplant	The child or adolescent is enrolled in a randomised clinical trial on MMF	The randomised clinical trial is on MMF used in a corticosteroid reduction or withdrawal strategy.
6. MPS is used for a child or adolescent renal transplant recipient	0% of children or adolescents who have a renal transplant	None	

© NICE 2006. All rights reserved. Last modified April 2006

7. Sirolimus is used for a child or adolescent undergoing renal transplantation	0% of children or adolescents undergoing renal transplantation	The child or adolescent has proven intolerance to calcineurin inhibitors	'Proven intolerance to calcineurin inhibitors' includes nephrotoxicity and means necessitating complete withdrawal of these treatments. Clinicians will need to agree locally on how proven intolerance to calcineurin inhibitors is documented, for audit purposes.
8. If one of the medicines referred to in the guidance is prescribed outside the terms of its UK marketing authorisation, the responsible healthcare professional: a. makes the child or adolescent and/or parent or guardian aware of the use outside the terms of its marketing authorisation **and** b. obtains the person's consent for the use of the medicine outside the terms of its marketing authorisation	100% of children or adolescents for whom a medicine is prescribed outside its UK marketing authorisation	None	Basiliximab, daclizumab, tacrolimus, MMF, MPS or sirolimus used consistently with the guidance in this document will sometimes be outside the terms of the UK marketing authorisation for these medicines. Clinicians will need to agree locally on how a child or adolescent and his or her parents or guardians are made aware of the use, and on the written consent form used for this purpose.

© NICE 2006. All rights reserved. Last modified April 2006

Calculation of compliance

Compliance (%) with each measure described in the table above is calculated as follows.

Number of patients whose care is consistent with the **criterion plus** number of patients who meet any **exception** listed	x 100
Number of patients to whom the **measure** applies	

Clinicians should review the findings of measurement, identify whether practice can be improved, agree on a plan to achieve any desired improvement and repeat the measurement of actual practice to confirm that the desired improvement is being achieved.

© NICE 2006. All rights reserved. Last modified April 2006

Changes after publication

March 2014: implementation section updated to clarify that immunosuppressive therapy is recommended as an option following renal transplantation in children and adolescents. Additional minor maintenance update also carried out.

March 2012: minor maintenance

© NICE 2006. All rights reserved. Last modified April 2006

About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

The recommendations from this guideline have been incorporated into a NICE Pathway. We have produced a summary of this guidance for patients and carers. Tools to help you put the guidance into practice and information about the evidence it is based on are also available.

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

Copyright

© National Institute for Health and Clinical Excellence 2006. All rights reserved. NICE copyright material can be downloaded for private research and study, and may be reproduced for educational and not-for-profit purposes. No reproduction by or for commercial organisations, or for commercial purposes, is allowed without the written permission of NICE.