NICE National Institute for Health and Care Excellence

Immunosuppressive therapy for renal transplantation in adults

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1 Guidance

1.1 Basiliximab or daclizumab, used as part of a calcineurin-inhibitor-based immunosuppressive regimen, are recommended as options for induction therapy in the prophylaxis of acute organ rejection in adults undergoing renal transplantation. The induction therapy (basiliximab or daclizumab) with the lowest acquisition cost should be used.

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

1.3 Mycophenolate mofetil is recommended for adults as an option as part of an immunosuppressive regimen only:

- where there is proven intolerance to calcineurin inhibitors, particularly nephrotoxicity leading to risk of chronic allograft dysfunction, or
- in situations where there is a very high risk of nephrotoxicity necessitating minimisation or avoidance of a calcineurin inhibitor.

1.4 Sirolimus is recommended for adults as an option as part of an immunosuppressive regimen only in cases of proven intolerance to calcineurin inhibitors (including nephrotoxicity) necessitating complete withdrawal of these treatments.

1.5 These recommendations contain advice that may result in some medicines being prescribed outside the terms of their marketing authorisation. Clinicians prescribing these drugs should ensure that patients are aware of this, and that they consent to their use in such circumstances.

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2 Clinical need and practice

2.1 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. Immunosuppression has customarily constituted triple therapy with: (1) a calcineurin inhibitor (that is, ciclosporin); (2) an antiproliferative agent (that is, azathioprine); and (3) a corticosteroid. However, a small number of treatment centres use a policy of initial monotherapy with a calcineurin inhibitor, adding in other agents if necessary.

2.2 Ciclosporin for oral administration has been available in two forms. It was originally available as an oily solution (Sandimmun, Novartis) but is now only marketed as an oral solution/microemulsion (Neoral, Novartis). However, the pharmacokinetic profiles of the two agents are different.

In 2001, there were about 13,000 patients receiving immunosuppression after kidney transplantation in England, and about 900 in Wales. In 2001, about 1500 new renal transplants were performed in England and Wales with about 21% of organs coming from live donors. Over 90% of these transplants were performed in people aged 18 years or above.

2.3 The median age of all adults receiving a kidney transplant in 2001 was 49 years. There is a 7–10% annual increase in the UK dialysis population and the number of people needing a transplant is expected to rise over the next decade.

2.4 Renal transplants can be unsuccessful for a number of reasons, including technical failures, recurrence of 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

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rate of progression vary. Chronic allograft dysfunction may develop as early as within a few months of the transplant or it may emerge after several years. The course is generally unremitting and ultimately leads to total loss of graft function, necessitating re-transplantation or a return to dialysis.

2.6 Episodes of acute rejection are most frequently observed during the first few weeks after transplantation, but can occur at any time if the level of immunosuppression becomes inadequate. The response is cell-mediated and leads to injury to or destruction of the functioning cellular structures of the transplanted organ. Occasionally, the response may be more aggressive and include a vascular component.

2.7 Clinically, acute rejection tends to occur as acute episodes 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.

2.8 People who undergo renal transplantation are required to receive life-long (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 drug's side effects for the recipient. The ultimate aim of treatment is to prolong patient and graft survival.

2.9 Complications of immunosuppression include increased risk of developing infections (including viral infections such as cytomegalovirus, herpes simplex and zoster, and Epstein–Barr virus; and opportunistic protozoal, fungal and bacterial infections). As 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 direct their activity principally towards the components of the rejection response, recipients are at much higher risk of infections than the general population throughout their post-transplant life. Some drugs also cause bone marrow suppression.

2.10 Suppression of the immune system is also associated with an increase in the development of cancers, especially lymphoproliferative disorders.

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2.11 The risk of premature death due to cardiovascular disease is well documented in renal transplant recipients. Much of this is due to 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.

2.12 De novo post-transplant diabetes mellitus is a potentially serious side effect of treatment. Some patients are at increased risk of this complication, for example, because of ethnic background, obesity or family history of the condition.

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

2.14 Other treatment side effects, depending on the drugs used, may include hirsutism, alopecia, tremors, mood swings or gastrointestinal intolerance. Some side effects are temporary and resolve as dose reductions are implemented.

2.15 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 whether the recipient has received a previous kidney transplant. Most centres adopt different strategies for patients with delayed graft function, for patients who receive kidneys from non-heart-beating donors and for those who receive kidneys from live donors.

2.16 Immunosuppression can be categorised as follows:

- prevention of graft rejection, by induction therapy, initial therapy and maintenance therapy
- treatment of established acute rejection episodes.

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2.17 Induction therapy is a course of intensive immunosuppression for about 2 weeks immediately post-operatively (though often started immediately pre-operatively) with the aim of 'switching off' the immune system after transplantation to reduce the likelihood of accelerated rejection and acute rejection. It has also been used as a means of reducing exposure to calcineurin inhibitors in the early stages after transplantation when the graft may be particularly vulnerable to their nephrotoxic effects. The term induction therapy has usually been linked with the use of the following agents – the polyclonal antibodies antithymocyte immunoglobulin (ATG) and antilymphocyte immunoglobulin (ALG), and the monoclonal antibody muromonab-CD3 (previously known as OKT3). Induction therapy with these agents has been used extensively in the USA but its use has been more limited in the UK, where the agents' side effects are considered unacceptable. For this reason, the scope for this technology appraisal stated that 'placebo' or 'no induction drug' would be an acceptable comparison for the newer induction therapies in addition to the three drugs listed above.

2.18 Initial therapy is the treatment given to all recipients (except where the donor is an identical twin) for 0–3 months after transplantation. Initial therapy is usually '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 (ciclosporin plus corticosteroid) is used. Both of these regimens were stated as relevant comparators in the scope.

2.19 Maintenance therapy is the treatment that patients receive long-term, throughout the duration of allograft survival. Often, maintenance therapy is identical to initial therapy but at a reduced dosage 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 toxicity. Poor tolerability leading to non-adherence to treatment is another possible reason for changing drugs.

2.20 Acute rejection therapy. Maintenance therapies are sometimes adjusted either temporarily or permanently following acute rejection and especially following

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multiple rejection episodes. However, short courses of high-dose corticosteroids are the standard treatment for episodes of acute rejection. In most cases, corticosteroids will treat the problem quickly and effectively, although it is not unusual for two courses of corticosteroids to be required. 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.

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3 The technologies

3.1 Basiliximab

3.1.1 Basiliximab is a monoclonal antibody with specificity for CD25. It is licensed as an induction therapy for the prophylaxis of acute organ rejection in de novo allogenic renal transplantation. The licence 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 a triple-maintenance immunosuppressive regimen containing ciclosporin microemulsion, corticosteroids and either azathioprine or mycophenolate mofetil. The standard total dosage is 40 mg given in two doses of 20 mg each.

3.1.2 One dose of basiliximab costs approximately £840 (excluding VAT; *British National Formulary*, 45th edition). A two-dose course therefore costs approximately £1680 (excluding VAT). However, costs may vary in different settings because of negotiated procurement discounts.

3.2 Daclizumab

3.2.1 Daclizumab is also a monoclonal antibody with specificity for CD25 and is used as an induction agent in the prophylaxis of acute rejection. It is licensed as an induction therapy for the prophylaxis of acute organ rejection in de novo allogenic renal transplantation used concomitantly with an immunosuppressive regimen, including ciclosporin and corticosteroids in patients who are not highly immunised. The recommended dose for daclizumab in adults is 1 mg/kg. It should initially be given at least 24 hours before transplantation. Further doses are given at intervals of 14 days, for a total of five doses.

3.2.2 One dose of daclizumab costs about £720 for a person weighing 70 kg (excluding VAT; *British National Formulary*, 45th edition). A five-dose course therefore costs about £3600 (excluding VAT). However, costs may vary in different settings because of negotiated procurement discounts.

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3.3 Tacrolimus

3.3.1 Tacrolimus is a calcineurin inhibitor. It is licensed for primary immunosuppression in kidney allograft recipients and kidney allograft rejection resistant to conventional immunosuppressive regimens. It can be given intravenously or orally. According to the licence, oral tacrolimus therapy should start at 150–300 µg/kg per day; it is subsequently adjusted according to whole blood or plasma trough concentrations. Tacrolimus is also licensed for the treatment of acute rejection episodes. Rejection episodes can be treated with increased doses of tacrolimus.

3.3.2 Initial doses of 150–300 µg/kg per day for a person weighing 70 kg cost about £16.30–£32.60 per dose (excluding VAT; *British National Formulary*, 45th edition). Using an average dose of 3 mg twice daily equates to an annual cost of about £4000 (excluding VAT). However, costs may vary in different settings because of negotiated procurement discounts.

3.4 Mycophenolate mofetil

3.4.1 Mycophenolate mofetil is a prodrug of mycophenolic acid, prepared as the mofetil compound to increase bioavailability. It is an antiproliferative agent that acts through inhibition of the purine biosynthetic pathway. Mycophenolate mofetil is licensed for initial and maintenance therapy and is indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogenic renal transplants. For adults, oral mycophenolate mofetil should be initiated within 72 hours after transplantation. The recommended dose in renal transplant patients is 1 g twice daily (2 g daily dose). Patients with a body surface area of 1.25–1.5 m^2 may be prescribed mycophenolate mofetil capsules at a dosage of 750 mg twice daily (1.5 g daily dose).

3.4.2 A 2 g dose of mycophenolate mofetil costs about £9 (excluding VAT; *British National Formulary*, 45th edition). Using a defined daily dose of 2 g equates to an annual cost of approximately £3300 (excluding VAT). However, costs may vary in different settings because of negotiated procurement discounts.

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3.5 Sirolimus

3.5.1 Sirolimus is a non-calcineurin inhibiting immunosuppressant. Sirolimus is licensed 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. Suggested ciclosporin trough concentration ranges for the first 2–3 months after transplantation are 150–400 ng/ml (monoclonal assay or equivalent technique). Ciclosporin should be progressively discontinued over 4–8 weeks and the sirolimus dose should be adjusted to obtain whole blood trough levels of 12–20 ng/ml. Sirolimus should be given with corticosteroids. 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. In such patients, when clinically appropriate, sirolimus should be discontinued and an alternative immunosuppressive regimen instituted.

3.5.2 A 4 mg dose costs £12 per day (excluding VAT; *British National Formulary*, 45th edition). Using a 6 mg dose immediately post surgery, followed by 2mg per day for the first 2-3 months in combination with ciclosporin and then an average of 4 mg per day thereafter, equates to a cost of about £4000 per annum (excluding VAT). However, costs may vary in different settings because of negotiated procurement discounts.

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4 Evidence and interpretation

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

4.1 Clinical effectiveness

4.1.1 Basiliximab

4.1.1.1 A total of eight randomised controlled trials (RCTs) were included in the Assessment Report. Four of the RCTs compared basiliximab with placebo within regimens comprising either ciclosporin/corticosteroid dual therapy (two trials) or ciclosporin-based triple therapy (two trials) with either azathioprine or mycophenolate mofetil as the antiproliferative component. One trial compared basiliximab with no induction agent in a ciclosporin/ corticosteroid/azathioprine triple regimen with a third group receiving ciclosporin/ corticosteroid/ mycophenolate mofetil triple therapy. All five of these trials only recruited patients considered to be at low-to-moderate immunological risk of graft-failure. The three remaining trials compared basiliximab with another induction agent (either ATG or muromonab-CD3); one of these also included an arm where there was no induction therapy.

4.1.1.2 At 6- or 12-month follow-up, a pooled analysis of comparisons with other induction agents found no statistically significant differences in patient survival, graft loss or rates of biopsy-confirmed acute rejection. A pooled analysis of the comparisons with placebo also found that basiliximab was not associated with statistically higher patient or graft survival rates compared with placebo, but that it was associated with a lower incidence of biopsy-confirmed acute rejection (odds ratio [OR] 0.57; 95% confidence interval [CI] 0.45 to 0.72).

4.1.1.3 The risk and severity of side effects and adverse events were considered to be similar across treatment groups.

4.1.1.4 No data with a longer follow-up than 12 months were available, nor were there data relating to health-related quality of life.

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4.1.2 Daclizumab

4.1.2.1 Three RCTs assessing the use of daclizumab were included in the Assessment Report. The two larger studies (n = 275 and n = 260) compared the use of daclizumab with a placebo, as an adjunct to double or triple ciclosporin-based initial and maintenance therapy. The third trial compared the adjunctive use of daclizumab with muromonab-CD3, but involved only 28 patients and is excluded from the rest of this document. The majority of patients included in these were considered to be at low-to-moderate immunological risk of graft-failure.

4.1.2.2 The pooled 12-month analysis showed that all-cause mortality was statistically significantly lower for patients who received daclizumab than for those who received placebo (OR 0.22; 95% CI 0.06 to 0.79), although the absolute difference in terms of aggregate patient numbers was very small and, in both trials, patient mortality was defined as a secondary outcome. The rate of biopsy-confirmed acute rejection (OR 0.47; 95% CI 0.32 to 0.67) was also lower for patients who received daclizumab. However, the pooled difference in graft loss was not statistically significantly different (OR 0.59; 95% CI 0.34 to 1.03).

4.1.2.3 The risk and severity of side effects and adverse events were considered to be similar across the two treatment groups.

4.1.2.4 The pooled 3-year analysis did not reveal any statistically significant differences in all-cause mortality (OR 0.67; 95% CI 0.17 to 2.69) or graft loss (OR 0.59; 95% CI 0.34 to 1.03) between the daclizumab and placebo treatment groups. No other outcomes at 3 years were reported.

4.1.3 Tacrolimus

4.1.3.1 Thirteen RCTs comparing tacrolimus with either of the two ciclosporin formulations were included in the Assessment Report. Six of these RCTs assessed the use of tacrolimus against the older oily formulation of ciclosporin (Sandimmun), whereas the remaining seven assessed its use against the newer microemulsion formulation (Neoral). Most of the RCTs assessed the use of ciclosporin or tacrolimus in combination with an antiproliferative agent

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(azathioprine or mycophenolate mofetil) and a corticosteroid. In some of the studies, induction therapy with antilymphocyte agents was also used.

4.1.3.2 Pooling the 1-year results for the RCTs that compared tacrolimus with the original, older formulation of ciclosporin showed that the probability of biopsy-confirmed acute rejection favoured treatment with tacrolimus (OR 0.46; 95% CI 0.35 to 0.61). However, there was no statistically significant difference in the probability of all-cause mortality or graft loss.

4.1.3.3 The comparisons with ciclosporin microemulsion also favoured tacrolimus for the endpoint of biopsy-confirmed acute rejection (OR 0.44; 95% CI 0.33 to 0.58). Again, there was no statistically significant difference in the probability of all-cause mortality or graft loss.

4.1.3.4 Across the trials there was evidence at 12 months of an increase in the incidence of tremor with tacrolimus compared with ciclosporin microemulsion. Conversely, with ciclosporin microemulsion, there was a significant increase in hirsutism, hyperlipidaemia and gingivitis.

4.1.3.5 Only one of the 13 RCTs collected information on health-related quality of life, using the generic SF-36 and a disease-specific measure, the Bergner Appearance Scale. No statistically significant difference in SF-36 was reported between tacrolimus and the oily ciclosporin groups. However, results on the Bergner Scale showed a statistically significant difference favouring tacrolimus.

4.1.4 Mycophenolate mofetil

4.1.4.1 Seven RCTs comparing mycophenolate mofetil with azathioprine were included in the Assessment Report. Five of these studies compared mycophenolate mofetil with azathioprine in ciclosporin-based regimens. The remaining two studies compared mycophenolate mofetil with azathioprine in tacrolimus-based regimens; one of these trials appeared to be a dose-ranging study. A study comparing mycophenolate mofetil with placebo in a ciclosporin-based regimen was not included in the Assessment Report (see Section 4.1.3.4) and another RCT comparing the ciclosporin reductions under cover of mycophenolate mofetil with a continued regimen of ciclosporin in patients with chronic allograft dysfunction was made available to the Committee. Two

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separate analyses using UNOS (United Network for Organ Sharing) registry data were also available to the Committee.

4.1.4.2 The pooled data from the comparisons with azathioprine in ciclosporin-based regimens demonstrated a statistically significant lower probability of biopsy-confirmed acute rejection (OR 0.45; 95% CI 0.34 to 0.59) at 6 months or 1 year with mycophenolate mofetil than with azathioprine. There was no statistically significant difference in all-cause mortality (OR 1.12; 95% CI 0.56 to 2.24) or graft loss (OR 0.77; 95% CI 0.52 to 1.13) associated with mycophenolate mofetil at a dose of 2 g per day.

4.1.4.3 The pooled analysis of the two trials comparing mycophenolate mofetil with azathioprine in tacrolimus-based regimens demonstrated no statistically significant difference in the probability of all-cause mortality (OR 1.71; 95% CI 0.50 to 5.37), graft loss (OR 0.75; 95% CI 0.30 to 1.53) or biopsy-confirmed acute rejection (OR 0.43; 95% CI 0.10 to 1.84) for mycophenolate mofetil at a dose of 2 g per day.

4.1.4.4 One additional RCT compared mycophenolate mofetil with placebo in a ciclosporin-based regimen. In this study, mycophenolate mofetil reduced the incidence of biopsy-confirmed acute rejection in the first 6 months after transplantation, but the study lacked the power to demonstrate a difference in patient survival or graft survival.

4.1.4.5 The side-effect profile of mycophenolate mofetil differs from that of azathioprine. In comparative clinical trials, there was a higher incidence of gastrointestinal adverse events (diarrhoea and bleeding) and cytomegalovirus infection in the mycophenolate mofetil groups, but a lower incidence of nausea, thrombocytopenia and jaundice than in the azathioprine groups.

4.1.4.6 Four of the mycophenolate mofetil RCTs reported longer-term results, of up to 3 years follow-up. Results were pooled from three of the trials. There was some evidence of reductions in graft loss and all-cause mortality with mycophenolate mofetil at 3 years (neither outcome was statistically significant: OR 0.62, 95% CI 0.34 to 1.13 for reduction in graft loss, and OR 0.77 95% CI 0.47 to 1.26 for all-cause mortality).

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4.1.4.7 The RCT that compared reduced ciclosporin doses, under cover of mycophenolate mofetil, with a continued regimen of ciclosporin in patients with chronic allograft dysfunction showed that people in the ciclosporin dose-reduction arm of the trial were more likely to have responded to treatment ($p = 0.006$).

4.1.4.8 The results from the UNOS registry analyses suggested that mycophenolate mofetil reduced the 4-year probability of graft failure compared with azathioprine by 27% ($p < 0.001$) at the most.

4.1.5 Sirolimus

4.1.5.1 Although there are no RCTs comparing the licensed regimen for sirolimus with a standard calcineurin-based dual or triple therapy, two studies compared two regimens that both included sirolimus (n = 525 and n = 246). One arm received a regimen of sirolimus initially combined with ciclosporin, followed by tapering of the ciclosporin dose to discontinuation after 2–3 months, with a concomitant increase in the dose of sirolimus adjusted according to whole blood concentrations (this regimen is now licensed). The other arm received sirolimus nominally 2 mg per day with continued ciclosporin (the subsequent marketing authorisation specifically excluded this regimen). Three-year follow-up data was available for the larger RCT. In both studies, no statistically significant differences in the incidences of biopsy-confirmed acute rejection were found. However, in both studies, renal function was significantly better in the group in which ciclosporin was withdrawn from the regimen. Also, in both studies, hypertension was reported to be significantly less frequent in the group that discontinued ciclosporin. The results from a third RCT, in which the use of sirolimus plus low-dose steroids as a maintenance regimen with or without low-dose ciclosporin adjunctive therapy was evaluated, were marked 'commercial in confidence' because the manuscript was unpublished.

4.1.5.2 Other studies have compared sirolimus 2 mg or 5 mg daily versus either azathioprine 2–3 mg/kg per day (one study, n = 719) or placebo (one study, n = 576). All patients received concomitant ciclosporin and corticosteroids. In both studies, the incidence of acute rejection was lower in the groups that received sirolimus. However, because there was no attempt to withdraw

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ciclosporin, these studies are not directly relevant to estimating the effectiveness of the licensed regimen.

4.1.5.3 Two smaller RCTs compared sirolimus-based triple therapy with ciclosporin-based triple therapy. The rate of biopsy-confirmed acute rejection and levels of serum creatinine were not statistically significantly different in either trial at 1 year. Neither sirolimus-treatment arm included an initial phase where people received sirolimus and ciclosporin as specified in the marketing authorisation.

4.2 Cost effectiveness

4.2.1 Basiliximab

4.2.1.1 Eight economic evaluations of basiliximab were included in the Assessment Report.

4.2.1.2 Six of the eight evaluations were published studies (at the time of submission). Two of these six compared the addition of basiliximab or ATG to initial therapy regimens. The remaining four published evaluations assessed the addition of basiliximab alone to ciclosporin-based immunosuppressant regimens. Four of the published studies were cost-consequence analyses, one was a cost-effectiveness analysis and one a cost-utility analysis. One cost-consequence study was conducted from an NHS perspective; the remaining five studies were all non-UK-based evaluations.

4.2.1.3 All the studies included healthcare costs only, which included drug acquisition costs, and the costs of acute rejection episodes and of graft failure treatment.

4.2.1.4 The cost-utility analysis reported the incremental cost of basiliximab to be over US$150,000 per quality-adjusted life year (QALY) at 1 year (basiliximab versus muromonab-CD3). The Assessment Report states that the cost-effectiveness analysis found basiliximab to be 'superior' to placebo at 1 and 10 years.

4.2.1.5 The UK cost-consequence analysis found the 1-year healthcare costs of basiliximab and placebo to be similar.

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4.2.1.6 The sponsor's model assessed the use of basiliximab as an adjunct to initial therapy from an NHS perspective over a 10-year period. When basiliximab was added to triple therapy with ciclosporin, azathioprine and a corticosteroid, the basiliximab regimen was more effective and less costly compared with triple therapy alone. When it was added to triple therapy with ciclosporin, mycophenolate mofetil and a corticosteroid, the incremental cost effectiveness of the basiliximab regimen was about £1800 per QALY.

4.2.1.7 The Assessment Group's own economic model showed the adjunctive use of basiliximab to be less costly and more effective than ciclosporin-based triple therapy alone.

4.2.2 Daclizumab

4.2.2.1 Three economic evaluations of daclizumab were available to the Committee, including one by the Assessment Group.

4.2.2.2 One (non-UK) published economic evaluation for daclizumab was identified. It compared the cost effectiveness of adding daclizumab to a variety of different drug combinations, including ciclosporin-based triple therapy.

4.2.2.3 Few details of the results are available in the Assessment Report but it states that at 10 years, the cost effectiveness of daclizumab plus triple therapy was 'superior' to triple therapy alone.

4.2.2.4 The sponsor estimated the 1-year cost effectiveness of the licensed five-dose daclizumab plus ciclosporin-based triple therapy regimen compared with ciclosporin-based triple therapy alone to be £153,000 per QALY gained. However, for a two-dose regimen, they provided an estimate of £8400 per QALY gained, again at 1 year. Costs were restricted to those incurred by the NHS.

4.2.2.5 The Assessment Group's economic evaluation predicted that the licensed five-dose daclizumab plus ciclosporin-based triple therapy regimen would be more clinically effective and less costly than ciclosporin-based triple therapy alone.

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4.2.3 Tacrolimus

4.2.3.1 Nine economic evaluations of tacrolimus were included in the Assessment Report. Six of the nine evaluations were published studies, two were from the drug sponsor, and one was undertaken by the Assessment Group.

4.2.3.2 All of the published economic evaluations assessed the use of tacrolimus versus ciclosporin, both in combination with other agents. Although all six studies included healthcare costs only, four of them were performed specifically from an NHS perspective. Four of the published studies evaluated the oily formulation of ciclosporin (Sandimmun) and the remaining two evaluated the microemulsion formulation (Neoral).

4.2.3.3 Three of the six evaluations were either cost-effectiveness or cost-utility analyses. The first of the three studies modelled the cost-utility of tacrolimus over 1- and 10-year periods, producing incremental cost-effectiveness ratios (ICERs) of £120,000–£220,000 and £75,000 per QALY, respectively. The second evaluation produced a cost-effectiveness estimate of £30,000 per additional graft saved or patient death avoided, although the time period for this evaluation was unclear.

4.2.3.4 The remaining published cost-effectiveness analysis was based on 6 months' clinical data, which was collected retrospectively from a European multi-centre clinical trial. The differing cost structures for each country resulted in variable per-patient cost differences, but all analyses suggested tacrolimus was the least costly treatment option.

4.2.3.5 The three remaining published studies were cost analyses. One of these studies reported that there was no cost difference between tacrolimus and ciclosporin, whereas the remaining two studies suggested that tacrolimus was the less costly treatment option.

4.2.3.6 The sponsor provided two cost-effectiveness analyses. The first evaluation was performed alongside an RCT at a single UK treatment centre. An NHS perspective was used and follow-up was for a minimum of 1 year. The results of the analysis showed that tacrolimus cost about £200 more over the follow-up period than did ciclosporin, but it was also associated with fewer episodes

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of acute rejection, leading to an incremental cost of about £6000 per rejection-free graft.

4.2.3.7 The sponsor's second evaluation had a longer time horizon – 10 years instead of one. The analysis, which was essentially based on a model, was performed from the perspective of a UK transplant unit. The results from the analysis suggested that the mean cost per additional patient death avoided was about £8000.

4.2.3.8 The results from the Assessment Group's economic model suggested that the combination of tacrolimus with azathioprine and corticosteroids is less costly and more effective than is the combination of ciclosporin with azathioprine and corticosteroids at the baseline. However, the ICER increased to £28,500 per QALY in the sensitivity analysis when the annual cost of providing tacrolimus was assumed to be £5,500 (which is likely to be at the high end of mean treatment costs) instead of £3,500.

4.2.4 Mycophenolate mofetil

4.2.4.1 Nine economic evaluations of mycophenolate mofetil versus azathioprine were included in the Assessment Report. Seven of these evaluations were published studies, one was performed by the sponsor and another by the Assessment Group.

4.2.4.2 Four of the seven published evaluations were cost-consequence analyses and the remaining three were cost-effectiveness analyses. All of the published evaluations included healthcare costs only, although their exact content varied, but none were UK-based evaluations. Only one of the published studies included a time horizon that was greater than 1 year.

4.2.4.3 All but two of the published cost analyses found the costs of mycophenolate mofetil to be greater at 6 months or 1 year compared with those of azathioprine. The one cost analysis that considered the outcomes of treatment over a longer period suggested that this cost difference was maintained at 10 years. The remaining two cost analyses estimated the short-term costs of mycophenolate mofetil to be lower than those associated with azathioprine.

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4.2.4.4 Of the published cost-effectiveness analyses, two estimated both the cost and the effectiveness of mycophenolate mofetil to be superior to those of azathioprine at 10 years. Another produced an incremental cost per QALY estimate of approximately CAN$50,000.

4.2.4.5 The results from the Assessment Group's economic evaluation showed the cost per QALY of replacing azathioprine with mycophenolate mofetil in a ciclosporin-based treatment regimen was about £130,000.The sponsor submitted a cost–utility analysis, which was performed from an NHS perspective over 1- and 10-year periods. Both analyses compared the use of mycophenolate mofetil with azathioprine in ciclosporin-based treatment regimens. Switching to mycophenolate mofetil but not reducing the dose of ciclosporin produced an incremental cost per QALY of about £40,000. The critical difference between the assessment group's and the sponsor's models concerned the risk of graft failure. The sponsor used the assessment group's model but its own more optimistic estimates of graft failure, and found ICERs of £56,000 and £42,000 per QALY. The former ICER was based on acute rejection rates and the latter on registry data on graft survival.

4.2.4.6 The sponsor in addition provided an estimate of £23,000 per additional QALY, based on ciclosporin dose reduction. They also used the Assessment Group's model with reduced doses of ciclosporin (based on a number of analyses of RCT and registry data). This reduced the ICER to £54,000 from £130,000 per QALY. Furthermore, they argued that the adjusted ciclosporin dose and the optimistic graft failure rate generated an ICER of £22,000 per QALY using the Assessment Group's model. This is consistent with their first estimate of £23,000 per QALY.

4.2.4.7 The Assessment Group calculated an ICER per QALY for people in whom renal function was deteriorating (see Section 4.1.4.7). For this group, mycophenolate mofetil was both less costly and more effective compared with continued treatment with full dose ciclosporin.

4.2.5 Sirolimus

4.2.5.1 Three economic evaluations of sirolimus were considered by the Committee. One was a published study, one was performed by the Assessment Group and

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the third was submitted by the sponsor. All three studies included healthcare costs only.

4.2.5.2 The published study was a US-based cost analysis that compared the 1-year costs of using sirolimus instead of azathioprine. Costs included the consequences of treatment but did not include the actual cost of the study drugs. The study reported the costs of these treatments to be similar (US$122,033 for sirolimus versus US$126,627 for azathioprine).

4.2.5.3 The sponsor's economic evaluation compared the cost-effectiveness of sirolimus with ciclosporin withdrawal and a corticosteroid to a standard calcineurin-inhibitor-based treatment regimen. As there has not been an RCT of these treatments, 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.

4.2.5.4 The Assessment Group's economic model compared the cost effectiveness of sirolimus with ciclosporin withdrawal and a corticosteroid with that of sirolimus, ciclosporin and a corticosteroid. However, the Committee considered this to be an inappropriate comparison.

4.3 Consideration of the evidence

4.3.1 The Committee reviewed the data available on the clinical and cost effectiveness of immunosuppressive therapy for renal transplantation in adults, having considered evidence on the nature of the condition and the value placed by users on the benefits of immunosuppressive therapy from recipients of renal transplants, those who represent them, and clinical experts. It was also mindful of the need to take account of the effective use of NHS resources.

Basiliximab and daclizumab

4.3.2 The Committee considered that the evidence from the RCTs and economic evaluations demonstrated that basiliximab and daclizumab for adults used concomitantly with calcineurin-inhibitor-based immunosuppression were

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clinically and cost effective relative to no induction therapy in preventing acute rejection in the first year after renal transplantation in patients at low to moderate immunological risk. However, the Committee was also aware of the equivocal nature of the evidence that acute rejection in these circumstances predicts long-term graft survival.

4.3.3 The Committee heard from the experts that these agents are more commonly used for patients with higher levels of immunological risk, although basiliximab and daclizumab are not licensed for patients who are at high immunological risk. The Committee were persuaded that there was 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. The Committee was aware that the Department of Health and Welsh Assembly Government had indicated that the Institute should consider the use of immunosuppressants as they are used in current practice, which may include use outside the terms of the marketing authorisation. It therefore concluded that basiliximab and daclizumab should be options for all adults undergoing renal transplantation, irrespective of their immunological risk.

4.3.4 The Committee considered that, on the basis of data from clinical studies and the opinion of experts, there was no convincing evidence that either of these agents should be preferred over the other. The Committee noted that the costs associated with the use of these drugs are potentially quite different, given the different dosing regimens, and they concluded that the drug regimen with the lowest acquisition costs should be prescribed unless it is contraindicated.

Tacrolimus

4.3.5 The Committee considered that the evidence from the RCTs demonstrated that tacrolimus was at least as effective as ciclosporin as initial or maintenance immunosuppression and there was some evidence to suggest that it may be more effective in preventing acute rejection. However, the Committee heard from experts that interpretation of studies was complicated by differences in the dosage regimens used in the trials and those currently used in clinical practice. The experts also emphasised the different side-effect profiles of the calcineurin inhibitors and therefore the need for both options to be available.

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The economic evidence suggested that tacrolimus was likely to be cost effective. The Committee therefore concluded that tacrolimus should be available for adults as an alternative to ciclosporin.

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

Mycophenolate mofetil

4.3.7 The evidence from RCTs comparing mycophenolate mofetil with azathioprine or placebo in ciclosporin-based immunosuppressive regimens demonstrated that mycophenolate mofetil was effective in reducing the incidence of acute rejection in the first 6–12 months after renal transplantation. The Committee also noted that registry data suggested that mycophenolate mofetil might reduce the likelihood of graft failure. However, evidence both from the Assessment Group's and from the sponsor's economic models suggested that mycophenolate mofetil with full dose ciclosporin (as per the licensed indication) was unlikely to be cost effective compared with a regimen containing azathioprine.

4.3.8 The Committee considered the possibility that, when mycophenolate mofetil is used, the dose of ciclosporin (and drug costs overall) could be reduced without loss of clinical effectiveness. However, only when optimistic assumptions were made about the effect of mycophenolate mofetil both on graft survival and on reduction of ciclosporin dosage could mycophenolate mofetil be considered to be cost effective. Even so, the Committee was persuaded that for a subgroup of patients in whom renal function gradually decreases after transplantation, as evidenced by progressively rising creatinine levels (that is, where chronic allograft dysfunction is evident and reduction of ciclosporin dose is required), mycophenolate mofetil was likely to be both clinically and cost effective.

4.3.9 The Committee was also persuaded that mycphenolate mofetil has a potentially clinically significant role in situations where there is a very high risk

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of calcineurin inhibitor nephrotoxicity, as it allows the use of these drugs to be minimised or avoided. For example, in delayed graft function, or where kidneys are at particular risk of developing delayed grat function (for example kidneys from non-heart beating donors or where 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 mycophenolate mofetil therapy to cover this period of increased risk from calcineurin inhibitor nephtotoxicity 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.

Sirolimus

4.3.10 The Committee noted that there were no clinical studies directly comparing the sirolimus regimen that is currently licensed (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 arm of the trial. The Committee did not accept that this licensed regimen was more clinically effective than standard ciclosporin-based immunosuppression on the basis of the available evidence.

4.3.11 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.

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5 Recommendations for further research

5.1 A randomised controlled trial comparing the following three regimens is required: (1) sirolimus, with corticosteroids and, after the initial treatment period, withdrawal of calcineurin inhibitor; (2) mycophenolate mofetil, with corticosteroids and, after the initial treatment period, withdrawal of calcineurin inhibitor; and (3) standard calcineurin-inhibitor-based triple therapy.

5.2 A trial should be carried out to determine whether starting a strategy of calcineurin inhibitor monotherapy and adding in an antiproliferative and a corticosteroid when necessary is clinically and economically preferable to using calcineurin-inhibitor-based triple therapy from the outset or vice versa.

5.3 Future clinical studies of immunosuppressants following renal transplantation should consider including people who are at a high immunological risk, such as those who have had a previous aggressive graft rejection. Studies should consider assessing the benefits of stratifying levels of immunosuppression according to risk.

5.4 Future clinical studies should also measure health-related quality of life.

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6 Implications for the NHS

6.1 On balance, it is not anticipated that this guidance will increase the total cost of prescribing immunosuppressants for renal transplantation because, in general terms, it is likely to lead to a consolidation of current treatment patterns.

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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 is undergoing 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 adults 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 adults undergoing renal transplantation should incorporate the guidance.

7.4 Adults currently receiving immunosuppressive drugs for renal transplantation but using approaches that are not supported by this guidance (whether as routine therapy or as part of a clinical trial) could suffer loss of well being if their treatment were to be discontinued at a time they did not anticipate. Because of this, all NHS patients who are on such therapy at the date of publication of this guidance should have the option to continue treatment until they and their consultant consider it is appropriate to stop.

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

7.5.1 Basiliximab or daclizumab, used as part of calcineurin-inhibitor-based immunosuppression, are considered as options for induction therapy in the prophylaxis of acute organ rejection in adults undergoing renal transplantation. The induction therapy with the lowest acquisition cost is used, unless it is contraindicated.

7.5.2 Tacrolimus is considered as an alternative to ciclosporin when a calcineurin inhibitor is indicatedas part of an initial or maintenance immunosuppression in renal transplantation for adults.

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7.5.3 Mycophenolate mofetil, as part of an immunosuppressive regimen, is considered as an option only when an adult has proven intolerance to calcineurin inhibitors, particularly nephrotoxicity leading to risk of chronic allograft dysfunction or in situations where there is a very high risk of nephrotoxicity, necessitating minimisation or avoidance of the calcineurin inhibitor.

7.5.4 Sirolimus, as part of an immunosuppressive regimen, is considered as an option only when an adult has proven intolerance to calcineurin inhibitors necessitating complete withdrawal of these treatments.

7.5.5 When any of these medicines is prescribed outside the terms of their marketing authorisation, the responsible clinician makes the person aware of this and obtains the person's consent to their use in the circumstances.

7.6 Local clinical audits could also include measures of the timing and dosages of drug therapy used for people undergoing renal transplantation.

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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).
- Immunosuppressive therapy for renal transplantation in children and adolescents. NICE technology appraisal guidance 99 (2006).

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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 August 2007.

Andrew Dillon
Chief Executive
September 2004

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Appendix A. Appraisal Committee members and NICE project team

A. Appraisal Committee members

NOTE 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 three times a month except in December, when there are no meetings. The Committee membership is split into three branches, with the chair, vice-chair and a number of other members between them attending meetings of all 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

Dr Sunil Angris
General Practitioner, Waterhouses Medical Practice, Staffordshire

Dr Darren Ashcroft
Senior Clinical Lecturer, School of Pharmacy and Pharmaceutical sciences, University of Manchester

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

Dr Peter Barry
Consultant in Paediatric Intensive Care and Honorary Senior Lecturer, Department of Child Health, Leicester Royal Infirmary

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Professor John Brazier
Health Economist, University of Sheffield

Professor John Cairns
Professor of Health Economics, Health Economics Research Unit, University of Aberdeen

Professor Mike Campbell
Statistician, Institute of General Practice & Primary Care, Sheffield

Dr Peter I Clark
Consultant Medical Oncologist, Clatterbridge Centre for Oncology, Wirral, Merseyside

Dr Mike Davies
Consultant Physician, University Department of Medicine & Metabolism, Manchester Royal Infirmary

Mr Richard Devereaux-Phillips
Public Affairs Manager, Medtronic Ltd

Professor Cam Donaldson
PPP Foundation Professor of Health Economics, School of Population and Health Sciences & Business School, Business School - Economics, University of Newcastle upon Tyne

Professor Jack Dowie
Health Economist, London School of Hygiene

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

Professor Terry Feest
Clinical Director and Consultant Nephrologist, Richard Bright Renal Unit; Chair of UK Renal Registry, Bristol

Ms Sally Gooch
Director of Nursing, Mid-Essex Hospital Services NHS Trust, Chelmsford

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Professor Trisha Greenhalgh
Professor of Primary Health Care, University College London

Miss Linda Hands
Clinical Reader in Surgery, University of Oxford

Professor Peter Jones
Professor of Statistics and Dean, Faculty of Natural Sciences, Keele University

Professor Robert Kerwin
Professor of Psychiatry and Clinical Pharmacology, Institute of Psychiatry, London

Ms Joy Leavesley
Senior Clinical Governance Manager, Guy's and St Thomas' NHS Trust

Ms Ruth Lesirge
Lay Representative, previously Director, Mental Health Foundation, London

Dr George Levvy
Lay Representative, Chief Executive, Motor Neurone Disease Association, Northampton

Ms Rachel Lewis
Staff Nurse (Nephrology) Hull Royal Infirmary

Dr Rubin Minhas
General Practitioner with a Special Interest in Coronary Heart Disease, Primary Care CHD Lead, Medway PCT and Swale PCT

Dr Gill Morgan
Chief Executive, NHS Confederation, London

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

Dr Stephen Saltissi
Consultant Cardiologist, Royal Liverpool University Hospital

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Mr Miles Scott
Chief Executive, Harrogate Health Care NHS Trust

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

Professor Mary Watkins
Professor of Nursing, University of Plymouth

Dr Norman Waugh
Department of Public Health, University of Aberdeen

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.

Dr Alec Miners and Janet Robertson
Technical Leads, NICE project team

Nina Pinwill
Project Manager, NICE project team

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Appendix B. Sources of evidence considered by the Committee

A. The assessment report for this appraisal was prepared by Department of Public Health and Epidemiology, The University of Birmingham. Health Economics Facility, Health Services Management Centre, The University of Birminhgam and the Department of Nephrology, Queen Elizabeth Hospital, Birmingham.

- Taylor R, Woodroffe R, Yao GL, et al, Clinical and cost effectiveness of immunosuppressive regimens in renal transplantation, December 2002.

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 the Appraisal Consultation Document. Consultee organisations are provided with the opportunity to appeal against the Final Appraisal Determination.

I) Manufacturer/sponsors:

- Fujisawa Limited
- Novartis Pharmaceuticals (UK) Limited
- Roche Producte Limited
- Wyeth UK

II) Professional/specialist and patient/carer groups:

- Addenbrookes NHS Trust
- Association of Renal Industries
- British Association for Paediatric Nephrology
- The British Renal Society
- The British Transplantation Society
- Department of Health

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- National Kidney Federation
- National Kidney Research Fund
- Oxford Radcliffe NHS Trust
- The Renal Association
- Renal Pharmacists Group
- Royal College of General Practitioners
- Royal College of Nursing
- Royal College of Paediatrics and Children's Health
- Royal College of Pathologists
- Royal College of Physicians
- Royal Pharmaceutical Society of Great Britain
- Society for DGH Nephrologists
- The Transplant Support Network
- UK Renal Transplant Nurses Association
- United Kingdom Transplant Coordinators Association
- Welsh Assembly Government
- Welsh Kidney Patients Association

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

- British National Formulary (BNF)
- NHS Quality Improvement Scotland
- UK Transplant

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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 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 Ali Bakran, Transplant and Vascular Surgeon, The Royal Liverpool University Hospitals, nominated by the National Kidney Research Fund and the Department of Heath
- Ms Rachel Jones, Transplant Patient/Patient Representative for the National Kidney Research Fund
- Mr Christopher G Koffman, Consultant Surgeon & Head of Transplantation, Guy's and St Thomas' Hospital NHS Trust, London, nominated by Department of Health
- Dr John Marsden, Chairman, Welsh Kidney Patients Association
- Dr Chas Newstead, Consultant Renal Physician, Renal Unit, St James's University Hospital, Leeds, nominated by British Transplantation Society
- Dr Donal J O'Donoghue, Consultant Nephrologist, Department of Renal Medicine , Hope Hospital , Salford Royal Hospitals NHS Trust, nominated by British Renal Society
- Professor Stephen Powis, Professor of Renal Medicine, Centre for Nephrology, Royal Free Campus, Royal Free & University College Medical School, University College London, nominated by Oxford Transplant Centre, Oxford Radcliffe Hospital
- Dr Michelle Webb, Consultant Nephrologist, Kent & Canterbury Hospital, East Kent Hospitals NHS Trust Renal Unit, nominated by DGH Nephrology Society

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Appendix C. Detail on criteria for audit of the use of immunosuppressive therapy for renal transplantation

Possible objectives for an audit

An audit on the appropriateness of use of immunosuppressive therapy for renal transplantation could be carried out to ensure the following.

- Basiliximab or daclizumab are considered as options for induction therapy in the prophylaxis of acute organ rejection.
- Tacrolimus is considered as an alternative to ciclosporin when a calcineurin inhibitor is indicated as part of an initial and maintenance immunosuppression.
- Mycophenolate mofetil or sirolimus are considered as options only in appropriate situations.
- When any of these medicines is prescribed outside the terms of their marketing authorisation, the patient formally consents to their use.

Possible patients to be included in the audit

An audit could be carried out on adults undergoing renal transplantation in a suitable time period for audit, for example, 6 months. The audit could focus on groups of people at different stages of transplantation, for example, immediate pre- and post-operative, 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 people, as described above.

Criterion	Standard	Exception	Definition of terms

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1. Basiliximab or daclizumab are considered as options for induction therapy in the prophylaxis of acute organ rejection	100% of adults undergoing renal transplantation	None	The drugs are used as part of a calcineurin-inhibitor-based immunosuppressive regimen. Clinicians will need to agree locally on how consideration of options for therapy is documented, for audit purposes. Also see 6 below.
2. If an individual is treated with basiliximab or daclizumab as part of induction therapy, the therapy with the lowest acquisition cost is used	100% of adults who are treated with basiliximab or daclizumab	A. 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.
3. Tacrolimus is considered as an alternative to ciclosporin when a calcineurin inhibitor is indicated as part of an initial or maintenance immunosuppression	100% of adults who have had renal transplantation	None	The initial choice of tacrolimus or ciclosporin is based on the relative importance of their side-effect profiles for the individual patient. Clinicians will need to agree locally on how consideration of options for therapy is documented, for audit purposes.

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4. Mycophenolate mofetil is considered as an option only in the following situations: a. the person has proven intolerance to calcineurin inhibitors b. situations where there is a very high risk of nephrotoxicity	100% of adults who have a renal transplant and who have proven intolerance to calcineurin inhibitors or experience a Situations where there is a very high risk of nephrotoxicity	None	Clinicians will need to agree locally on how proven intolerance to calcineurin inhibitors and consideration of options for therapy are documented, for audit purposes. Intolerance can include nephrotoxicity leading to risk of chronic allograft dysfunction necessitating minimisation or avoidance of the calcineurin inhibitor. Also see 6 below.
5. Sirolimus is considered as an option only when a personhas proven intolerance to calcineurin inhibitors necessitating complete withdrawal of these treatments	100% of adults who have proven intolerance to calcineurin inhibitors necessitating complete withdrawal of these treatments	None	Clinicians will need to agree locally on how consideration of options for therapy and proven intolerance to calcineurin inhibitors is documented, for audit purposes. Also see 6 below.

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6. When one of the medicines referred to in the guidance is prescribed outside the terms of their marketing authorisation, the responsible clinician: a. makes the person aware of the use outside the terms of their marketing authorisation **and** b. obtains the person's consent for the use of the medicine outside the terms of their marketing authorisation	100% of adults for whom a medicine is used beyond its licensed indications	None	Basiliximab, daclizumab, mycophenolate mofetil or sirolimus used consistent with the guidance in this document will sometimes be outside the terms of the marketing authorisation for these medicines. Clinicians will need to agree locally on how people are made aware of the use and on the written consent form used for this purpose.

An alternative to measuring the appropriateness of use of mycophenolate mofetil and sirolimus is illustrated in the measures that follow.

Criterion	Standard	Exception	Definition of terms
1. Mycophenolate mofetil is prescribed	0% of adults who have renal transplantation	A. The person has proven intolerance to calcineurin inhibitors B. Situations where there is a very high risk of nephrotoxicity	See above for relevant definitions.

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2. Sirolimus is prescribed as part of an immunosuppressive regimen	0% of adults who have renal transplantation	A. A person has proven intolerance to calcineurin inhibitors necessitating complete withdrawal of these treatments	See above for relevant definitions.

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.

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Changes after publication

March 2014: implementation section updated to clarify that immunosuppressive therapy is recommended as an option for treating people who are undergoing renal transplantation. Additional minor maintenance update also carried out.

March 2012: minor maintenance

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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.

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