Appendix A

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Proposed Health Technology Appraisal

Immunosuppresive therapy for renal transplantation in children and adolescents (review of existing guidance 99)

Draft scope (pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost-effectiveness of immunosuppressive regimes for renal transplantation, both immediately after transplantation and as far as the evidence allows at subsequent stages, including those using the newer agents.

Background

Established renal failure is the result of progressive disease of the kidneys leading to irreversible loss of function. The most common causes of renal failure in children are birth defects, hereditary and glomerular diseases. Over the past three decades, kidney transplantation has become established as a treatment for many patients with established renal failure. The only alternative treatment is renal dialysis.

One of the major problems after kidney transplantation is the rejection of the transplanted organ . Immunosuppressant therapy is used to prevent acute rejection and chronic graft dysfunction (including drug related nephrotoxicity) thereby prolonging graft survival. Standard immunosuppressive therapy in kidney transplantation consists of induction therapy, using a short course of intensive immunosuppression postoperatively, maintenance therapy to prevent rejection, and short courses of 'rescue' therapy as necessary to treat episodes of acute rejection.

Kidney transplantation in children can differ from the situation in adult in several important aspects, including the underlying aetiology of organ failure, the complexity of the surgical procedure, the metabolism and 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.

[1] NICE Technology Appraisal Guidance No 99 – Immunosuppressive therapy for renal transplantation in children and adolescents (April 2006)

The Department of Health's remit to the Institute was

[2] To appraise the clinical and cost effectiveness of basiliximab (Simulect, Novartis), daclizumab (Zenepax, Roche), mycophenolate mofetil (CellCept, Roche), mycophenolate sodium (Myfortic, Novartis), sirolimus (Rapamune, Wyeth) and tacrolimus (Prograf, Fujisawa) as immunosuppressive therapy for renal transplantation in children and adolescents, and to provide guidance to the NHS in England and Wales.

Between April 2009 and March 2010 a total of 2,479 kidney transplant operations were performed in the UK. Of these, approximately 137 were for people under the age of 18 years of age. Figures from the 2003 Renal Registry Report suggested that approximately 595 children and adolescents were receiving immunosuppressive therapy following renal transplantation.

Most children receive triple therapy comprising a calcineurin inhibitor (usually ciclosporin), a DNA proliferation inhibitor (usually azathioprine) and a corticosteroid, or dual-therapy (calcineurin inhibitor plus corticosteroid) immunosupression regimens. Current NICE guidance (TA99) recommends the use of basiliximab, daclizumab (which no longer has a UK marketing authorisation), mycophenolate mofetil and tacrolimus in children and adolescents who receive a kidney transplant.

The technologies

Basiliximab (Simulect, Novartis) is a CD25 monoclonal antibody which has a UK marketing authorisation in combination with ciclosporin microemulsion- and corticosteroid-based immunosuppression for the prophylaxis of acute organ rejection in *de novo* allogeneic renal transplantation in children and adults. Mycophenolic acid inhibits DNA proliferation.

Mycophenolic acid is available in two formulations. Mycophenolate mofetil (CellCept, Roche) has a UK marketing authorisation in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in children and adults receiving allogenic renal transplants. Mycophenolate sodium (Myfortic, Novartis) has a UK marketing authorisation for use in combination with ciclosporin and corticosteroids, for the prevention of acute rejection in kidney allografts in adults.

Sirolimus (Rapamune, Wyeth) is a non-calcineurin inhibiting immunosuppressant. It has a UK marketing authorisation for the prophylaxis of organ rejection in adults at low- to moderate- immunological risk who have received a renal transplant.

Tacrolimus (Modigraf and Prograf, Astellas Pharma) is a calcineurin inhibitor. It has a UK marketing authorisation for use in children and adults for primary immunosuppression in kidney allograft recipients and the treatment of kidney allograft rejection resistant to conventional immunosuppressive regimens. It can be administered intravenously or orally.

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Rabbit anti-human thymocyte immunoglobulin (Thymoglobuline, Genzyme Therapeutics) is a selective immunosuppressive agent which acts mostly on T lymphocytes. It has a UK marketing authorisation in children and adults for immunosuppression in solid organ transplantation, prevention of graft rejection in renal transplantation and treatment of steroid resistant graft rejection in renal transplantation. It is administered intravenously and usually in combination with other immunosuppressive drugs.

Everolimus (Certican, Novartis) is a proliferation signal inhibitor of the mammalian target of rapamycin [mTOR] protein and is an analogue of sirolimus. It is an oral immunosuppressant that targets the primary causes of progressive allograft dysfunction (also known as chronic rejection) following organ transplantation.

Everolimus does not currently have a UK marketing authorisation for immunosuppressive treatment in kidney transplantation but has been studied in clinical trials of children and adolescents (up to 16 years) in combination with ciclosporin and corticosteroids.

Intervention(s)	Induction therapy: basiliximab as adjunctive therapy Maintenance therapy: drug regimens containing mycophenolate mofetil, mycophenolate sodium, everolimus, sirolimus, tacrolimus or rabbit anti-human thymocyte immunoglobulin.
Population(s)	Children and adolescents undergoing renal transplantation
Comparators	Induction therapy: no adjunctive therapy Maintenance therapy: triple combination therapy with ciclosporin, a corticosteroid and azathioprine Where appropriate, the interventions will be compared to each other.

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Outcomes	The outcome measures to be considered include: • patient survival • graft survival / graft half-life • graft functioning (serum creatinine / glomerular filtration rate) • incidence of acute rejection • growth • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.

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Other considerations	The Appraisal Committee will consider making recommendations about the use of drugs outside the terms of their existing marketing authorisation where there is compelling evidence of their safety and effectiveness. If the evidence allows subgroups will be considered. These include subgroups according to heterogeneity between different age groups, the degree of HLA histocompatibility between the recipient and donor, and donor type (e.g. cadaveric or living donors). If the evidence allows, the use of mycophenolate mofetil will be considered in corticosteroid reduction or withdrawal strategies for child and adolescent renal transplant recipients. The use of immunosuppressive drugs in patients receiving multiple organ transplants (for example, combined kidney and pancreas transplantation) is excluded from this appraisal.

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Related NICE recommendations	Related Technology Appraisals: Technology Appraisal No. 48, Sep 2003, 'Guidance on the use of home compared with hospital haemodialysis for patients with end-stage renal failure'. Technology Appraisal No. 85, Sep 2004, 'Guidance on the use of immunosuppressive therapy for renal transplantation in adults'. Technology Appraisal No.99, Apr 2006, 'Guidance on the use of immunosuppressive therapy for renal transplantation in children and adolescents'. Technology Appraisal No. 165, Jan 2009, 'Machine perfusion systems and cold static storage of kidneys from deceased donors'. Technology Appraisal in Preparation: 'Belatacept for the prevention of organ rejection in renal transplantation' Earliest anticipated date of publication TBC Technology Appraisal in Preparation: 'Everolimus for the prevention of organ rejection in renal transplantation' Earliest anticipated date of publication TBC Related Guidelines: Clinical Guideline No. 73, Sep 2008, 'Early identification and management of chronic kidney disease in adults in primary and secondary care'.

Questions for consultation

Have the most appropriate comparators used in immunosuppressive therapy for renal transplantation in children and adolescents been included in the scope?

Are there any differences in the clinical effectiveness of the different tacrolimus formulations?

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Are tacrolimus, everolimus and rabbit anti-human thymocyte immunoglobulin intended to be used as induction, initial or maintenance treatment for the prevention of graft rejection?

Are there any subgroups of patients in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Are there any issues that require special attention in light of the duty to have due regard to the need to eliminate unlawful discrimination and promote equality?

What do you consider to be the relevant clinical outcomes and other potential health related benefits of these technologies in immunosuppressive therapy for renal transplantation in children and adolescents, particularly when compared with currently used treatment options?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

(Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp)

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