NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

Immunosuppressive therapy for kidney transplantation in children and adolescents (review of technology appraisal guidance 99)

Final scope

Appraisal objective[1]

To appraise the clinical and cost-effectiveness of immunosuppressive regimens for kidney transplantation in children and adolescents.

Background

Kidney transplantation is used to treat people with established renal failure, which is severe and irreversible impairment of kidney function. The most common causes of renal failure in children are birth defects, hereditary and glomerular diseases. After a kidney transplant, immunosuppressive therapy is used to reduce the risk of rejection of the transplanted kidney (or 'graft') and prolong its survival. Between April 2012 and March 2013, 121 kidney transplant operations were performed in the UK for children and adolescents under 18 years of age. In 2012, approximately 690 children and adolescents in the UK were receiving immunosuppressive therapy after kidney transplantation.

Kidney transplantation in children and adolescents can differ from adults in several important aspects, including the cause 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, the susceptibility to post-transplant complications, and the degree of adherence to treatment.

Immunosuppressive therapy can be categorised as induction therapy, initial maintenance therapy, and long-term maintenance therapy. Induction therapy may be used for up to 2 weeks around the time of transplantation; the aim is to prevent acute rejection, optimise the function of the transplanted organ, and minimise the risk of infection. Initial maintenance therapy starts immediately after transplantation and lasts for about 3–6 months; the aim is to prevent acute rejection, optimise the function of the transplanted organ, and minimise the long-term consequences of immunosuppression such as an increased risk of cancer, infection and cardiovascular disease. Long-term maintenance therapy is often the same as initial maintenance therapy, but with a reduced dose. The choice of immunosuppressive therapy is informed by the level of

[1] The Department of Health and Welsh Assembly Government remit to the Institute was to advise on 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.

immunological risk, determined by risk factors such as age and antibody reactivity (measured by human leukocyte antigen and panel reactive antibody status). During the maintenance phases, people may experience episodes of acute rejection which require short courses of additional immunosuppressive therapy. This technology appraisal only considers the prevention of organ rejection; the treatment of episodes of acute rejection is outside the scope of this appraisal.

Induction therapy is a short course of intensive immunosuppressive therapy, often involving polyclonal antibodies (for example, anti-human thymocyte immunoglobulin) or monoclonal antibodies (for example, basiliximab). NICE technology appraisal 99 recommends basiliximab or daclizumab as part of a calcineurin-inhibitor-based immunosuppressive regimen. The marketing authorisation for daclizumab has been withdrawn at the request of the manufacturer.

For maintenance therapy, the treatment options used in clinical practice include calcineurin inhibitors (such as ciclosporin or tacrolimus) and antiproliferative agents (such as azathioprine, sirolimus or mycophenolic acid), which are often used in combination regimens with or without corticosteroids. NICE technology appraisal guidance 99 recommends tacrolimus as an alternative to ciclosporin when a calcineurin inhibitor is appropriate. Mycophenolate mofetil is recommended as part of an immunosuppressive regimen only when there is proven intolerance to calcineurin inhibitors or a very high risk of nephrotoxicity. The use of mycophenolate mofetil in corticosteroid reduction or withdrawal strategies is only recommended in the context of clinical trials. Mycophenolate sodium is not recommended for use as part of an immunosuppressive regimen. Sirolimus (a non-calcineurin inhibiting immunosuppressant) is recommended only when proven intolerance to calcineurin inhibitors (including nephrotoxicity) requires complete withdrawal of these treatments.

Some of the recommendations in NICE technology appraisal guidance 99 are outside the marketing authorisations for the respective drugs; the guidance recommends that clinicians should ensure patients and/or their legal guardians are aware of this and consent to this use. The recommendations outside the marketing authorisations concern the use of the treatments in people with high immunological risk, in unlicensed drug combinations, or for children or adolescents.

Since the publication of NICE technology appraisal guidance 99, new technologies have received marketing authorisations for induction therapy (rabbit anti-human thymocyte immunoglobulin) and maintenance therapy (belatacept, prolonged-release tacrolimus, and an oral suspension of immediate-release tacrolimus). Another new technology (everolimus) has been studied. Additional research on several of the treatments included in NICE technology appraisal 99 has been published. Some of these treatments are now available generically, and the marketing authorisation for daclizumab has been withdrawn.

The technologies

The technologies to be appraised are those that: were included in technology appraisal guidance 99, have obtained a relevant marketing authorisation in the UK since the publication of technology appraisal 99, or have been referred to NICE by the Department of Health for appraisal. The technologies that will be appraised are listed in the table below.

Technology	Induction therapy	Maintenance therapy	Marketing authorisation for children and adolescents?
Basiliximab	✓		Yes, 1–17 years
Rabbit anti-human thymocyte immunoglobulin	✓		The marketing authorisation is not restricted to adults. The SPC* includes dosage recommendations for children, age range not specified
Immediate-release tacrolimus		✓	Yes, age range not specified
Prolonged-release tacrolimus		✓	No
Belatacept		✓	No
Mycophenolate mofetil		✓	The marketing authorisation is not restricted to adults. The SPC* includes dosage recommendations for patients aged 2–18 years
Mycophenolate sodium		✓	No
Sirolimus		✓	No
Everolimus		✓	Does not currently have a UK marketing authorisation

*SPC: summary of product characteristics. In this table, a technology is defined as an induction therapy if the SPC recommends treatment duration of less than 14 days.

For induction therapy

Basiliximab (Simulect, Novartis Pharmaceuticals) is a monoclonal antibody which acts as an interleukin-2 receptor antagonist. It has a UK marketing authorisation for the prophylaxis of acute organ rejection in de novo allogeneic renal transplantation in paediatric patients (1–17 years). The summary of product characteristics states it is to be used concomitantly with ciclosporin for microemulsion- and corticosteroid-based immunosuppression, in patients with panel reactive antibodies less than 80%, or in a triple maintenance immunosuppressive regimen containing ciclosporin for microemulsion, corticosteroids and either azathioprine or mycophenolate mofetil. Higher panel reactive antibody scores indicate higher immunological risk. Basiliximab is administered intravenously.

Rabbit anti-human thymocyte immunoglobulin (Thymoglobuline, Sanofi) is a gamma immune globulin, generated by immunising rabbits with human thymocytes. It has a UK marketing authorisation for the prevention of graft rejection in renal transplantation. The summary of product characteristics states it is usually used in combination with other immunosuppressive drugs. It is administered intravenously. The UK marketing authorisation is not restricted to adults only.

For maintenance therapy

Tacrolimus is a calcineurin inhibitor. It is available in a prolonged-release formulation (Advagraf, Astellas Pharma) and immediate-release formulations (Adoport, Sandoz; Capexion, Mylan; Modigraf, Astellas Pharma; Perixis, Accord Healthcare; Prograf, Astellas Pharma; Tacni, Teva; Vivadex, Dexcel Pharma). All of these formulations can be administered orally. Prograf can also be administered intravenously. All of these formulations of tacrolimus have UK marketing authorisations for prophylaxis of transplant rejection in kidney allograft recipients. The marketing authorisation for the prolonged-release formulation is restricted to adults; the summary of product characteristics states that the safety and efficacy of Advagraf in children under 18 years of age have not yet been established. The marketing authorisations for the immediate-release formulations include adults and children. The Commission on Human Medicines advises that all oral tacrolimus medicines in the UK should be prescribed and dispensed by brand name only.

Belatacept (Nulojix, Bristol-Myers Squibb) is a soluble fusion protein designed to selectively inhibit CD28-mediated co-stimulation of T-cells. Belatacept has a UK marketing authorisation for prophylaxis of graft rejection in adults receiving a renal transplant, in combination with corticosteroids and a mycophenolic acid. The summary of product characteristics recommends that an interleukin-2 receptor antagonist for induction therapy is added to this belatacept-based regimen. The summary of product characteristics states that the safety and efficacy of belatacept in children and adolescents 0 to 18 years of age have not yet been established. An ongoing clinical trial is assessing the safety and efficacy of belatacept, tacrolimus, and corticosteroids in children and adolescents aged 6–17 years who have had a kidney transplant. Belatacept is administered intravenously.

Mycophenolate mofetil (Arzip, Zentiva; CellCept, Roche Products; Myfenax, Teva; generic mycophenolate mofetil is manufactured by Accord Healthcare, Actavis, Arrow Pharmaceuticals, Dr Reddy's Laboratories, Mylan, Sandoz, and Wockhardt) is a prodrug formulation for mycophenolic acid, which is an antiproliferative. It has a UK marketing authorisation for use in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in people undergoing kidney transplantation. The UK marketing authorisation is not restricted to adults. It can be administered orally or intravenously.

Mycophenolate sodium (Myfortic, Novartis Pharmaceuticals) is an enteric-coated formulation of mycophenolic acid and has the same UK marketing

authorisation as mycophenolate mofetil, however, this is restricted to adults. Mycophenolate sodium has been studied in clinical trials that included children and adolescents. The summary of product characteristics states that insufficient data are available to support the efficacy and safety of Myfortic in children and adolescents. It is administered orally.

Sirolimus (Rapamune, Pfizer) is a non-calcineurin inhibiting immunosuppressant and acts as an antiproliferative. It has a UK marketing authorisation for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving a renal transplant. It is recommended to be used initially in combination with ciclosporin and corticosteroids for 2 to 3 months. It may be continued as maintenance therapy with corticosteroids only if ciclosporin can be progressively discontinued. The summary of product characteristics states that the safety and efficacy of sirolimus in children and adolescents less than 18 years of age have not been established. Sirolimus has been studied in clinical trials that included children and adolescents. It is administered orally.

Everolimus (Certican, Novartis Pharmaceuticals) is a proliferation signal inhibitor and is an analogue of sirolimus. Everolimus does not currently have a UK marketing authorisation for immunosuppressive treatment in kidney transplantation. An ongoing clinical trial is comparing everolimus, tacrolimus, and steroid withdrawal with mycophenolate mofetil, tacrolimus, and standard-dose steroids in children and adolescents aged 1–17 years who have had a kidney transplant. Everolimus is administered orally.

Intervention(s)	**Induction therapy** For prevention of organ rejection, regimens containing: • Basiliximab • Rabbit anti-human thymocyte immunoglobulin **Initial and long-term maintenance therapy** For prevention of organ rejection, regimens containing: • Mycophenolate mofetil • Mycophenolate sodium • Sirolimus • Immediate-release tacrolimus • Prolonged-release tacrolimus • Everolimus • Belatacept
Population(s)	Children and adolescents undergoing kidney transplantation

Comparators	**Induction therapy** • Regimens without monoclonal or polyclonal antibodies, for example regimens that include methylprednisolone • Interventions should also be compared with each other **Initial and long-term maintenance therapy** • A calcineurin inhibitor with or without an antiproliferative agent and/or corticosteroids • Interventions should also be compared with each other Where appropriate the interventions will be appraised as part of combination regimens.
Outcomes	The outcome measures to be considered include: • patient survival • graft survival • graft function • time to and incidence of acute rejection • severity 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.

Other considerations	Under an exceptional directive from the Department of Health, the Appraisal Committee may 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 evidence allows, subgroups based on factors that affect the risks associated with transplant and immunosuppressive treatment will be considered, including: • Different age groups • Level of immunological risk (including human leukocyte antigen compatibility and blood group compatibility) • People at high risk of rejection within the first 6 months • People who have had a re-transplant within 2 years • Previous acute rejection • People at high risk of complications from immunosuppression (including new-onset diabetes). If evidence allows, the appraisal will consider treatment regimens that aim to reduce or withdraw corticosteroids or calcineurin inhibitors. If evidence allows, adherence to treatment will be considered. The use of immunosuppressive drugs in patients receiving multiple organ transplants (for example, combined kidney and pancreas transplantation) is excluded from this appraisal.

Related NICE recommendations	Related Technology Appraisals: Technology Appraisal No. 85, Sep 2004, 'Immunosuppressive therapy for renal transplantation in adults'. Technology Appraisal No.99, Apr 2006, 'Immunosuppressive therapy for renal transplantation in children and adolescents'. Technology Appraisal No.165, Nov 2008, 'Machine perfusion systems and cold static storage of kidneys from deceased donors'. Static list. Technology Appraisal in Preparation: 'Immunosuppressive therapy for renal transplantation in adults (review of existing guidance 85)'. Date of publication TBC. Related Guidelines: Clinical Guideline No. 73, Sep 2008, 'Chronic kidney disease: early identification and management of chronic kidney disease in adults in primary and secondary care'. Currently being updated, earliest anticipated date of publication July 2014. Related Quality Standards: Quality Standard No. 5, Mar 2011, 'Chronic kidney disease'. Related NICE Pathways: NICE Pathways: Chronic kidney disease, Pathway created May 2011. http://pathways.nice.org.uk/pathways/chronic-kidney-disease
Related National Policy	NHS England Manual for Prescribed Specialised Services 2013/14. 127. Specialist renal services for children and young people: http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf