NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

Immunosuppressive therapy for kidney transplantation in adults (review of technology appraisal guidance 85)

Draft scope

Appraisal objective[1]

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

Background

Kidney transplantation is used to treat people with established renal failure, which is severe and irreversible impairment of kidney function. 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, 2699 kidney transplants were performed in adults in the UK, including 2246 performed in adults in England. At the end of 2012, approximately 27,600 adults in the UK were receiving immunosuppressive therapy after kidney transplantation, including 23,100 people in England.

Immunosuppressive therapy can be categorised as induction therapy, initial maintenance therapy, and long-term maintenance therapy. Induction therapy is 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 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

[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.

immunoglobulin) or monoclonal antibodies (for example, basiliximab). NICE technology appraisal 85 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 85 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 requiring minimisation or avoidance of a calcineurin inhibitor. 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 85 are outside the marketing authorisations for the respective drugs; the guidance recommends that clinicians should ensure patients 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 and in unlicensed drug combinations.

Since the publication of NICE technology appraisal guidance 85, new technologies have received marketing authorisations for induction therapy (rabbit anti-human thymocyte immunoglobulin) and maintenance therapy (mycophenolate sodium, belatacept, and a prolonged-release formulation of tacrolimus), and another new technology (everolimus) has been studied. Some of the treatments included in NICE technology appraisal 85 are now available generically, and the marketing authorisation for daclizumab has been withdrawn.

The technologies

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 adults. 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, and is administered intravenously.

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 have UK marketing authorisations for the prophylaxis of transplant rejection in adults undergoing kidney transplantation, and all are administered orally. Prograf can also be administered intravenously. 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 chimeric 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 is added to this belatacept-based regimen. Belatacept is administered intravenously.

Mycophenolic acid is an antiproliferative agent and is available as a prodrug formulation 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), and as an enteric-coated formulation mycophenolate sodium (Myfortic, Novartis Pharmaceuticals). Mycophenolate mofetil and mycophenolate sodium have UK marketing authorisations for use in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in people undergoing kidney transplantation. Both drugs can be administered orally; mycophenolate mofetil can also be administered intravenously.

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. 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. It has been studied in clinical trials in numerous regimens containing one or more additional immunosuppressant (including ciclosporin, tacrolimus, anti-thymocyte immunoglobulin, mycophenolate, corticosteroids and basiliximab), and compared with various alternative immunosuppressive regimens, in adults undergoing kidney transplantation. 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 or sodium) • Sirolimus • Tacrolimus (prolonged-release or immediate-release formulation) • Everolimus • Belatacept
Population(s)	Adults undergoing kidney transplantation
Comparators	**Induction therapy** • Induction regimens without monoclonal or polyclonal antibodies • Interventions should also be compared with each other **Initial and long-term maintenance therapy** • A calcineurin inhibitor and an anti-proliferative agent with or without 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 half-life • graft function

	• time to and incidence of acute rejection • severity of acute rejection • 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	Subject to exceptional direction 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, the following subgroups will be considered: • 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. If evidence allows, the use of treatments in corticosteroid reduction or withdrawal strategies 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 children and adolescents (review of existing guidance 99)'. 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. 15. Adult specialist renal services: http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf

Questions for consultation

Would a review of the recommendations in NICE technology appraisal guidance 85 provide value to the NHS?

- If so, should all of the current recommendations be reviewed, or is it only appropriate to review some of the recommendations (that is, undertake a partial review)?

- Is it anticipated that the evidence that has emerged since the publication of technology appraisal guidance 85 would lead to a change in the recommendations?

Are immunosuppressive treatments frequently used outside of their marketing authorisations in the NHS (for example, in unlicensed combinations or in people with high immunological risk)? Would an appraisal that only considers the use of immunosuppressive treatments *within* their marketing authorisations reflect current clinical practice and would it be of value to the NHS?

Should immunosuppressive treatment for episodes of acute rejection also be included in the appraisal? If so, which interventions and comparators should be considered for this?

Have the most appropriate interventions and comparators used in immunosuppressive therapy for kidney transplantation in adults been included in the scope? Are the comparators listed routinely used in clinical practice?

- Is azathioprine routinely used in clinical practice as part of immunosuppressive regimens?
- Should any other induction therapies be considered as comparators for induction therapy?
- Should the different tacrolimus formulations (immediate- and prolonged-release) be considered separately?
- Should the different brands of immediate-release tacrolimus be considered separately?
- Should the different mycophenolate formulations be considered separately?
- In clinical practice is an induction therapy always used? Or should the comparator of 'no induction therapy' be considered?

Are the subgroups suggested in 'other considerations' appropriate? Are there any other subgroups of people in whom the technologies are expected to be more clinically effective and cost effective or other groups that should be examined separately?

- Does immunosuppressive treatment differ depending on donor type (cadaveric or living donor)? Should this be considered as a subgroup?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatments are and will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Are there any groups of people who would choose not to take any of the technologies included in this appraisal (for example, those manufactured using human or animal blood products) because of religious or other beliefs?

Do you consider the technologies to be innovative in their potential to make a significant and substantial impact on health-related benefits and how they might improve the way that current need is met (is there a 'step-change' in the management of the condition)?

Do you consider that the use of any of the technologies can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

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