Complete Summary

GUIDELINE TITLE

Immunosuppressive therapy for renal transplantation in adults.

BIBLIOGRAPHIC SOURCE(S)

National Institute for Clinical Excellence (NICE). Immunosuppressive therapy for renal transplantation in adults. London (UK): National Institute for Clinical Excellence (NICE); 2004 Sep. 45 p. (Technology appraisal; no. 85).

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references drugs for which important revised regulatory information has been released.

- June 30, 2008, CellCept (mycophenolate mofetil) and Myfortic (mycophenolate acid): Novartis and Roche have agreed to include additional labeling revisions to the WARNINGS and ADVERSE REACTIONS sections of the Myfortic and CellCept prescribing information, based on post-marketing data regarding cases of Progressive Multifocal Leukoencephalopathy (PML) in patients treated with these drugs.
- October 29, 2007, CellCept (mycophenolate mofetil): Roche has agreed to include additional labeling revisions to the BOXED WARNING, WARNINGS/Pregnancy and Pregnancy Exposure Prevention, PRECAUTIONS/Information for Patients, and ADVERSE REACTIONS/Postmarketing Experience sections.

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SCOPE

DISEASE/CONDITION(S)

Acute organ rejection in renal transplantation

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Prevention
Treatment

CLINICAL SPECIALTY

Internal Medicine
Nephrology

INTENDED USERS

Advanced Practice Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To examine the clinical and cost-effectiveness of the newer immunosuppressive drugs for renal transplantation (i.e., basiliximab, daclizumab, tacrolimus, mycophenolate [mofetil and sodium], and sirolimus)

TARGET POPULATION

Adults who are undergoing renal transplantation

INTERVENTIONS AND PRACTICES CONSIDERED

Immunosuppressive therapy

1. Calcineurin-inhibitor-based regimen (basiliximab, daclizumab)
2. Tacrolimus as an alternative to ciclosporin
3. Mycophenolate mofetil
4. Sirolimus

MAJOR OUTCOMES CONSIDERED

- Clinical effectiveness:
    - Patient survival
    - Graft survival

    - Acute rejection episodes
    - Quality of life
    - Graft functioning (e.g., serum creatinine, glomerular filtration rate)
    - Adverse events and side effects (e.g., cardiovascular complications, malignancies, diabetes, infections, and nephrotoxicity)
    - Growth (in children)
    - Patient-related quality of life
- Cost-effectiveness

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the West Midlands Health Technology Assessment Group (see the "Companion Documents" field).

Search Strategy

A search for reviews and primary studies was undertaken using a variety of sources:

- Bibliographic databases: Cochrane Library Issue 3 2002, MEDLINE (Ovid) 1966-July 2002, EMBASE (Ovid) 1980-July 2002. The National Research Register Issue 2 2002 was searched to identify ongoing and unpublished research. Details of specific search strategies are given in Appendix 1 of the assessment report.
- Citation lists of relevant papers (including reviews identified at the scoping stage)
- Internet searches using Alta Vista, Dogpile, OMNI. Website searching on United Kingdom (UK), European, and USA registries. UK Transplant, British Transplant Society, Renal National Service Framework, National Kidney Research Fund, British Renal Society
- Hand searches of the most recent issues of the following journals: *Transplantation, Nephrology Dialysis and Transplantation, Transplantation Proceedings, Clinical Transplantation, Kidney International, American Journal of Kidney Disease, Journal of American Society of Nephrology, Paedatric Nephrology, Paediatric Transplantation* [up to October 2002]
- Contact with the Cochrane Collaboration Renal Disease Group based in Sydney, Australia

- Citations in the industry submissions to National Institute for Clinical Excellence
- Contact was made with clinical experts and with authors of papers where there were any queries.
- Current Clinical Trials register (includes number of individual trials registers, such as the UK National Research Register and MRC Clinical Trials Register), was also searched for information on registered trials that are currently under way.

No language or age restrictions were applied to the searches. All references were exported to Reference Manager version 9.5.

Inclusion Criteria and Exclusion Criteria

Two reviewers independently scanned all the titles and abstracts and identified the potentially relevant articles to be retrieved. Where there was uncertainty, full text copies of papers were obtained. Studies were considered eligible if they met the following criteria (see Appendix in the assessment report for inclusion/exclusion criteria form).

Study Design

Randomised controlled trials (RCTs) that include comparison of included drugs (see below) and any or all of the listed outcomes. RCTs were excluded where the trial had not finished recruiting, or if trial baseline characteristics or follow up results for only a small proportion of the trial participants were reported.

Participants

Adults or children (<18 years) who had received a kidney transplant from either live donor, cadaveric, or asystolic donor. Trials including only patients with concomitant other organ transplants were excluded.

Outcomes

Refer to "Major Outcomes Considered Field" in this summary.

Interventions

Drug comparisons were included according to three categories of immunosuppression: induction therapy, initial/maintenance treatment, or treatment of acute rejection ("rescue therapy"). The immunosuppressive drugs assessed in each of these categories are summarised in Table 5 in the assessment report.

Any comparisons that were identified but not currently licensed in UK were included for comprehensiveness.

Reviewer's inclusions and exclusion decisions were checked for agreement and any differences were discussed and resolved with a third reviewer. Given the large volume of material, a good level of agreement was obtained between reviewers.

Data Extraction and Quality

Data extraction was performed by three reviewers. One reviewer independently extracted the effectiveness and quality assessment data from all included studies. The data was then checked by a second reviewer.

Three reviewers independently evaluated the included RCTs for methodological quality using a modified version of the Jadad scale (Appendix 3 in the assessment report).

NUMBER OF SOURCE DOCUMENTS

95 papers were included in the report.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the West Midlands Health Technology Assessment Group (see the "Companion Documents" field).

Data Synthesis and Analysis

A detailed tabular summary of the characteristics (i.e., patients, intervention, comparator, and outcomes) and methodological quality of all included studies was undertaken.

Any information specified by companies as "commercial in confidence" was underlined in one version of the draft report and omitted from the other.

Where appropriate, meta-analysis was undertaken using a fixed effects model except in those situations where there was evidence of statistical heterogeneity, and a random effects model was used instead.

Dependent upon the distribution of an outcome, data is expressed as either means plus 95% confidence interval (95% CI), or as medians plus a range. All analyses were undertaken using StataV.6.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Clinical Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients, and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE website. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

See Section 4.2 of the original guideline document for a detailed discussion of the cost-effectiveness analysis.

METHOD OF GUIDELINE VALIDATION

External Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Consultee organizations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- 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.

- 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.
- 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.
- 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.
- 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.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is not specifically stated.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of immunosuppressive therapy for renal transplantation in adults

POTENTIAL HARMS

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

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

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- This guidance represents the view of the Institute, which was arrived at after careful consideration of the available evidence. Health professionals are expected to take it fully into account when exercising their clinical judgement. This guidance does not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- 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.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Implementation and Audit

- 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 of the original guideline document (and the "Major Recommendations" field).
- Local guidelines, protocols, or care pathways that refer to the care of adults undergoing renal transplantation should incorporate the guidance.
- 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 National Health Service (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.

- To measure compliance locally with the guidance, the following criteria could be used. Further details on suggestions for audit are presented in Appendix C of the original guideline document.
    - 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.
    - Tacrolimus is considered as 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.
    - 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.
    - 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.
    - 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.
- Local clinical audits could also include measurement of time timing and dosages of drug therapy used for people undergoing renal transplantation.

IMPLEMENTATION TOOLS

Audit Criteria/Indicators
Foreign Language Translations
Patient Resources
Quick Reference Guides/Physician Guides

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

National Institute for Clinical Excellence (NICE). Immunosuppressive therapy for renal transplantation in adults. London (UK): National Institute for Clinical Excellence (NICE); 2004 Sep. 45 p. (Technology appraisal; no. 85).

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2004 Aug

GUIDELINE DEVELOPER(S)

National Institute for Health and Clinical Excellence (NICE) - National Government Agency [Non-U.S.]

SOURCE(S) OF FUNDING

National Institute for Health and Clinical Excellence (NICE)

GUIDELINE COMMITTEE

Appraisal Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

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.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455. 11 Strand, London, WC2N 5HR.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Immunosuppressive therapy for renal transplantation in adults Quick reference guide. London (UK): National Institute for Health and Clinical Excellence (NICE); 2004 Sep. 2 p. (Technology appraisal 85). Electronic copies: Available in Portable Document Format (PDF) format from the National Institute for Health and Clinical Excellence (NICE) Web site.
- Clinical and cost-effectiveness of immunosuppressive regimens in renal transplantation. Assessment report. Birmingham (UK): West Midlands Health Technology Assessment Group; 2002 Dec. 258 p. (Technology appraisal 85).

Electronic copies: Available in PDF from the National Institute for Health and Clinical Excellence (NICE) Web site.

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455. 11 Strand, London, WC2N 5HR.

Additionally, Audit Criteria can be found in Appendix C of the original guideline document.

PATIENT RESOURCES

The following is available:

- Drugs to prevent the rejection of kidney transplants in adults: understanding NICE guidance - information for people undergoing kidney transplants, their families and carers, and the public. London: National Institute for Health and Clinical Excellence. 2004 Sep. 10 p. Available in English and Welsh in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This NGC summary was completed by ECRI on November 10, 2005. This summary was updated by ECRI Institute on November 6, 2007, following the U.S. Food and Drug Administration advisory on CellCept (mycophenolate mofetil). This summary was updated by ECRI Institute on July 8, 2008, following the updated U.S. Food and Drug Administration (FDA) advisory on CellCept (mycophenolate mofetil) and Myfortic (mycophenolate acid).

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Date Modified: 10/6/2008