Immunosuppressive therapy for kidney transplantation in:
   Adults (ID456; review of TA85)
   Children and young people (ID346; review of TA99)

Multiple Technology Appraisals

3rd Appraisal Committee meeting
29 March 2017
Background

• 2 MTAs on immunosuppressive therapy (induction and maintenance) for kidney transplant
  – Adults (review of TA85, 2004)
  – Children and young people (review of TA99, 2009)

• Appraisal timeline
  – 2 committee meetings
  – FADs issued to consultees December 2015
  – Appeal hearing March 2016
    • Several appeal points upheld
  – 3rd appraisal committee meeting
    • To consider the upheld appeal points
Scope for review of TA85 and TA99

Appraisal objective - To appraise the clinical and cost-effectiveness of immunosuppressive regimens for kidney transplantation

- The remit from DH and the Welsh Assembly Government was to advise on the clinical and cost-effectiveness of immunosuppressive regimes for renal transplantation, immediately after transplantation and as far as the evidence allows at subsequent stages, including those using the newer agents

Population - People undergoing kidney transplantation

Other considerations - If evidence allows, subgroups will be based on factors including:

- People who have had a re-transplant within 2 years
- Previous acute rejection
- People at high risk of complications from immunosuppression
FAD recommendations

For both adults and children and young people:

- Basiliximab, immediate-release tacrolimus and mycophenolate mofetil were **recommended** as options
- Rabbit anti-human thymocyte immunoglobulin, prolonged-release tacrolimus, mycophenolate sodium, sirolimus, everolimus and belatacept were **not recommended**
  - Committee was **unable to make recommendations** on these technologies for people who have:
    - nephrotoxicity associated with calcineurin inhibitors, or
    - thrombotic microangiopathy
Immunosuppressive therapy for kidney transplantation in adults (review of TA85)

Recap of evidence and discussion of appeal points
Recap: Clinical evidence
Assessment Group’s systematic review and network meta-analysis

- 86 RCTs identified
  - 11 induction, 73 maintenance, 2 induction & maintenance trials
    - 63 new trials since TA85
  - Substantial heterogeneity across the trials; only 11 trials matched current NHS practice
  - Insufficient evidence for subpopulation analysis
  - Outcomes included mortality, graft loss and rejection, graft function, adverse events; limited data on quality of life

- AG presented results from head-to-head comparisons and network meta-analyses, for both induction and maintenance regimens
Recap: Clinical evidence
Clinical effectiveness results

Induction
• In both head-to-head comparisons and the NMA, basiliximab and rATG associated with reduction in acute rejection compared with no induction
• No significant differences between basiliximab and rATG in any outcomes

Maintenance
• **Tacrolimus** - Improved acute rejection vs ciclosporin and sirolimus, improved graft function vs ciclosporin
  – No consistent differences between immediate- and prolonged-release
• **Belatacept** - Improved graft function and graft loss vs ciclosporin, but more acute rejection
• **Mycophenolate** - Fewer acute rejections vs azathioprine; improved graft function vs tacrolimus
  – No discernible differences between mycophenolate mofetil and mycophenolate sodium
• **Sirolimus** - Longer time to acute rejection than mycophenolate mofetil
• **Everolimus** - More acute rejection than ciclosporin
• **In the NMA**, none of the regimens performed consistently well on all outcomes – limited conclusions can be drawn
Recap: Economic evidence

Assessment Group’s economic model

- Discrete-time state transition model; 50 year time horizon
- Long term graft loss modelled using surrogate relationship between graft loss and acute rejection, estimated glomerular filtration rate (graft function) and new onset diabetes after transplantation
Recap: Economic evidence
Induction and maintenance therapies

Induction
- Basiliximab dominated both rATG and no induction
- rATG was more costly and more effective than no induction, with ICERs of £63,100 to £333,000 per QALY gained

Maintenance
- Immediate-release tacrolimus dominated prolonged-release tacrolimus, sirolimus and ciclosporin and was less costly and less effective than belatacept and ciclosporin, with ICERs of £131,000 to £389,000 per QALY lost
- Mycophenolate mofetil dominated sirolimus and azathioprine, and was less costly and less effective than mycophenolate sodium (£144,000 per QALY lost) and everolimus (£1,530,000 per QALY lost)
- All the other interventions were dominated or were more effective and more costly than their respective comparators, with ICERs greater than £50,000 per QALY gained
Submitted appeals: Common themes (1)

• The ‘not recommended’ decision does not take into account the:
  – reduced access to transplants or increase in failed transplants resulting from the inability to prescribe alternative therapies
  – quality of life impact resulting from lost transplants for people who can’t tolerate the recommended treatments, who are unable to access alternative agents
  – increased mortality of people unable to access transplantation because alternative treatments are not available
  – the cost of graft failure, including dialysis, as a consequence of inadequate immunosuppression
Submitted appeals: Common themes (2)

• The recommendations also:
  – reduces effective options for patients who have poor adherence or marked variability of drug levels with immediate-release tacrolimus by not recommending prolonged-release tacrolimus
  – reduces effective options for future patients who are intolerant of, or unsuitable for, the interventions recommended in the FAD
  – is contrary to current best clinical practice
Appeal panel conclusions (1)

- The panel considered the scope of the appraisal was pivotal to the appeal points raised.
- It understood that the recommendations in the FAD:
  - covered treatment of ‘de novo’ patients
  - did not cover patients for whom the recommended cost-effective treatment was not clinically appropriate.
- However it concluded that ‘downstream’ treatments were not excluded in the scope.
- It also noted the inconsistency in the FAD which describes 2 circumstances relating to patients who are unable to continue the recommended initial treatment, upon which the committee was unable to make a decision.
The panel concluded that the FAD did not make it clear whether the recommendations covered:

- **Subsequent (‘second-line’) treatments** in patients who were unable to take the initial treatment (other than because of nephrotoxicity or thrombotic microangiopathy)
- Patients receiving a **subsequent kidney transplant** after the failure of earlier transplant
  - Including patients for whom it had already been established that the recommended treatment was not clinically appropriate

If committee was unable to make recommendations on uses that fall within the scope, this should be explained clearly and consultees given an opportunity to comment:

- The population and treatment scenarios covered by the FAD should be clearly identified

All other appeal points were dismissed
Update following appeal:
Overview of issues for consideration

• Based on panel’s conclusions, the key issues centre on whether the guidance covers only initial treatment for the first transplant, or whether it also includes:
  – subsequent (second-line) treatments in patients who are unable to take the initial treatment
  – patients receiving a second or subsequent kidney transplant

• Committee should consider whether it can make recommendations for these situations:
  – Are they included within the scope for the appraisal?
  – If so, is there sufficient evidence on which to base a recommendation?
Update following appeal: Second and subsequent transplant

Scope for appraisal

- **Remit:** “… both immediately after transplantation and as far as the evidence allows at subsequent stages, including those using the newer agents”
- **Population:** “Adults undergoing kidney transplantation”
- **Subgroups:** “Including: …People who have had a re-transplant within 2 years”
- Second and subsequent transplants are not precluded by the marketing authorisations
- **NICE advice to committee:** We interpret that people having a 2nd/subsequent transplant are included within the scope

Does committee consider that second and subsequent transplants are included in the scope?
**Update following appeal: Second and subsequent transplant**

**Evidence available**

- AG confirmed that the clinical and economic evidence already discussed did include people having second or subsequent transplants
  - The AG summarised which studies include 2\textsuperscript{nd}/subsequent transplants; \sim30\% included 2\textsuperscript{nd}/subsequent transplants, <15\% of population in all except 2 cases
  - In its initial evidence review the AG stated there was insufficient evidence for subgroup analyses
- The economic model gives the same results whether it considers the 1\textsuperscript{st} or 2\textsuperscript{nd} transplant
- Conclusions from the model may change if 1 or more interventions is removed (if previously found to be clinically inappropriate)
  - Removing interventions from the current model does not lead to any additional interventions becoming cost effective at £20,000–£30,000 per QALY gained
  - This approach assumes clinical outcomes are identical for people who have been found to be unsuitable for the removed drug – highly uncertain
- To fully address this, it would be necessary to establish when interventions become inappropriate (e.g. treatment failure, intolerance, non-adherence), and identify relevant evidence for each treatment permutation in each situation

*Has committee seen sufficient evidence to make recommendations for second and subsequent transplants?*
Update following appeal: Subsequent treatments during the life of a graft

Scope for appraisal

- **Remit:** “To advise on the clinical and cost-effectiveness of immunosuppressive regimes … both immediately after transplantation and as far as the evidence allows at subsequent stages, including those using the newer agents”
- **Population:** “Adults undergoing kidney transplantation”
- Subsequent treatments during the life of the graft are not precluded by the marketing authorisations

- **NICE advice to committee:**
  - Acknowledge that the scope is potentially unclear and ambiguous – no explicit statement
  - The remit implies that subsequent treatments are included in the scope
  - TA85 included subsequent treatments

*Does committee consider that subsequent treatments during the life of a graft are included in the scope?*
Update following appeal: Subsequent treatments during the life of a graft

Evidence available

• Acknowledge that the systematic review did not include the use of subsequent maintenance treatments during the life of the graft
  – The systematic review included only studies randomised at the time of transplant
  – Therefore none of the studies included in the systematic review investigated the effect of switching regimens while maintaining a functioning graft
  – Partial review of excluded studies found some published evidence, but a systematic search has not been completed

• Comments from stakeholders during the appraisal acknowledged:
  – The lack of robust published clinical trial data
  – The wealth of clinical experience using these treatments which informs national consensus and established practice

• To fully address this, it would be necessary to establish when patients need new treatment during the life of a graft (e.g. treatment failure, intolerance, non-adherence), and identify relevant evidence for each treatment permutation in each situation

Has committee seen sufficient evidence to make recommendations for subsequent treatments during the life of a graft?
Immunosuppressive therapy for kidney transplantation in children and young people (review of TA99)

Recap of evidence and discussion of appeal points
Recap: Clinical evidence
Systematic review and network meta-analysis

- 3 paediatric RCTs (2 induction, 1 maintenance trials)
  - All 3 trials are likely to be generalisable to the NHS
  - 1 RCT had not been included in TA99
- 10 paediatric non-randomised studies (1 induction, 1 induction & maintenance, 8 maintenance studies)
  - At least 3 of the studies are unlikely to be generalisable to the NHS
  - 6 studies had not been included in TA99
- No paediatric studies compared rATG, prolonged-release tacrolimus, mycophenolate sodium, everolimus or belatacept with the comparators; 1 small study assessed sirolimus
- Insufficient data for subgroups analysis
- Some of the analyses used effectiveness estimates from the adult network meta-analysis used in the review of TA85
Recap: Clinical evidence
Clinical effectiveness of induction therapy

Two paediatric RCTs
• No significant differences between basiliximab and placebo or no induction for mortality, graft loss, acute rejection or graft function
• Basiliximab associated with increased infection, toxic nephropathy and abdominal pain

One non-randomised paediatric study
• Less acute rejection with basiliximab than no induction

Network meta-analysis of adult RCTs
• No evidence that basiliximab and rATG are more effective than placebo for graft loss, mortality and graft function
• For acute rejection, both basiliximab and rATG more effective than placebo or no induction
• No evidence that either treatment was more effective than the other
Recap: Clinical evidence
Clinical effectiveness of maintenance therapy

One paediatric RCT
- Immediate-release tacrolimus improved graft function and reduced the incidence of acute rejection compared with ciclosporin

One paediatric non-randomised study
- Lower rates of graft loss with mycophenolate mofetil than with azathioprine
- Three further non-RCTs reported no differences

Network meta-analysis of adult RCTs
- No regimen was consistently better than any other, although ciclosporin and azathioprine were associated with poorer graft function and higher risk of acute rejection

Adult RCTs
- Mycophenolate mofetil and mycophenolate sodium, and also immediate- and prolonged-release tacrolimus, have similar effectiveness
Recap: Economic evidence
Assessment Group’s economic model

- 2 types of analysis, both with 50-year time horizon
  1. Effectiveness estimates from paediatric RCTs
     - Decision tree to model outcomes over the trial duration, extrapolated using adult semi-Markov model adapted for children and young people but using adult quality of life data
     - Surrogate relationships to predict graft loss: hazard ratios for graft function from paediatric data, and for acute rejection and new-onset diabetes from adult data
     - Separate analyses for each trial
     - Assumes no re-transplantation during trial
  2. Effectiveness estimates from adult RCTs
     - Semi-Markov model only (no decision tree)
     - States defined by first or subsequent transplant
- Compared treatment regimens rather than individual drugs
Recap: Economic evidence

Cost effectiveness results – induction

Paediatric RCTs
- Contradictory results - basiliximab dominant using 1 study and dominated using the other

Adult RCTs
- No induction dominated rATG
- Basiliximab dominated no induction

Network meta analysis of adult RCTs
- No induction dominated rATG
- Basiliximab dominated no induction
- Probabilistic sensitivity analysis: at £20,000 per QALY gained, basiliximab predicted to be cost effective in 92% of simulations
Recap: Economic evidence
Cost effectiveness results – maintenance

Paediatric RCTs
• **Immediate-release tacrolimus** dominated ciclosporin

Network meta-analysis of adult RCTs
• **Immediate-release tacrolimus** dominated ciclosporin, prolonged-release tacrolimus and sirolimus (cost savings >£16,000)
• **Prolonged-release tacrolimus** was dominated by immediate-release tacrolimus (inc. costs £16,446; inc. QALYs −0.054)
• **Belatacept** ICER £533,449 per QALY gained compared with immediate-release tacrolimus
• **Mycophenolate mofetil** dominated azathioprine in regimens containing ciclosporin (inc. costs between −£7017 and −£10,188; inc. QALYs 0.10 to 0.12). Mycophenolate mofetil was dominated by azathioprine in regimens containing tacrolimus (inc. costs £4730 to £6446; inc. QALYs −0.06 to −0.07)
• **Mycophenolate sodium** ICER £51,770 per QALY gained compared with mycophenolate mofetil
• **Sirolimus** dominated by ciclosporin, immediate-release tacrolimus, azathioprine and mycophenolate mofetil
• **Everolimus** ICER £632,246 per QALY gained compared with mycophenolate mofetil
Submitted appeals: Common themes (1)

• Very similar to the appeals against the adult FAD
• The ‘not recommended’ decision does not take into account the:
  – reduced access to transplants or increase in failed transplants as a result of the inability to prescribe alternative therapies
  – quality of life impact resulting from lost transplants for people who can’t tolerate the recommended treatments, who are unable to access alternative agents
  – increased mortality of people unable to access transplantation because alternative treatments are not available
  – the cost of graft failure, including dialysis, as a consequence of inadequate immunosuppression
Submitted appeals: Common themes (2)

• The recommendations also:
  – reduces effective options for patients who have poor adherence or marked variability of drug levels with immediate-release tacrolimus by not recommending prolonged-release tacrolimus
  – reduces effective options for future patients who are intolerant of, or unsuitable for, the interventions recommended in the FAD
  – is contrary to current best clinical practice
The panel considered the scope of the appraisal was pivotal to the appeal points raised.

It understood that the recommendations in the FAD:
- covered treatment of ‘de novo’ patients
- did not cover patients for whom the recommended cost-effective treatment was not clinically appropriate

However it concluded that ‘downstream’ treatments were not excluded in the scope.

It also noted the inconsistency in the FAD which describes 2 circumstances relating to patients who are unable to continue the recommended initial treatment, upon which the committee was unable to make a decision.
Appeal panel conclusions (2)

• The panel concluded that the FAD did not make it clear whether the recommendations covered:
  – Subsequent (‘second-line’) treatments in patients who were unable to take the initial treatment (other than because of nephrotoxicity or thrombotic microangiopathy)
  – Patients receiving a subsequent kidney transplant after the failure of earlier transplant
    • Including patients for whom it had already been established that the recommended treatment was not clinically appropriate
• If committee was unable to make recommendations on uses that fall within the scope, this should be explained clearly and consultees given an opportunity to comment
  – The population and treatment scenarios covered by the FAD should be clearly identified
• All other appeal points were dismissed
Update following appeal: Overview of issues for consideration

- Appeal panel’s conclusions focus on the same key issues as the adults appraisal.
  - That is, whether the guidance covers only initial treatment for the first transplant, or whether it also includes:
    - subsequent (second-line) treatments in patients who are unable to take the initial treatment
    - patients receiving a second or subsequent kidney transplant

- Committee should consider whether it can make recommendations for these situations:
  - Are they included within the scope for the appraisal?
  - If so, is there sufficient evidence on which to base a recommendation?
Update following appeal:
Second and subsequent transplant

Scope for appraisal

• Follows the same pattern as for the adults appraisal
• NICE advice to committee: We interpret that people having a 2\textsuperscript{nd}/subsequent transplant are included within the scope

Does committee consider that second and subsequent transplants are included in the scope for children and adolescents?
Update following appeal: Second and subsequent transplant

Evidence available

• Some of the studies included re-transplantation
  – At least 1 of the RCTs and 1 of the non-randomised studies included first and subsequent transplants
• Comments from stakeholders during the appraisal acknowledged that:
  – The small numbers of children undergoing transplantation makes subgroup analysis (e.g. re-transplant) very difficult
• To fully address this, it would be necessary to establish when interventions become inappropriate (e.g. treatment failure, intolerance, non-adherence), and identify relevant evidence for each treatment permutation in each situation

Has committee seen sufficient evidence to make recommendations for second and subsequent transplants?
Update following appeal: Subsequent treatments during the life of a graft

Scope for appraisal

• Follows the same pattern as for the adults appraisal
• NICE advice to committee:
  – Acknowledge that the scope is potentially unclear and ambiguous – no explicit statement
  – The remit implies that subsequent treatments are included in the scope
  – TA99 included subsequent treatments

Does committee consider that subsequent treatments during the life of a graft are included in the scope for children and young people?
Update following appeal: Subsequent treatments during the life of a graft

Evidence available

• None of the studies included in the systematic review investigated the effect of switching regimens while maintaining a functioning graft
  – The systematic review included only studies randomised at the time of transplant
• Comments from stakeholders during the appraisal acknowledged:
  – The lack of good quality evidence, particularly in children undergoing kidney transplantation, but recognised there is some evidence of second-line use, including RCTs
  – Immunosuppression therapy in children has often been informed by adult studies
• To fully address this, it would be necessary to establish when patients need new treatment during the life of a graft (e.g. treatment failure, intolerance, non-adherence), and identify relevant evidence for each treatment permutation in each situation

Has committee seen sufficient evidence to make recommendations for subsequent treatments during the life of a graft?
Key issues for consideration

• Are second and subsequent transplants included in the scope?
• Has the committee seen enough evidence to make a recommendation about treatments for subsequent grafts?
  – For adults, and for children and young people?
• Are subsequent treatments during the life of the graft included in the scope?
• Has the committee seen enough evidence to make a recommendation about subsequent treatments during the life of a graft?
  – For adults, and for children and young people?
• Is there any other evidence that the committee should consider?
  – Value to the NHS of conducting further work within the context of a technology appraisal for these issues? Additional literature searches to identify any clinical evidence on which it may be able to make recommendations on second/subsequent treatments and treatments for subsequent grafts?
• Are there any other issues that the committee needs to discuss as a result of the appeal?