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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

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

- 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 2nd/subsequent transplants; ~30% included 2nd/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 1st or 2nd 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

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

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 2nd/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?