NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Immunosuppressive therapy for kidney transplantation in children and adolescents (review of technology appraisal guidance 99) [ID346]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Dr David V Milford

Name of your organisation: [redacted]

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology

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What is the expected place of the technology in current practice?

Renal transplantation is an essential treatment option for children and adolescents with advanced or progressive chronic kidney disease (CKD) and is undertaken in tertiary specialist paediatric nephrology units in collaboration with adult renal transplant services. Effective immunosuppression allows renal transplantation to be successful; however, the optimal immunosuppressive regime for children is yet to be determined. The reason for this uncertainty is a lack of clinical trials in children coupled with the widespread adoption of therapies for which there is no paediatric data but for which there is some adult data, leading to extrapolation of practice. The widespread popularity of mycophenolate mofetil is a good example. Nonetheless, in the UK there is a remarkable degree of conformity of immunosuppression regime across the paediatric renal units, with a majority using a tacrolimus, basiliximab, MMF and short course prednisolone regime as a result of a trial of the regime published in 2010. However, other regimes are used and a drug trial using everolimus is presently recruiting patients.

Several immunosuppressive therapies have been used for many years, but newer drugs are available and more are in development. Children rarely have access to new therapies because companies frequently do not undertake clinical trials that include children, presumably because the cost:benefit ratio is perceived to be unfavourable as the paediatric market is small. Furthermore, newer therapies tend to be more expensive, so the use of unlicensed drugs leads to issues of funding. There is consequently a delay in when children benefit from new drug regimes. This review

of the guidance provided in TA99 is essential to ensure recent developments in the use of drugs after renal transplantation in children is recognised and reflected in new guidance. It also allows the opportunity to emphasise the importance of undertaking more clinical trials of immunosuppression in children who have undergone renal transplantation.

The advantages and disadvantages of the technology

The current understanding is children who have successfully undergone renal transplantation require immunosuppression for the life time of the transplanted organ. However, as discussed in the scoping document, the amount of immunosuppression changes with time. In general, the highest amount of immunosuppression is used at the time of transplantation and for a short time afterwards – this is termed induction immunosuppression. This strategy is adopted as it is known the time of the greatest immunological stimulation is soon after the organ is implanted and the immune system exposed to a large amount of foreign antigen. Subsequent immunosuppression (maintenance immunosuppression) is gradually reduced to allow the immune system to become increasingly 'tolerant' of the transplanted organ. A combination of therapies are used to modulate the response of different arms of the immune system and, by acting in concert, to allow lower doses of individual drugs to be used. Correct immunosuppression is advantageous as it optimises transplant function and longevity.

Experience shows that with conventional immunosuppression it is rare for complete tolerance to develop such that immunosuppression can be discontinued. Consequently, long term therapy is required, bringing with it concerns about side

effects. The side effects of immunosuppression can be considered as: the effect of too little immunosuppression; the effect of too much immunosuppression; drug specific side effects.

Too little immunosuppression: inadequate immunosuppression can occur for several reasons – in adolescents, the commonest is non-concordance with the prescribed regime. This is a complex and difficult area, but drug companies can help by producing therapies that need to be taken infrequently (preferably once daily) and that do not produce adverse reactions such as nausea, vomiting or diarrhoea. Measurement of therapeutic drug levels helps to optimise immunosuppression prescribing and can help identify non-concordance. Unfortunately most immunosuppressive drugs have no routine measurement of therapeutic drug level, consequently dosing is based on weight or surface area which does not allow variation in drug metabolism to be accounted for. Pharmacogenomics is an emerging area of research that may prove fruitful in developing immunosuppressive regimes that allow more individualised dosing. The consequence of too little immunosuppression is an increased risk of rejection; recurrent episodes of rejection have a detrimental effect on long term graft outcome.

Too much immunosuppression: The main consequence of over immunosuppression is increasing frequency and severity of infections, either bacterial, viral or fungal. Bacterial infections include relatively common illnesses such as urinary tract infection, but can include serious infections such as pneumocystis leading to life threatening pneumonia. Viral infections of note include: cytomegalovirus (especially if the recipient was not immune to CMV before the transplant and receives a kidney from a donor who is positive for the virus) causing gut, lung, liver or haematological

abnormalities; Epstein Barr virus, which can lead to post transplant lymphoproliferative disease, a serious malignancy driven by EBV; polyoma virus infection in the transplanted kidney leading to progressive graft damage.

Drug specific side effects are usually dose dependant, for example: steroids have many side effects, the most significant being: an increase in weight mainly through appetite stimulation; a reduction in height velocity and blunting of the pubertal growth spurt; a stimulation of acne and hirsuitism; mood swings and aggressive outbursts; development of new onset diabetes after transplantation (NODAT). Calcineurin inhibiting (CNI) drugs such as ciclosporin and tacrolimus can cause electrolyte disturbances, acute kidney injury if drug levels are too high, NODAT and progressive damage to the transplant through exposure to high drug levels (CNI nephrotoxicity).

Drug side effects are particularly important in children because of the impact on growth and psychosocial development, consequently drug trials in children have moved away from only demonstrating which drug regime has the lowest rejection rate to trials focussed on improved outcome through minimising steroid side effects and reducing CNI toxicity resulting in longer graft survival.

Equality and Diversity

I do not believe this appraisal will lead to the exclusion of any patient group from accessing the technology.

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Any additional sources of evidence

Data regarding the use of immunosuppressive regimes across UK paediatric renal units is not routinely reported. However, this information is gathered by both NHS Blood and Transplant and by the UK Renal Registry. Both organisations will provide information if requested.

Implementation issues

The technologies listed in the scoping document (with the exception of belatacept) are familiar to clinicians working in paediatric renal units so additional training will not be required to implement this guidance. Therapeutic drug monitoring is now widely available for tacrolimus and sirolimus, but measurement of mycophenolic acid level is still limited to a few laboratories, although the lack of widespread availability does not presently impact on the use of mycophenolate preparations.