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)

Submisssion on behalf of the British Transplantation Society (BTS)

Prepared by [redacted], October 2014

Introduction

We very much welcome the above MTA as the current practice of using immunosuppression therapy in children and young people has changed since the publication of TA99.

Many of the issues affecting adult renal transplant recipients also apply to children. These are outlined in the BTS submission responding to the final scope for the MTA Immunosuppressive therapy for kidney transplantation in adults.

The many differences between children and adults are noted in the final scope for this MTA. In addition it is important to note that there are differences in the management of children and adolescents both on haemodialysis and post transplantation compared to adults. Children have higher levels of dependency whilst being nursed in hospital and this needs to be taken into account during cost-benefit analyses. This is particularly important when considering the management of pre-school children, who e.g. need one to one nursing on haemodialysis.

A sick child, especially those on dialysis, places an enormous strain on a family, and the benefits of transplantation in this situation extent to the parents and siblings as well as the child. Parents may be able to return to work and the children themselves are able to spend more time in education and improve their chances of employment in later life.

Evidence

It is difficult to perform drug trials in children and as a result there are fewer randomised controlled trials (RCT) available in children compared with adults. As a result paediatric practice is influenced by non-RCT data, adult data and registry data. The RCT studies that are available are often based on a short follow-up period with transplant survival at one year as the commonest hard endpoint. While these short-term data may predict long-term outcomes, patient and graft survival with a horizon of 10-30 years is essential. Clinical trials rarely provide these data but registries do, although there are some limitations of the quality of immunosuppression prescribing data.UK specific paediatric follow-up data are available through NHS Blood and Transplant and North American Registry data are available through NAPRTCS.

Preparations of Medications

The age range of paediatric renal transplant patients varies from 1 to 18 years. The pharmacokinetics of many drugs changes significantly during childhood, furthermore young children or older children unable to swallow tablets will require different preparations from

older patients. The use of Modigraf allows the use of a more consistent preparation to be available to young children in contrast to 'hospital specials' which may vary.

Current practice in the UK

A recent 20 year review of paediatric renal transplantation using NHS B&T data has been submitted for publication (1). Figure 6 from this document is shown below and illustrates that during 2007-2011 the majority of recipients received tacrolimus (~90%) as recommended in MTA 99. Mycophenolate mofetil is used in between 40-50% of patients in contrast to the recommendations in MTA 99. The use of steroid free regimens is now more commonplace. Other changes in practice are the use of HLA and ABO incompatible transplants.

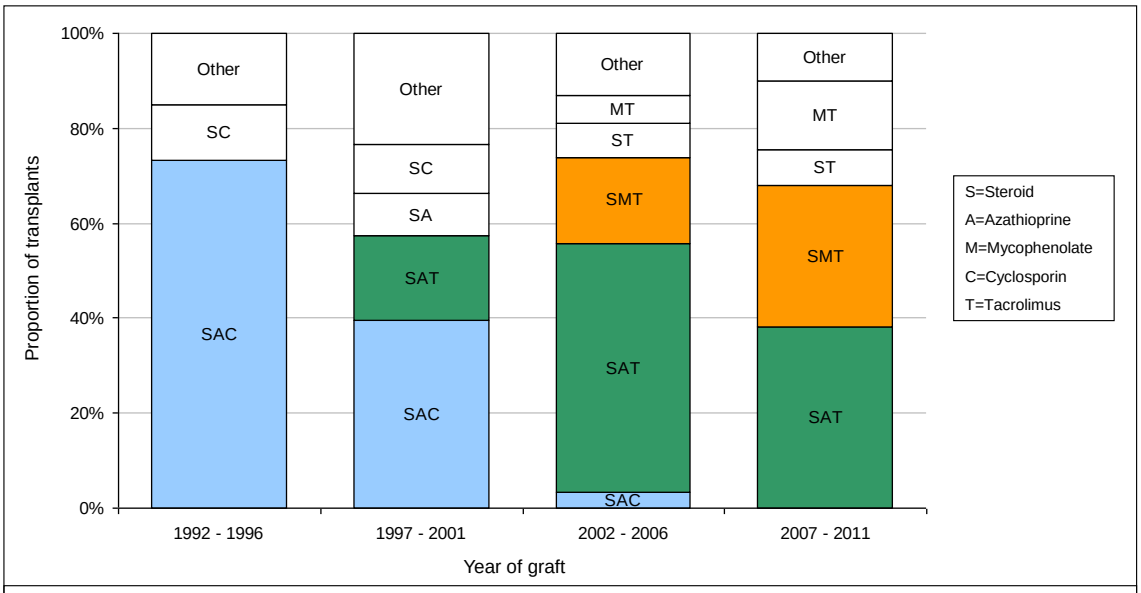

Figure 6. Reported immunosuppression after deceased paediatric kidney only transplant (3mth), 1992 - 2011

Medications to be assessed

Alemtuzumab is mentioned in the adult document and is used in children in some North American centres, but will not be included here. Similarly Modigraf is used in paediatrics in the UK and is not included in the MTA.

Generic preparations

The calcineurin inhibitors have a narrow therapeutic index. It is particularly important that generic calcineurin inhibitors meet the more stringent bioequivalence criteria (90-111%) and, ideally have pharmacokinetic data in renal transplant recipients. The European Society for Organ Transplantation has published guidelines on the appropriate use of generic immunosuppressive drugs (2).

Adherence

Evidence that non-adherence is a major factor in long-term renal allograft failure due to chronic antibody-mediated rejection is accumulating (3). It is very important that adherence is included in this MTA.

Marketing Authorisation
Many medications in children are not licensed for such use. Whilst patients and families need to be aware of this, perhaps it is as important to lobby for the collection of more data to extend the marketing authorisation of more drugs to include children.

References

1. Twenty years of paediatric renal transplantation in the united kingdom: a review of changing practice and improved outcomes. Lisa Bradbury, Heather Maxwell, Stephen D Marks, Niaz Ahmad, Jane Tizard on behalf of the UK Paediatric Sub-Group of the Kidney Advisory Group, NHS B&T.

2. van Gelder T. European Society for Organ Transplantation Advisory Committee recommendations on generic substitution of immunosuppressive drugs. Transpl Int 2011;24: 1135-1141.

3. Sellares J, de Freitas DG, Mengel M et al. Understanding the causes of kidney transplant failure: the dominant role of antibody-mediated rejection and nonadherence. Am J Transplant 2012;12: 388-399.