Personal Statement

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I am a Consultant Transplant Surgeon based in the Institute of Transplantation in the Freeman Hospital, Newcastle-upon-Tyne. I am responsible for the assessment, consenting, surgical procedure and initiation of immunosuppressive medications in patients with kidney failure undergoing kidney transplantation. Part of my academic role includes an editorial position with the Cochrane Renal Group based at Westmead Hospital in Sydney, Australia. They have nominated me to present the evidence currently published in the Collaboration in this field and I will present this with a personal account of what medications we currently use and would envisage using in NHS clinical practice.

Summary

1) Recent evidence suggests that the harmful effects of steroids can be avoided using protocols that include alemtuzumab induction, tacrolimus, mycophenolic acid and sirolimus (3C trial). Once a day tacrolimus preparations may increase compliance and long term graft survival.
2) Belatacept will also have a role as a “once a month” therapy to improve compliance and improve access to transplantation for patients who are currently denied transplantation or who are at high risk for rejection due to oral drug absorption problems.
3) Early graft and patient survival after kidney transplantation are excellent using current drug regimens. However, what lies hidden behind these figures, are patients who are denied access to transplantation and remain on dialysis because they have had a cancer, can’t reliably digest drugs. Access to different drug combinations would also help some patients return to work and live truly normal lives.

Current outcome measures

The current Freeman Hospital immunosuppressive protocol for kidney transplant recipients has evolved over a 30 year period and the current graft and patient at 1 year is now 93% and 96% respectively in 2014 (NHSBT online data). In this respect kidney transplantation is now a routine procedure with patients and physicians expecting and achieving long term graft survival (5yr plus) in excess of 80%. Even in high risk “acute rejection” situations, with current technologies, we can offer kidney transplantation to highly sensitised patients who have multiple antibodies and an incompatible donor on initial screening.

There is therefore a powerful argument that the metrics of success in kidney transplantation should now include lifestyle outcomes- for instance "return to employment", "pregnancy leading to live birth" and even Patient Reported Outcome Measures (PROMs)- in line with other surgical sub-specialities. The current rate of return to employment in the North East of England has not been specifically audited, but in our anecdotal experience it is less than 15% (international rates c.30%).

Obviously the societal economic impact of returning to gainful employment after kidney transplant is considerable and I would hope that this would influence the decision making during this Technology Appraisal, although reliable cost-effectiveness analysis incorporating this data may be impossible.

Current standard practice

Our standard practice, in line with current NICE guidance, is that patients are given antibody induction with basiliximab (Simulect, Novartis) and methylprednisone at the time of surgery and on day 4. Tacrolimus (Adoport) is initiated on day 1 at a dose of 0.1mg/kg/bid with azathioprine at a dose of 1mg/kg. In various situations where a high risk of acute rejection is anticipated (HLA incompatible transplantation or ABO incompatible) we would change antibody induction to alemtuzumab or ATG (antithymocyte globulin). In recipients of Donation after Circulatory Death (DCD) or in immunological "high risk" kidneys we would change azathioprine to MMF or myfortic.

In heart or heart-lung transplant patients having a kidney transplant we would still consider continuing their ciclosporin therapy, rather than tacrolimus, in the immediate post transplant period.

Basiliximab

This cost effectively reduces the incidence of acute rejection without an excess of extra infections or tumours in recipients and is the current standard of care [1].

Corticosteroids and Alemtuzumab

Prednisone remains the cornerstone of our immunsuppressive protocol. At the time of surgery 500mg is given intravenously and most patients receive 20mg for at least the first 6 weeks. After this we try to reduce and eliminate steroids as quickly as possible to reduce the adverse side effects (diabetes, reduced bone mineral density, psychological fluctuations, wound healing, obesity and body image) to maximise the long term survival benefits of transplantation and improve the patient experience. In this respect the combination of tacrolimus and mycophenolate mofetil are necessary potent alternatives- as demonstrated by the recently published 3C study [2].

The Cochrane review on steroid avoidance published in 2007 suggested there was an excess of acute rejection using historical protocols containing azathioprine without antibody indcution when steroids were stopped early [3]. However, the 3C study has shown that steroids can be safely avoided from the start using a protocol that includes alemtuzumab induction and reduced dose tacrolimus with conversion to sirolimus. In years to come this may well be considered the "standard of care" and access to these drugs for all kidney transplant patients is essential.

Calcineurin inhibitors (tacrolimus and ciclosporin)

Tacrolimus is a more potent and more effective immunosuppressant. There is little doubt from the evidence reviewed by Angela Webster [4] and summarised below that this is the primary maintenance immunosuppressant of choice in kidney transplantation. The Elite-Symphony study published in the New England Journal of Medicine [5] has also confirmed these findings. The monthly costs of the various different generic twice daily preparations are relatively comparable, whereas the once daily preparations are more expensive (Advagraf and Envarsus). The advantage of the once daily preparations appears to be to reduce within patient-variability potentially by increasing compliance.

We continue to use ciclosporin (Neoral) in patients who demonstrate significant disabling neurotoxicity (tremor, shaking) with tacrolimus and in non-renal transplant patients (lung, heart) who are stable on this medication after a subsequent kidney transplant for calcineurin induced nephrotoxicity.

4 Applicability in clinical practice - absolute risk per 100 treated recipients

Immunological risk	Acute rejection*			Graft loss			Diabetes mellitus		
	Cyclosporin	Tacrolimus	Avoided cases+	Cyclosporin	Tacrolimus	Avoided cases	Cyclosporin	Tacrolimus	Avoided cases
LOW	20	14	6	6	5	1	6	11	5
MEDIUM	40	28	12	9	7	2	6	11	5
HIGH	55	38	17	11	8	3	6	11	5
+ see results section	* see results section								

Table 1. Taken from reference [4]

MTOR inhibitors (sirolimus and everolimus)

The MTOR inhibitors are not used in the United Kingdom for primary immunosuppression as they have adverse effects on wound healing after renal transplantation. The Cochrane Collaboration has published a review on the use of these drugs and the conclusions were generally favourable [6]. Thirty three trials were identified: sirolimus (27 trials) and everolimus (5) trials with one being a head to head comparison of the two. The most promising results were when MTOR inhibitors were used to replace calcineurin inhibitors 3 to 6 months after transplantation. The mean difference in GFR at 2 years was 15 ml/min in favour of MTOR inhibitors with no excess of graft loss, biopsy proven rejection or patient mortality. *This could equate to an extra 8 years of graft life if the attrition rate per year is the commonly quoted 1-2 ml/min*. The late results of the 3C study will provide further evidence as to the efficacy of these findings.

Whatever the effect on long term kidney graft survival, MTOR inhibitors are increasingly being used to facilitate transplantation in patients with a history of malignancy or who develop tumours on immunosuppression (particularly cutaneous malignancies). Although the scientific evidence is sparse, increasingly clinicians are more confident to use these agents rather than deny patients with tumours access to transplantation or remove immunosuppression from transplant patients when a cancer is diagnosed.

Antimetabolites (mycophenolic acid and azathioprine)

The Cochrane Collaboration review of anti-metabolites is currently incomplete. However, the steroid avoidance data suggests that this can only be achieved in patients who are on a mycophenolic acid derived anti-metabolite. In my personal experience I am aware of several cases where patients have stopped MMF or Myfortic and experienced acute rejection on azathioprine. In the most recent case the patient was hospitalised for 3 weeks.

Belatacept (Nulojix)

This drug was not available to be considered in the 2004 technology appraisal. Since then the drug has been licensed and undergone multiple Phase 1 and Phase 2 trials. As a “once a month” injection this medication has significant potential advantages for various patient groups.

In 2 cases in the last year we have requested funding for belatacept (Individual Funding Request)- both of these cases were patients who could not ingest or digest tablets reliably. In several other situations we would have utilised this drug if the funding could have been agreed within a reasonable timeframe.

The patients we believe would benefit include diabetic patients with significant autonomic neuropathy affecting their stomach causing them to vomit, patients undergoing kidney transplant as part of a small bowel and/or pancreas transplant, patients whose lifestyle commitments predispose to poor compliance (mothers with young children) and individuals with special educational needs who are reliant on carers to give their immunosuppression.

In addition Masson et al. [7] have published a comprehensive review of the evidence in the latest edition of the Cochrane Collaboration and concluded that there is a significant role for this drug to reduce the long term effects of calcineurin inhibitors on renal scarring, high blood pressure and lipid profiles. They reviewed 5 RCT's (1535 transplants) and concluded that this benefit was not at the expense of an excess of rejection, graft loss or patient survival.

However, the data on post transplant lymphoproliferative disorder (lymphoma) is incomplete. There is a suggestion from the early studies that there is an excess of this potentially fatal condition in the subgroup of recipients who are Epstein-Barr virus (EBV) negative and receive an EBV positive organ. In the published RCT's there was no excess of this complication and the three post marketing clinical studies should help address some of the data deficiencies.

References

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