Immunosuppression in renal transplantation: where are we now?

The development of potent and well-tolerated immunosuppressive agents has established renal transplantation as the treatment of choice for patients with end-stage renal disease. This is the result of two therapeutic revolutions; the introduction of azathioprine in the 1960s that made renal transplantation possible, and the introduction of cyclosporin in the 1980s that enabled other solid organ transplants and radically improved the outcome of renal transplantation.

Following the introduction of cyclosporin, acute rejection rates fell to around 50% and 1-year graft survival improved to over 80%. Since then progress has been slower, but there are now several new immunosuppressive agents with varying potency and side-effect profiles (*Table 1*). At present (Danovitch, 2000; Vincenti, 2003) most immunosuppressive regimens involve lifelong combination therapy with three agents: a corticosteroid, an antiproliferative agent (e.g. azathioprine) and a calcineurin inhibitor (CNI, e.g. cyclosporin). Following transplantation, the dose of each agent is gradually reduced over 6–12 months, the relative dose of each drug depending on efficacy, plasma levels and side effects in individuals. In addition, 'induction' therapy may be used at the time of transplantation to reduce the risk of rejection or to permit the delayed introduction of CNI that may have nephrotoxic effects.

Induction agents are usually monoclonal antibodies against T cell epitopes, e.g. CD-3 (OKT3), or polyclonal antibodies against activated T cells (e.g. anti-lymphocyte sera). Treatment may also be altered as a consequence of an acute rejection episode that is generally treated (and reversed) with a 3–5-day course of high-dose steroids. Resistant or severe rejection episodes may require alternative oral agents or antibody therapy.

A final generalization is that the focus of immunosuppression is changing away from prevention of rejection episodes. Currently, with reduced acute rejection rates and improved 1-year graft survival, the optimization of short and long-term graft function (Hariharan et al, 2002) and minimization of long-term consequences of transplantation, most importantly preventing cardiovascular disease and malignancy, have assumed greater importance (Jardine, 2001).

AVAILABLE AGENTS: EFFICACY AND SIDE EFFECTS

Corticosteroids are part of most therapeutic regimens and the first choice for reversal of rejection episodes. A conventional regimen might start with prednisolone 0.3 mg/kg/day, tapered to 0.1 mg/kg/day over 3–12 months. Although weak immunosuppressants at this dose, steroids are synergistic with other agents, and steroid withdrawal is associated with a risk of acute rejection (at least with older drug combinations). The major side effects in transplant recipients are hypertension, hyperlipidaemia, post transplant diabetes (PTDM) and osteoporosis.

The CNIs (cyclosporin and tacrolimus) inhibit calcineurin-dependent T-cell activation. Side effects include hypertension, hyperlipidaemia, PTDM (worse with tacrolimus), acute and chronic nephrotoxicity, hirsutism and gum hyperplasia (worse with cyclosporin). Tacrolimus may be the more potent immunosuppressive agent (although dose equivalence is difficult to establish) and, in combination with mycophenolate and steroids, acute rejection rates of approximately 20% have been reported.

Antiproliferative agents – azathioprine and the more potent and lymphocyte-specific agents mycophenolate and mycophenolic acid – are the third component of most immunosuppressive regimens. Neither is potent enough to be used alone or as dual therapy with steroids, but allows the use of lower doses of steroids and CNI. They do not

TABLE 1.
The influence of currently available oral immunosuppressants on rejection, graft function, cardiac risk factors and other potential adverse effects in renal transplant recipients

Drug	Rejection	Hypertension	Lipids	PTDM	SeCt	Infection	Malignancy	Other
Steroid	↓	↑↑	↑↑	↑↑↑	–	↑	↑	Cushing's syndrome
Cyclosporin		↑↑↑	↑↑	↑	↑↑	↑↑	↑↑	CNS (tremor), hirsuitism, gum hypertrophy, HUS
Tacrolimus	↓↓	↑↑↑	↑	↑↑	↑↑	↑↑	↑↑	CNS (tremor), HUS
Rapamycin	↓↓↓	–	↑↑↑	–	-/↑	↑↑	-/↑	Bronchiolitis, platelets ↓
MMF	↓↓/↓	–	–	–	–		↑	Marrow suppression
Azathioprine	↓	–	–	–	–	↑	↑	Marrow suppression

HUS = haemolytic uraemic syndrome; MMF = mycophenolate mofetil; PTDM = post transplant diabetes; SeCT = serum creatinine

adversely affect cardiovascular risk factors and their use is limited by marrow toxicity and gastrointestinal side effects (with mycophenolate).

Target of rapamycin inhibitors

The introduction of sirolimus, and the development of the related compound everolimus, provides a new group of drugs (Dupont and Warrens, 2003) that have antiproliferative effects on T cells and other cells – notably vascular cells. These agents are potent immunosuppressants and although high doses cause marked hyperlipidaemia they do not cause nephrotoxicity, hypertension or PTDM. Other specific side effects are marrow suppression and an uncommon reversible bronchopulmonary syndrome that affects 1–2% of patients.

The role of sirolimus is evolving. In combination with cyclosporin its use is associated with an acute rejection rate of approximately 20% but it aggravates the nephrotoxic effects of cyclosporin and concomitant use of cyclosporin and sirolimus is limited to the first 3 months following transplantation, after which time one agent should be withdrawn. Initial data also suggest that sirolimus may be associated with improved graft function and lower rates of malignancy compared to other agents.

Antibodies

Polyclonal (e.g. antilymphocyte globulin) and monoclonal antibodies (e.g. OKT3 against CD-3) are used as induction agents and in treatment of severe rejection. Their use is complicated by their origin in other species, resulting in production of neutralizing antibodies, release of cytokines from activated T cells (especially OKT3-activated T cells), increased risk of post-transplant lymphoproliferative disease and cost.

Two monoclondal antibodies against the interleukin-2 (IL-2) receptor (basiliximab and dacluzimab) are in clinical use as induction agents. They have minimal side effects and two treatments provide 6 weeks of immunosuppression equivalent to cyclosporin, allowing the delayed introduction of CNI. They are of particular use in patients with delayed graft function at risk of acute CNI nephrotoxicity.

Design of therapeutic regimens

There is no consensus on the design of immunosuppressive regimens except that the aim of therapy is to provide optimum graft function with minimal side effects, while maintaining cost efficiency (Danovitch, 2000; Dupont and Warrens, 2003; Vincenti, 2003). Few centres in the UK use induction therapy; most use a CNI-based regimen, with steroids plus mycophenolate. Cyclosporin may be favoured over tacrolimus to reduce PTDM or for reasons of cost; tacrolimus may be favoured for efficacy, compliance or cosmetic reasons and would generally be favoured in patients with a high risk of rejection (e.g. following a rejection episode or in patients who have lost a previous graft to early rejection).

Increasing recognition of the importance of good graft function and the adverse effects of CNI nephrotoxicity make target of rapamycin inhibitors an attractive option for the future. Moreover, although high doses of target of rapamycin inhibitors are associated with hyperlipidaemia, the overall impact on cardiovascular risk is likely to be low, in the absence of adverse effects on blood pressure, PTDM or graft function (Jardine, 2001).

New agents

FTY-720 (Brinkmann and Lynch, 2002), a new agent in phase II clinical trials, is a sphingosine phosphate (EDG) receptor agonist that causes relocalization of T cells to lymphoid tissues, thus limiting their involvement in rejection. Transient bradycardia was an unexpected consequence of FTY therapy that is now known to reflect the presence of EDG receptors on the sino-atrial node.

FTY, together with mycophenolate/mycophenolic acid or sirolimus/everolimus, is likely be part of future multi-drug regimens that will minimize acute rejection rates and optimize long-term graft function while allowing the avoidance or withdrawal of CNI.

CONCLUSIONS

In the foreseeable future the management of solid organ transplant recipients will involve the use of long-term combination immunosuppression with shifting focus – away from minimizing acute rejection and improving 1-year graft survival (both of which are close to achievable limits) and towards improved short-term graft function and long-term graft survival, and reduced risk of long-term cardiovascular disease and malignancy. HM

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KEY POINTS

- Current management of solid organ transplant recipients involves lifelong combination immunosuppression.
- Most regimens are based on a calcineurin inhibitor, steroids and a third agent – azathioprine, mycophenolate or sirolimus.
- Acute rejection rates of 20% are attainable and 1-year graft survival rates of more than 90% are the norm with current therapeutic regimens.
- Limiting the long-term consequences of immunosuppression is now a powerful influence on the development and use of immunosuppressive agents.