LETTER TO THE EDITOR

Interleukin 2 receptor blockers may directly inhibit lymphocyte mediated ischaemia reperfusion injury

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We read with interest the article by Sanchez-Fructoso *et al.* [1] in the May edition of *Transplant International* describing the Madrid experience of daclizumab induction and reduced dose of calcineurin inhibitor for recipients of nonheart-beating renal transplants. They reported a reduction in delayed graft function rates from approximately 75% to 42% and concluded that there was evidence of effect, although being a retrospective review with no control group, the figures may be subject to an 'era' bias.

In conjunction with the Nicholson's group in Leicester, we have recently published a randomized controlled trial using a similar calcineurin sparing regime for nonheart-beating renal transplant recipients [2]. Patients were randomized to either daclizumab induction or control tacrolimus-based triple therapy. An initial dose of daclizumab (2 mg/kg) was given at induction, with further doses (1 mg/kg) given at 14-day intervals until there was significant evidence of graft function (serum creatinine = 350 μmol/l). At this point we started a calcineurin inhibitor aiming for a similar trough serum level (10–15 ng/ml) as Sanchez-Fructoso. Further initial background immunosuppression was in the form of mycophenolate mofetil (2 g/day) and steroids (prednisolone 20 mg/day). The control group received the same background immunosuppression and tacrolimus, in full dose, from the first day after transplantation.

Although there was no statistically significant difference in delayed graft function rates (daclizumab 65% vs. 78% control) overall, in the subgroup of uncontrolled donor kidneys that were machine-perfused during cold ischaemia, the delayed graft function rate was significantly reduced (daclizumab 47% vs. 87% control, $P = 0.015$). Similarly to Sanchez-Fructoso's study, we found no excess of acute rejection when tacrolimus was withheld in the presence of daclizumab induction.

Many centres use polyclonal antibody induction not only to minimize calcineurin use, but also to directly reduce ischaemia–reperfusion injury by inhibiting neutrophil adhesion and migration [3]. Unfortunately these agents are associated with both infections and post-transplant lymphoproliferative disease [4], and we used a specific interleukin 2 receptor blocking agent, in common with Sanchez-Fructoso, only to safely minimize the early use of calcineurin inhibitors. However, it has been recognized recently that the lymphocyte may play a direct early initiating role in ischaemia–reperfusion injury [5].

In Sanchez-Fructoso's paper there was a clear excess of lymphocyte-mediated graft injury (Banff grade II or III rejection, 52.9% vs. 18.8%) on core biopsy in the absence of interleukin 2 blockade. We have also found a significant incidence of isolated endothelitis, not accompanied by tubulitis, on protocol biopsies of kidneys damaged by warm ischaemia [6]. What is unclear is whether this lymphocyte infiltrate is in response to the ischaemic insult alone or an atypical presentation of graft recognition via conventional alloantigen dependent mechanisms. Either way this observation suggests that the use of an induction interleukin 2 receptor blocker *per se*, and not just calcineurin inhibitor minimization, may be of specific benefit to NHBD graft recipients.

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