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Pharmaceutical development of immunosuppression in transplantation

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For many years acute cellular rejection (ACR) has been the greatest threat in transplantation for both graft and patient survival. As a result immunosuppressive strategy has concentrated on developing agents capable of reducing ACR episodes. This approach has been very fruitful and now with the use of a combination of immunosuppressive drugs, many transplant centres can achieve acute cellular rejection rates of less than 30% with one year graft and patient survival >90%. Recently developed drugs have contributed to this reduction in ACR episodes. Firstly, mycophenylate mofetil (CellCept) is superior to azathioprine, when used in combination with cyclosporin and prednisolone. Although CellCept reduced the acute rejection episodes during the first year of kidney transplants there was no improvement in either the 1 or 3 year graft or patient survival. It has been known for a long time that the use of ATG or ALG can reduce acute rejection episodes without improving long-term graft survival. In other words the intermittent use of pulse steroids to reverse a rejection episode was as effective in the long-term as continuous drug therapy. Novel chimeric and humanised monoclonal antibodies (MAbs) that blocked the interleukin-2 receptor also significantly reduced acute rejection episodes by a similar margin. Whereas CellCept was taken continuously, the MAbs were administered as 2 doses in the first week (basiliximab) or 5 doses over 8 weeks (dacluzimab). Neither MAb improved the 1 year patient or graft survival and it remains to be seen if there will be any difference at later times. One much desired feature with the MAbs was a complete lack of side effects and no increase in infections.

The good graft survival achieved during the first year contrasts with the steady graft loss that occurs in each of the subsequent years. Little difference has been made to this graft loss despite the reduction in ACR. Because chronic rejection correlates with the number and severity of acute rejection episodes it has been hoped that a reduction in acute cellular rejection would lead to improvement in long-term graft survival. At present there is little evidence for this. Both cyclosporin and tacrolimus have pharmaceutical effects that could pre-dispose to chronic graft dysfunction and loss. A number of studies are being performed to see whether CellCept would be a preferable drug to use for maintenance therapy. Rapamycin is another new drug that is effective in reducing both acute and chronic rejection. It is very potent in combination with cyclosporin, reducing acute rejection episodes to less than 20%. If in addition it manages to reduce chronic rejection, it would make a dramatic impact upon transplant immunosuppression. Leflunomide is another drug in there is experimental evidence of reducing chronic vascular rejection, but still lacking evidence from clinical trials.

It is always been hoped that some form of immunomodulation at the time of engraftment would lead to tolerance of the graft. The development of tolerance implies that long-term chemical immunosuppression with all of its unwanted side effects would be unnecessary. Unfortunately many of the approaches to tolerance induction that work in rats and mice have not been effective in man or other larger mammals. The use of MAbs to the T helper cells (CD4) has been one of the most intensively studied approaches to tolerance induction. The accumulated evidence to date suggests that it will not work in man, nor has it been effective in non-human primates. Nevertheless other approaches have been investigated including blockade of co-stimulating molecules and drastic T cell depletion at the time of transplantation. Whereas CD4 MAbs did not significantly improved graft survival in monkeys, the combination of MAbs blocking the two co-stimulating molecules (CD80 and CD40 ligand) has been effective in producing long-term graft survival in monkeys in the absence of further immunosuppression. In other studies elimination of T cells (CD3 immunotoxin) or lymphocytes (Campath 1) at the time transplantation are other approaches that may lead to graft tolerance.