Solid Organ and Composite Organ Transplantation -
the dynamic equilibrium of rejection and immunosuppression
Paul E. Herbert, MBBS, MRCS and A. N. Warrens, DM, PhD, FRCP

Abstract
Transplantation remains one of the most discussed surgical specialties within the media, from both a scientific and ethical point of view. From a speculative experiment to a relatively commonplace lifesaving set of procedures. Within medicine, transplantation offers interaction between some of the sickest patients and the crafts of surgery, clinical immunology, and various medical specialities, as well as being the subject of huge quantities of clinical and basic scientific research. The many high profile advances in transplantation in recent years have been made possible by some very significant developments in the armamentarium of immunosuppressive drugs available for combating the rejection process. In this article, we will briefly discuss the rejection process and the drugs which are used to counter it.

The Rejection Process.
Rejection of solid organ transplants revolves around the CD4+ T lymphocyte, the helper T cell. This cell is activated by the presentation to it of fragments of alloantigens by antigen-presenting cells (APCs) on their MHC class II molecules. This interaction of the T cell’s receptor with the MHC class II / antigen complex leads to internal signalling within the T-cell, which then increases the production of the cytokines, interleukin 2 (IL-2)/B. IL-2 is responsible for on-going activation of T-cells. This activation leads to the effector arm of the immune response being recruited to perform the task of destroying the transplanted graft. The effectors include cytotoxic T lymphocytes, which act to kill the graft directly, antibodies produced by B-lymphocytes, or antigen non-specific macrophages, which cause a local ‘delayed type hypersensitivity’. Since the helper T cell is the key to the generation of such immune responses all current immunosuppressive drugs have a role in preventing T cell activation, in addition to any other roles they may play.

Methods of Preventing Transplant Rejection.
Aside from the miraculous but apocryphal (St Cosmos and St Damian’s leg transplant), and twin-to-twin transplants, transplant survival generally depends upon a cocktail of various drugs. Immunosuppression is always a balance between preventing rejection of a given graft and leaving the patient vulnerable to overwhelming infection, or other adverse effects of the therapy, such as end organ toxicity or malignancy.

When organ transplantation first began, the immunosuppression used consisted of two drugs used in combination, azathioprine and corticosteroids. Up to the early 1980’s, this was really the only available prophylaxis against the rejection process, and it was not unsuccessful, many units still having long-standing patients in their care on this regimen. The introduction of the drug ciclosporin at this time markedly improved renal allograft survival. At the same time antibody therapy, with either polyclonal or monoclonal anti-lymphocyte antibodies was introduced. However, since 1995 several new drugs have been introduced, including Tacrolimus, mycophenolate mofetil (MMF), sirolimus, and two new monoclonal antibodies specific for the interleukin-2 receptor.

More recently the aim of inducing transplantation tolerance has crept in to the vocabulary of the transplant physician. Rather than simply blocking activation, it aims to manipulate the immune system in such a way as to enable the host immune system to tolerate a transplant, or more specifically be unresponsive to the antigens from the transplant, and thus greatly reduce the level, if any, of drugs needed to prevent rejection. It implies that only the T-cells and B-cells responsible for graft recognition would be immobilised or eliminated, leaving the rest of the T- and B-cell populations available to participate in their normal physiological role, thus reducing vulnerability to opportunistic infection, as well as reducing or preventing the adverse effects of immunosuppressants. This area of transplant immunology is the subject of much current interest and research. Current cellular experimental approaches include introducing donor cells into the circulation of the recipient, thus inducing chimerism.

From a pharmacological point of view, a number of approaches have been considered, but it is important to realise that generating tolerance is more than simply blocking the recognition of antigen specific responses, but rather is an active process. As described above, antigen recognition by T-cells leads to generation of intracellular messages. These messages are often referred to as “signal one”. However, when a T-cell interacts with an antigen presenting cell (APC), several non-antigen-specific interactions also occur, leading to a second signal “signal two”. The most important of these are between CD80 and CD86 on the APC and CD28 on the T-cell, and also CD40 on the APC and CD40L on the T cell.

A number of experimental agents (CTLA4 Ig, anti-B7 antibodies...
and anti-CD40L antibodies) have been investigated to prevent ‘signal two’ from being generated since, if signal one is delivered in the absence of signal two then antigen specific tolerance is induced.11, 12, 13 There is much ongoing interest in this area. A further method of inducing tolerance is to encourage deletion of graft-specific T-cells. Activated T-cells are susceptible to activation-induced cell death (AICD). The final drug described below, rapamycin, promotes the susceptibility of activated T-cells to this apoptotic process, and this attractive method of inducing tolerance is also under intense scrutiny.14

Immunosuppressive Drugs

Antimetabolites
Azathioprine inhibits purine metabolism, by competitively antagonising an enzyme central to purine synthesis.15 More recently, we have had access to the drug MMF, which is an ester prodrug with higher bioavailability than its active agent, mycophenolic acid (MPA).16 This drug acts in a far more targeted way than azathioprine, acting on the enzyme inosine monophosphate dehydrogenase, which converts IMP to a precursor of guanine. This pathway is important in nucleotide synthesis in lymphocytes, but less so in other cells. Furthermore MPA is almost five times more potent in inhibiting the isotype of IMP dehydrogenase present in activated compared to resting lymphocytes. Studies have shown that MMF decreases the frequency and severity of rejection compared to azathioprine.17 So far this difference has not been shown to improve graft survival, though it is hard to perform a suitably powered study to detect this difference.18 However MMF’s effects may in the long term be shown to improve renal allograft survival.19

Corticosteroids
Prednisolone and methylprednisolone are both still used in transplantation. They function by reducing gene activation, which occurs if the signal induced by engagement of the T-cell receptor is successfully transduced to the nucleus.20 Expression of genes that lead to the production of pro-inflammatory cytokines re among those inhibited by steroids, thus reducing T-cell activation. How exactly steroids do this is only now becoming clearer and is thought to be based mainly on interference with transcription factors, such as activator protein-1 (AP-1) and nuclear factor kappa B (NF-kappa B).21

The reduction of lymphocyte proliferation seen with the use of these drugs is likely to be due to the reduction of cytokine production. Reduced expression of genes coding for adhesion molecules leads to reduced leukocyte migration.22, 23 However, their long-term use has a well known plethora of adverse effects (such as Cushing’s syndrome, osteoporosis, cataracts, peptic ulcers, glucose intolerance, hypercholesterolemia, skin fragility, and adrenal suppression) and many units thus aim relatively rapidly to wean patients off corticosteroids.

Calcineurin Inhibitors.
Calcineurin is a phosphatase which is activated if an antigen is recognised by a T-cell. It allows a promoter called “nuclear factor of activated T cells” (NFAT) to enter the nucleus and promote the transcription of several cytokine genes, including IL-2. By inhibiting this enzyme, ciclosporin and more recently, tacrolimus prevent this from occurring.24, 25 Thus the message that the T-cell receptor has recognised antigen does not reach the nucleus.

Both drugs are in use, but evidence suggests that tacrolimus is associated with a lower incidence of acute rejection.26, 27 They have differing adverse effects, but both require monitoring of their blood levels, due to their narrow therapeutic windows28

Inteleukin-2 receptor blockade
The action of IL-2 can be blocked at its receptor (CD25), which has lead to the development of two anti-CD25 antibodies, basiliximab and daclizumab, produced by genetic engineering. They were developed from mouse monoclonal antibodies specific for the chain of the human interleukin-2 receptor, but importantly only the variable domains of the light and heavy chains of basiliximab, and the three complementarity-determining regions of each variable domain in daclizumab are of mouse origin.24, 25 This means that both these antibodies are much less likely to be seen as a foreign protein and thus be removed by the patient’s immune system. Trials have shown that these drugs both reduce acute rejection.29

mTOR Inhibitors
Successful interaction of IL-2 with its receptor leads to the generation of a signal within the cell, starting the cell cycle and leading to proliferation.30 Increasing evidence suggests that mTOR, a regulatory kinase, acts as a central controller in this, sensing cellular environment (mitogenic stimulation) and regulating translation initiation through the eukaryotic initiation factor 4E, and ribosomal p70 S6 kinase pathways, thus allowing the cell to enter the cell cycle.31 Rapamycin (now called sirolimus) inhibits this process. It is not yet clear how best to use this agent. We do know that adding this drug to the regimen of ciclosporin and prednisolone decreases acute rejection32, and it can also be substituted for ciclosporin33, avoiding the nephrotoxicity encountered with this drug.

Face, Hand and Other Composite Tissue (CT) Transplantation
The arguments against performing a face transplant are similar to those applied to hand transplantation. The performing of a hand transplant was not uncontroversial34, 35 as many argue that the risk of long term adverse effects of immunosuppression did not outweigh the benefits of gaining a hand. Indeed the first recipient of such a transplant was unable to tolerate the side effects of his drug regime and thus lost his transplant.36 However, as described above, over 20 hand transplants have been performed to date, and so far only two have been lost. The longest surviving hand transplant has been in situ for more than five years, with reports in the media of excellent function (CNN website, 28th February 2004). This has become possible because of the developments both in understanding the rejection process and also the continuing work in developing new drugs that target this process, as well as improved microsurgical technique.30

The regime used for hand transplants (tacrolimus/MMF/prednisolone) works by blocking the signals that generate an immune response in three different areas as described above. The fact that successful hand transplants have occurred demonstrates well the power of modern immunosuppressive drugs. The immunogenicity of composite tissues, particularly skin should not be underestimated, due to the presence within it of a large number of cells of the immune system, including high numbers of dendritic cells, which easily trigger an immune response.37 Furthermore it can be argued that there is a much more limited functional reserve in composite tissues, so any rejection episode may have more obvious effects than in solid organ transplants38.

High levels of immunosuppression are going to have long term adverse effects, as described above, and thus the development of mechanisms inducing tolerance would greatly benefit face transplantation. Work in small animal models has shown that it is possible to generate tolerance, though so far this has not been reproduced in larger animal models. Obviously the ability to induce tolerance to transplanted composite tissues would help overcome the scepticism that many in the transplant community have towards composite tissue transplantation. The final point to

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be made is that the long term survival of composite tissue grafts will be dependant on the avoidance of chronic rejection. Only time and experience will tell us what is in store for us here.

Conclusion
There is much work still ongoing in the development of strategies to counter transplant rejection in all areas of transplantation, and possibly develop tolerance. There are still many areas in which things can be improved. For example, the commonest cause for loss of a renal transplant is death of the patient with a functioning graft, at an age in advance of what would be predicted for a healthy, age-matched individual. Whilst part of this pathology will reflect the impact of past renal disease and dialysis, the adverse effects of immunosuppressive drugs will also have played a role. Reducing this pathology is a major focus within the transplant community today, and would greatly benefit recipients of all types of transplant.

Conflicting Interests - Non declared

References