

Immunosuppression after renal transplantation

Almost all patients who receive a solid organ transplant require long-term immunosuppression to prevent graft rejection. Often this is in the form of more than one medication administered soon after transplantation, with a gradual reduction in the number and dose of medications when successful and stable graft function is confirmed. Broadly speaking, the foremost aim in the first 12 months post-transplant is prevention of acute rejection; thereafter the goal of therapy is prevention of chronic rejection and maintenance of the graft – balancing the benefits of therapies against potential long-term toxicity.

The choice of the initial immunosuppressive “cocktail” and subsequent changes depends on a number of factors. These include:

- ◆ the perceived immunological risk of rejection
- ◆ donor factors
- ◆ any previous rejection episodes
- ◆ adverse effects
- ◆ unit protocols
- ◆ the stability of graft function.

Immunosuppressive medication currently in use for transplant patients can be essentially divided into three categories:

1. Calcineurin inhibitors
2. Antiproliferative agents
3. Corticosteroids.

Most solid organ recipients tend to be on a combination of one or more agents from the above categories as long as their graft is functional. In addition, other agents are considered for induction therapy at the time of transplantation and, if necessary, to treat rejection episodes; however, such agents (e.g. basiliximab and daclizumab) are used exclusively in tertiary care settings.

It is generally accepted that immunosuppressant initiation and/or changes should be co-ordinated in secondary or tertiary care settings but, for patients with stable graft function on long-term stable immunosuppression, it might be appropriate for these medicines to be prescribed in the community within effective shared care arrangements.

The relative efficacy of the various immunosuppressive regimens is not considered here but is discussed in the references cited, including the technology appraisals issued by the National Institute for Health and Clinical Excellence (NICE).

Calcineurin inhibitors

Ciclosporin (*Neoral*[®], *Sandimmun*[®])

Tacrolimus (*Prograf*[®])

Calcineurin inhibitors are responsible for making solid organ transplantation clinically viable. They inhibit secretion of key cytokines that are required for immune activation and predominantly affect T cells. Although bio-chemically distinct, ciclosporin and tacrolimus have similar modes of action, efficacy, and adverse effect profiles. For both these agents, doses need to be administered twice a day (every 12 hours) to maintain efficacy.

Ciclosporin and tacrolimus are metabolised predominantly in the liver through the cytochrome *P*-450 enzyme system. Other medications that either induce or inhibit this enzyme system may result in decreases or increases in calcineurin exposure. Appendix 1 in the BNF lists medicines reported to interact with calcineurin inhibitors. Differences in the activity of this enzyme system are responsible for differences in dosing requirements between individuals.

Ciclosporin and tacrolimus have relatively narrow therapeutic indices. Initial doses are calculated according to weight. Subsequent exposure is controlled by measuring 12-hour trough plasma concentrations (i.e. concentrations from samples taken immediately before the next dose is due) and modifying doses accordingly. Target trough concentrations are higher in the first 12 months post-transplant with a gradual reduction thereafter.

For practical purposes, patients are advised to take their medications in the same way each day with respect to food (i.e. either with meals or on an empty stomach); a consistent approach is the key to preventing large fluctuations in blood concentrations. Because of differences in bioavailability, the brand of ciclosporin to be dispensed should be specified by the prescriber.

The most common adverse effects associated with these medicines include:

- ◆ nephrotoxicity (the risk of chronic graft dysfunction must be balanced against the risk of rejection)
- ◆ cosmetic problems
 - excessive facial hair (hypertrichosis) and gingival hypertrophy with ciclosporin
 - hair loss with tacrolimus
- ◆ glucose intolerance
 - approximately 10-15% of patients may develop new onset diabetes as a result of post-transplant immunosuppression
- ◆ hyperlipidaemia
- ◆ hypertension
- ◆ neurotoxic symptoms, such as tremors.

Antiproliferative agents

Azathioprine

Mycophenolate mofetil (*CellCept*[®]) or mycophenolate sodium (*Myfortic*[®])

Sirolimus (*Rapamune*[®])[▼]

Antiproliferative agents are predominantly anti-metabolites and act as immunosuppressives by preventing immune cell replication. Azathioprine and sirolimus have relatively long half-lives and are administered once a day, whereas mycophenolate is administered twice a day.

All three agents are metabolised in the liver and the enzyme status of the patient influences drug exposure. Slow acetylators are at risk of bone marrow suppression with azathioprine.* Great caution needs to be exercised if prescribing allopurinol to patients on azathioprine as bone marrow toxicity can be potentiated. Medicines that affect the cytochrome *P*-450 system may affect plasma concentrations of sirolimus.

Azathioprine and mycophenolate are administered as fixed doses. Sirolimus dosing is controlled by measuring 24-hour trough plasma concentrations.

The most common adverse effects reported with these agents include:

- ◆ bone marrow suppression
- ◆ diarrhoea (with mycophenolate)
- ◆ nephrotoxicity (sirolimus)
- ◆ impaired wound healing (sirolimus)
- ◆ hyperlipidemia (sirolimus)
- ◆ mouth ulcers (sirolimus)
- ◆ rash (sirolimus).

Corticosteroids

Corticosteroids have been an integral part of transplantation for more than 30 years, but regimens that either avoid or withdraw steroids are becoming increasingly common. Corticosteroids act in a variety of ways to induce an immunosuppressive state. They are administered once a day and doses are gradually tapered post-transplantation.

Common side effects include:

- ◆ endocrine effects with cosmetic problems (weight gain, moon face, and striae)
- ◆ glucose intolerance
- ◆ osteoporosis
- ◆ impaired wound healing.

* Approximately one person in every 300 lacks thiopurine s-methyltransferase (TPMT) – the enzyme that metabolises thiopurines. To identify patients at risk of severe adverse effects with drugs such as azathioprine, tests of TPMT can be performed prior to treatment; however, the benefit of testing in the renal transplantation setting has not been established. Patients who are found to suffer severe bone marrow suppression during the intense surveillance period post-transplantation are weaned off the medication.

Combined therapies

As indicated earlier, most solid organ recipients will be on a combination of one or more agents and various combinations are associated with higher risks of certain adverse events. For example, concomitant use of calcineurin inhibitors and steroids carries a higher risk of diabetes; combinations of sirolimus and mycophenolate compounds are associated with an increased risk of bone marrow toxicity; and sirolimus combined with calcineurin inhibitors results in a higher risk of nephrotoxicity.

Adverse effects common to all immunosuppressive medication

Immunosuppression post-transplantation increases the risk of opportunistic infections like cytomegalovirus (CMV), *Pneumocystis carinii* pneumonia (PCP), fungal infections, and re-activation of tuberculosis or varicella-zoster. (It is worth noting that live vaccines should not be used in patients on immunosuppressive medication.)

The life-time risk of non-melanoma skin cancer is greatly increased (in the order of 4-21 times that in the general population*) and the risks of other solid or hollow viscus or haematological malignancies are slightly increased (in the order of 3 times higher*). There is no increase in the incidence of commonly observed malignancies in the population (breast, prostate, colon, and invasive cervical carcinoma). In general, post-transplant cancer risk is linearly related to the duration and intensity of immunosuppression.

Prophylactic measures

In addition to immunosuppressive medication, most transplant units routinely prescribe prophylactic therapy to prevent anticipated complications. For example:

- ◆ co-trimoxazole or dapsone to prevent PCP
- ◆ ganciclovir or valaciclovir to prevent CMV
- ◆ proton pump inhibitors to prevent steroid-induced gastritis
- ◆ bisphosphonates to prevent or treat steroid-induced osteoporosis
- ◆ aspirin to prevent thrombosis.

Agents used to prevent opportunistic infections are usually administered for 3-6 months after transplantation.

Clinical trials of new medicines

Organ transplantation is an intensively researched field of medicine and new agents are constantly being trialled to test if graft outcomes can be improved or adverse effects minimised. Depending on the transplant unit, patients may be approached to participate in clinical trials involving new immunosuppressive agents. Such trials are often centrally co-ordinated with trial medication available for prescription by the transplant unit. Follow-up is rigorous, with both face-to-face and telephone interaction with patients. Patients are often given contact details of key personnel involved in the trial who may be available even out-of-hours. For any queries regarding these medications, the transplant unit and/or the renal pharmacist at the relevant centre should be contacted directly.

* The reported incidences vary widely depending on the cancer and the patient population.

Patient compliance – from dialysis to transplantation

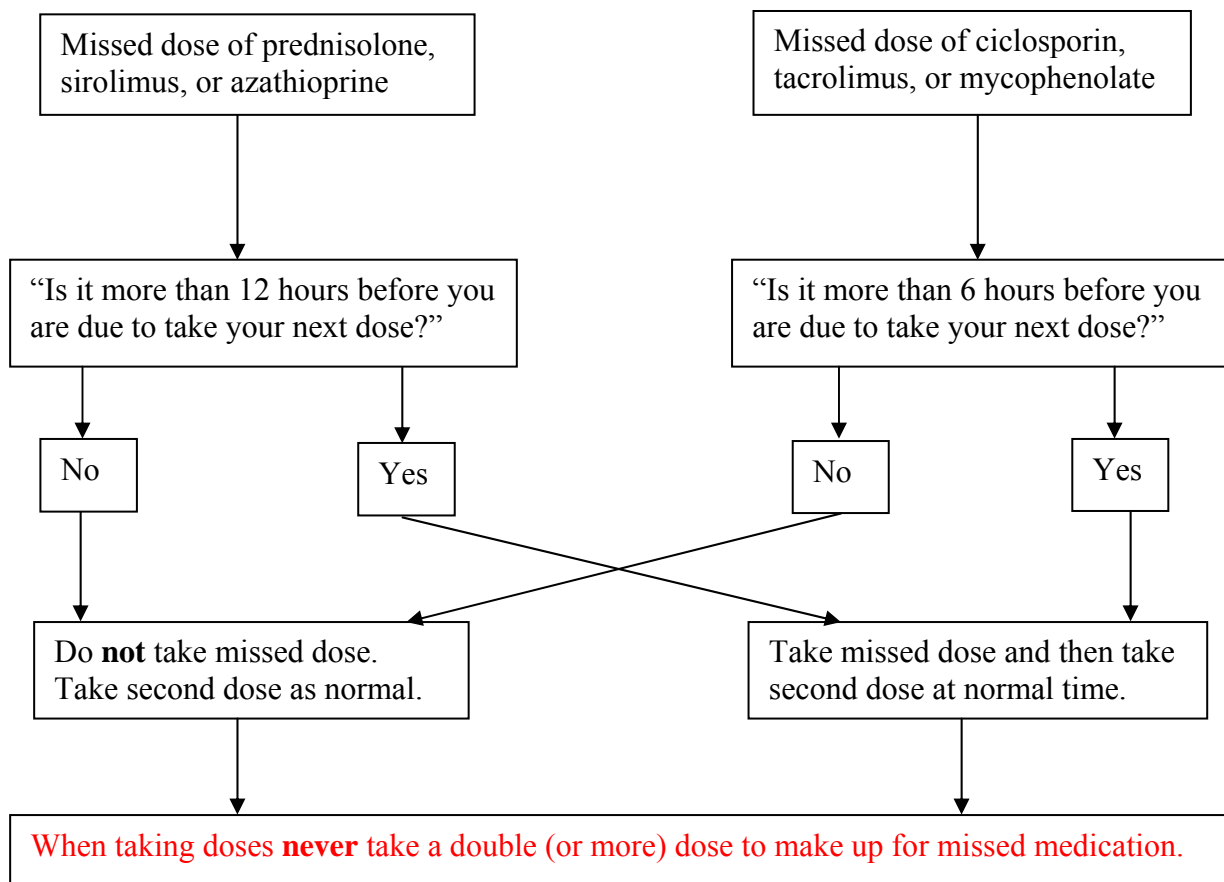
For most patients, medication that was routinely taken during dialysis (e.g. phosphate binders, erythropoietin, antihypertensive agents, iron tablets, and alfacalcidol etc.) may be stopped or the doses greatly reduced immediately post-transplantation. In most patients with a functioning renal transplant these medications are often not indicated. However, many patients receiving a transplant may not be expecting to have to adhere to a new regimen of essential immunosuppressive medications and compliance can be problematic.

Except in the case of identical twin-to-twin transplantation, immunosuppression is required to prevent graft rejection in the vast majority of organ recipients. Even in patients with stable graft function 10 years or more post-transplantation, missing prescribed immunosuppressive medication has been reported to trigger rejection and, hence, adherence is important to prevent irreversible rejection and graft failure.

The transplant team often advises patients to take their medications at the same times every day to avoid fluctuations in drug concentrations. For example, ciclosporin and tacrolimus are ideally taken every 12 hours (10 am and 10 pm are usually suggested) and need to be taken at the same time every day.

In cases where a patient misses a dose of a particular medication, the following flow chart can be useful to consult when providing advice.

Missed dose flow chart



Information sources, references and further reading

- ◆ Chapman JR et al. Chronic renal allograft dysfunction. *J Am Soc Nephrol* 2005; 16: 3015-3026.
- ◆ Meier-Kriesche H-U et al. Immunosuppression: Evolution in practice and trends, 1994-2004. *Am J Transplant* 2006; 6 (pt 2): 1111-1131.
- ◆ Offermann G. Immunosuppression for long-term maintenance of renal allograft function. *Drugs* 2004; 64: 1325-1338.
- ◆ Penn I. Post-transplant malignancy. The role of immunosuppression. *Drug Safety*. 2000; 23: 101-113.
- ◆ Samaniego M et al. Drug insight: Maintenance immunosuppression in kidney transplant recipients. *NCP Nephrology* 2006; 2: 688-699.

- ◆ Immunosuppressive therapy for renal transplantation in adults. The National Institute for Health and Clinical Excellence (NICE). Technology Appraisal 85. September 2004.
- ◆ Immunosuppressive therapy for renal transplantation in children and adolescents. The National Institute for Health and Clinical Excellence (NICE). Technology Appraisal 99. April 2006.

- ◆ British National Formulary, September 2006 (BNF 52). BMJ publishing Group Ltd and RPS Publishing; London 2006.

*This document is based on work prepared by **Dr Rommel Ramanan**
Consultant Nephrologist, University Hospital of Wales, Cardiff.*