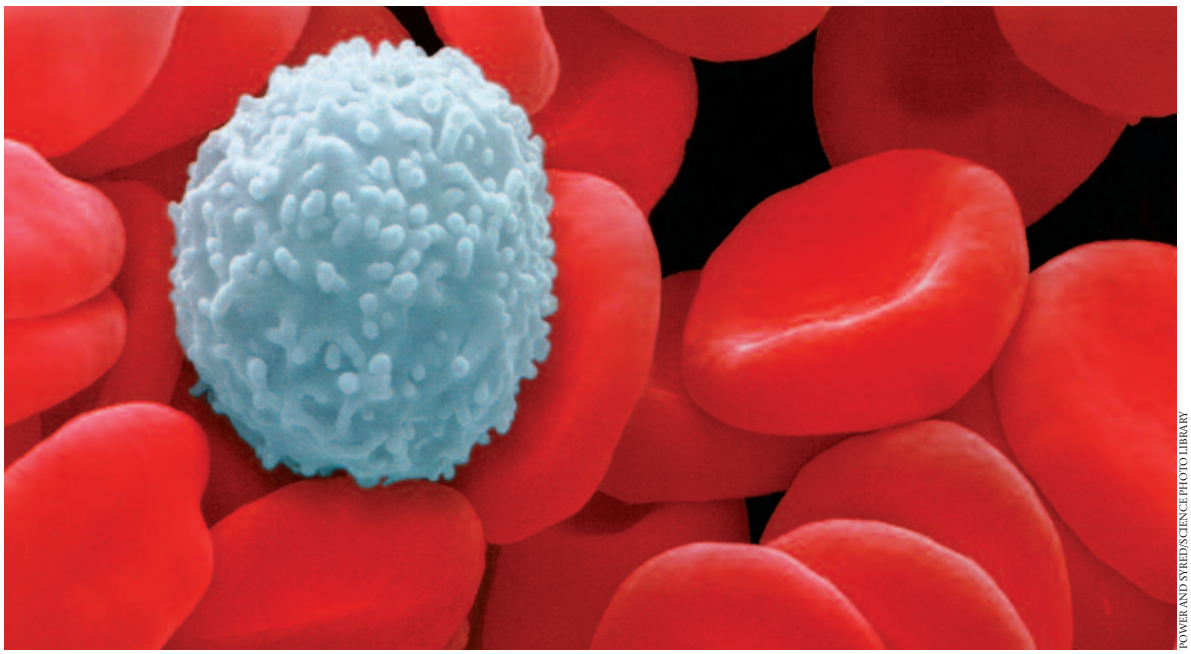

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Red and white blood cells. Some immunosuppressants can reduce the white cell count, making infection more likely

What I tell my patients about immunosuppression

It is recognised that for most patients with end-stage kidney disease, transplantation is the optimum treatment. It increases patient longevity and improves quality of life. Immunosuppression is the lifeline for a transplanted organ; it is needed to dampen down your natural defence system (immune system) to prevent it recognising and attacking the transplanted organ in a process called rejection. These immunosuppressive medications are also referred to as anti-rejection medicines, and they need to be taken every day for the life of the transplanted organ. It is important healthcare professionals work with you to establish a medication regimen that suits your lifestyle and that can be adhered to.

Which immunosuppression is best?

A number of points are considered during the transplant assessment and at the time of transplant – for example, organ type, organ source (deceased/living donor or non-heart beating donor), previous transplant(s), tissue typing (what is known as human leucocyte antigen mismatch), ethnicity, and ability to adhere to a strict medication regimen. Based on these, your immunosuppression regime is decided. Some transplant units have a number of immunosuppression regimes in place and will choose the one most appropriate for the individual patient, whereas others have a single immunosuppression regime that is prescribed for all their transplant patients.

Why do I need to take more than one?

A number of immunosuppressive medications can be used in combination, the aim being to use the lowest dose of each medication to minimise side-effects, and reduce the risk of infection and malignancy. Finding the right balance can be difficult and is individualised to each patient. Too little immunosuppression could potentially put you at risk of rejection, while too much increases the risk of infection.

Do these immunosuppressive medications change over time?

There are two distinct immunosuppression phases after transplantation – induction and maintenance. During induction, an antibody agent – such as basiliximab (Simulect®, Novartis, UK), alemtuzumab (MabCampath®, Genyzme, UK) or antithymocyte immunoglobulin

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(Thymoglobuline®, Genyzme, UK) – is given as an injection before or during the operation. One or more additional doses are usually given in the days after the operation. This is in combination with two or three oral immunosuppressive medications given at high doses, which then become maintenance agents at lower doses.

The induction phase usually relates to the first few months post-transplant when rejection is more common; this then passes into the maintenance phase, which lasts for the rest of the life of the graft. During the maintenance phase, the doses of oral immunosuppressive medications are minimised to reduce your risk of cardiovascular events, infection and malignancy, which strongly correlate with the overall amount of immunosuppression received.

What maintenance medications are available?

The choice of oral immunosuppressive medications currently available in the UK is listed below. Your maintenance immunosuppression regime will comprise a minimum of one, and usually two or three, of these medications. It is important that you know the exact name and brand of each immunosuppression drug that you are taking. The maintenance regime is tailored to each individual patient.

a. Calcineurin inhibitors: ciclosporin – Neoral®, Sandimmun® (both Novartis, UK), Deximune® (Dexcel, UK), Capimune® (Mylan, UK); tacrolimus – Prograf®, Advagraf®, Modigraf® (all Astellas, UK), Adoport® (Sandoz, UK), Tacni® (TEVA, UK), Vivadex® (Dexcel, UK), Mylan tacrolimus (Mylan, UK).
b. Antimetabolites: azathioprine; mycophenolate mofetil (MMF) – CellCept® (Roche, UK), along with several generic brands; mycophenolate sodium (MMS) – Myfortic® (Novartis, UK).
c. Steroids: prednisolone (non-branded).
d. Mammalian target of rapamycin (mTOR) inhibitor: sirolimus – Rapamune® (Wyeth, UK) (mTOR is a protein related to cell growth).

Box 1. Avoiding errors with ciclosporin and tacrolimus

- Make sure you always take the same brand of ciclosporin/tacrolimus
- Different brands are not interchangeable and cannot be swapped, unless closely supervised as a controlled switch by your transplant team
- Ask your doctor to prescribe ciclosporin/tacrolimus by brand name
- Query any changes in appearance or packaging with the pharmacist. If you are still unsure contact the transplant unit
- If you accidentally take the wrong brand or have mixed up your usual brand with a new brand then please contact your transplant team urgently for advice
- There are now several tacrolimus brands available in the UK and there are likely to be more brands available by the end of 2011. You will only be prescribed one brand by your transplant unit and that is the brand you must always take, unless advised otherwise by the transplant team
  – Prograf®, Adoport®, Tacni®, Vivadex®, Mylan tacrolimus – immediate-release tacrolimus capsules. Taken twice a day
  – Advagraf® – prolonged-release tacrolimus capsules. Taken once a day
  – Modigraf® – immediate-release tacrolimus granules for oral suspension. Taken twice a day
- There are three brands of ciclosporin widely available in the UK, and these brands are also not freely interchangeable
  – Neoral® capsules and liquid – taken twice a day
  – Deximune® capsules – taken twice a day
  – Capimune® capsules – taken twice a day

Is there a difference between the different brands?

When the patent or licence of the original drug brand has expired, other manufacturers are allowed to make a similar drug – a generic. Generic brands of ciclosporin, tacrolimus and MMF are now available in the UK. Most medicines are prescribed by their generic name to ensure cost-effective prescribing.

However, for ciclosporin and tacrolimus, drug levels are critical to the dose and effect so these are called 'critical-dose drugs'. As a result, these two medicines must be prescribed by brand name. This is because different brands of the same medicine can produce different drug levels in the blood.

Swapping between brands can alter blood levels which can then put you at risk of rejection (level too low) or toxicity (too high). For ciclosporin and tacrolimus, you must ensure you only take the brand prescribed by the transplant unit. The different available brands are not interchangeable and you cannot be swapped between brands unless supervised closely by the transplant team (see Box 1).

MMF is not a critical dose drug and the transplant community is in agreement that patients can switch to generic brands of mycophenolate mofetil with no adverse effect, as was the situation with azathioprine some years ago.

However, it should be remembered that MMF and MMS (Myfortic) are not interchangeable as they are different drugs.

When should I take my immunosuppression?

Refer to Box 2 for some golden rules on when it is best to take your immunosuppressive medications.

What should I do if a miss a dose of my immunosuppression?

Follow the guideline in Figure 1. Repeated missed doses can put you at risk of rejection and you should speak to your transplant team, who may be able to simplify or adjust the medication regime so that it is easier to take. If you are unable to take your medications for 24 hours because you have vomiting or diarrhoea, then you should contact your doctor or transplant unit for immediate advice. Seek urgent medical advice if you run out of immunosuppressants.

Will I experience any side-effects from these immunosuppressive medications?

All medications can cause side-effects, but not everyone will experience them. People vary in the way they react to taking medication. If you think your medicines are making you feel unwell or causing a side-effect, you should always speak to your doctor or transplant team – there is often an easy solution. You must not stop taking your medication without seeking medical advice.

Common side-effects

The most common side-effects of immunosuppressive medications include:

Ciclosporin: shakiness of hands; upset stomach (initially); excess hair growth; acne; overgrowth of gums; high blood pressure

Tacrolimus: shakiness of hands; upset stomach (initially); headaches; increased blood sugar (diabetes); hair thinning/loss

Mycophenolate: reduced white cell count, which can render the patient at increased risk of developing an infection; upset stomach (usually diarrhoea)

Azathioprine: reduced white cell count, which can render the patient at increased risk of developing an infection; upset stomach (usually nausea); hair thinning/loss

Sirolimus: swelling of extremities (the ankles, hands and feet); upset stomach; mouth ulcers; nosebleeds; acne; increased cholesterol

Prednisolone: upset stomach and indigestion; increased appetite; fluid retention (for example, swollen ankles); acne; increased blood sugar (diabetes); osteoporosis (weakened bones; usually after prolonged duration).

What medicines/foods should I avoid while taking immunosuppression?

Kidney transplant recipients should not take anti-inflammatory painkillers such as ibuprofen, diclofenac, or high-dose aspirin (at more than 600 mg/day), as they can damage the transplanted kidney.

You should not use anti-inflammatory topical creams and gels, but you can use other products such as the Deep Freeze® range or Tiger Balm® (Haw Par Healthcare Ltd).

If you have been prescribed azathioprine and need to start gout treatment with allopurinol, you must have your azathioprine dose reduced, as allopurinol inhibits the body's clearance of azathioprine, resulting in toxicity. Some

Box 2. Guidance on when to take your immunosuppresants

- Always take immunosuppressive medications with food as this will reduce any irritation to the stomach
- Always take immunosuppressive medications consistently before, with or after meals. The absorption of some immunosuppressive medication may be reduced by the presence of food, but if taken in a consistent manner then the dose of the medication will be adjusted over time to account for this
- Ciclosporin, tacrolimus and sirolimus – on the day of a blood test, always bring your morning dose with you and take it after the blood test. Your evening dose should be taken at the usual time. All your other morning medications can be taken at the usual time and not delayed
- Once-daily immunosuppressive medications are usually taken in the morning
- Twice-daily immunosuppressive medications are usually taken with breakfast and evening meal, about 12 hours apart

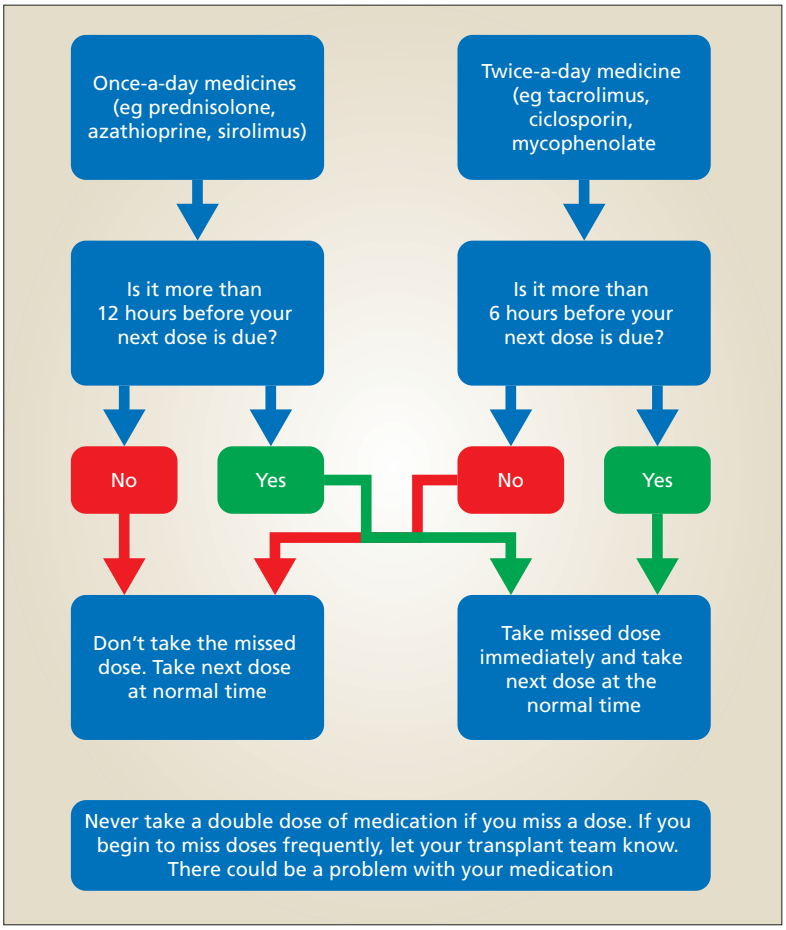

Figure 1. What to do if you miss doses of your medication

medicines will cause problems with blood levels of ciclosporin, tacrolimus and sirolimus and should only be used where there is no suitable alternative and with careful monitoring by a doctor or the transplant unit.

These are:

- Antimicrobial medicines – erythromycin, clarithromycin, ketoconazole, fluconazole, voriconazole, itraconazole, rifampicin
- Antiepileptic medicines – phenytoin, carbamazepine
- Blood pressure medicines – verapamil, diltiazem, nicardipine
- Always be safe and, if in doubt about a newly prescribed medication, always check with your transplant unit before taking.

Foods to avoid if taking ciclosporin, tacrolimus and/or sirolimus include grapefruit and star fruit, as they can increase blood levels of the immunosuppressant drug.

Can I become pregnant while taking immunosuppression?

Fertility may return quickly after receiving a transplant, so commencing a suitable form of contraception is important. It is recommended that women wait one to two years before trying for a family, to ensure that the lowest doses of immunosuppression are being used and the transplant is well established.

You should always discuss your wish to start a family with the transplant team first, as in some situations your immunosuppression medicines may need to be changed – this is the case for mycophenolate and sirolimus. You must inform the transplant unit immediately if you become pregnant, so that you can be reviewed and closely monitored.

Key points

- **Immunosuppressive medications must be taken every for the life of the transplant.**
- **If you are unable to take your medication for 24 hours, you must seek urgent medical advice.**
- **Do not accept a different brand of ciclosporin or tacrolimus, unless advised by the transplant team.**
- **Do not stop taking the medication without medical advice.**

Can I take herbal supplements or homeopathic remedies while on immunosuppression?

Always check with the transplant team before taking any herbal supplements. Some herbal remedies (such as echinacea) can boost the immune system, thus counteracting the immunosuppressive medicines and so should be avoided. Additionally, St John's wort should be avoided if you are taking ciclosporin, tacrolimus or sirolimus, as it can reduce the levels of these drugs in the blood, leaving you at risk of rejection. Some herbal supplements are also toxic to the liver, such as those containing kava. Remember – natural does not mean safe. Homeopathy, by virtue of its preparation, is extremely dilute and as long as it is supplied by a reputable company or registered homeopathic practitioner is generally considered safe to use.

What vaccines can I take while on immunosuppression?

All transplant patients should receive vaccination for swine (H1N1) flu and seasonal flu as they are at increased risk of developing severe complications during a flu outbreak. Flu vaccination programmes are run annually via GP surgeries and transplant patients should ensure they receive their dose as early as possible each autumn. However, the general rule is that transplant patients should avoid having any live vaccines as there is an increased risk they could actually develop the disease itself from the vaccine. Examples of live vaccines include yellow fever, mumps measles and rubella (MMR), oral polio, oral typhoid, smallpox and the Bacillus Calmette-Guérin (commonly known as the BCG) for tuberculosis.

Summary

Transplantation allows most patients to function normally again and offers an improved quality of life. However, following a transplant, you are required to take immunosuppressive medications every day to prevent organ rejection. A balance of immunosuppression is required to minimise the risk of rejection, but also to minimise opportunistic infections, cardiovascular risk, side-effects and malignancy in the transplanted individual ■