RENAL DISEASE

(4) IMMUNOSUPPRESSION AFTER ADULT RENAL TRANSPLANT

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The final article on renal disease deals with the drug treatment of patients who have had a kidney transplant

For many patients with chronic or end-stage renal failure (ESRF), kidney transplantation is the renal replacement therapy of choice. Unlike dialysis, it allows the majority of patients to function normally and offers a quality of life comparable to that of the general population.[1] It is also the most cost-effective therapy.[2] Unfortunately, kidney recipients are required to take immunosuppressive medication continuously to prevent allograft rejection.

Data from the United Kingdom Transplant Service Special Authority and the UK Renal Registry indicate that, in 1998,[3] only around 30 per cent of ESRF patients are on the active transplant waiting list at any time. This might be because of personal preference or because the patient is unsuitable for either surgery or immunosuppression. Between 1996 and 2000, a 13 per cent fall in transplants of cadaver origin was somewhat offset by an 80 per cent increase in living-donor operations (with the kidney usually donated by a relative). Despite this, the waiting list in the UK rose from 4,304 to 4,822 patients.

The changing pattern of organ donors is just one of the challenges when determining the optimum immunosuppressant drug combinations to give to kidney translplant recipients.

TRANSPLANT IMMUNOLOGY

Only a kidney donated to a recipient by an identical twin will be the same genetically. In all other cases, the organ will be recognised by the immune system of the new host as being foreign, and an immune response will attempt to destroy it. The risk of this is reduced by:

- Ensuring that the genetic make-up of the donor and recipient is closely matched (using human leukocyte antigen [HLA] tissue typing)
- Suppressing the immune system of the recipient with drugs for as long as the grafted kidney functions

Important antigens that are involved in rejection are those glycoproteins that are coded for by the histocompatibility complex of genes, and are found on the surface of cells. In man, the major histocompatibility complex is known as the HLA locus. HLA antigens vary between individuals, making perfect matching extremely difficult. Unfortunately, these antigens are also the strongest inducers of T-lymphocyte-mediated kidney rejection.[4] HLA tissue typing has been shown to reduce the frequency of rejection episodes, thus achieving a more successful outcome.[5]

Knowledge of the interaction of antigens with T-cells in the rejection process is essential to understanding how immunosuppressive drugs work. Donor HLA molecules are presented via antigen-presenting cells to resting T-cells that have receptors for that specific antigen. This recognition process activates the T-cells, which produce and secrete cytokines (eg, interleukins) and express cell-surface receptors to them (eg, interleukin-2 receptors). The lymphocyte colony recognises the donor HLA antigen, and differentiates and proliferates under the influence of interleukin-2 (IL-2), which has been called T-cell growth factor. Cytotoxic T-cells bind directly to donor cells and lyse them. Other T-cell sub-sets produce more cytokines (eg, IL-4 and interferon-γ) which lead to B-lymphocyte involvement, antibody production, complement fixation and macrophage infiltration.[6] The result is destruction of graft tissue, which impairs the ability of the transplanted kidney to function.

Previous exposure of a recipient to other HLA antigens (eg, from blood transfusions, previous transplants or pregnancy) increases the likelihood of rejection. The risk can be quantified using the panel reactive antibody (PRA) test, in which the higher the percentage score the greater the recipient's sensitivity. If the PRA score is greater than 85 per cent, the potential recipient is considered to be highly sensitised and might require additional or stronger immunosuppression.

The ABO blood group of the donor and recipient of a kidney must be compatible. In addition, blood should be cross-matched before the transplant operation to ensure that the recipient does not have existing antibodies against donor lymphocytes.

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TYPES OF REJECTION

Rejection is usually categorised into one of the following:

- Hyperacute — this occurs within hours of the transplant operation, and is rare because of the HLA tissue typing and blood cross-matching tests that are carried out before surgery
- Acute — this usually occurs within the first few months after a transplant and is common (around 50 per cent of patients experience acute rejection in the three months after transplant). After the first year, acute rejection is less likely to occur. Acute rejection is suspected when there is a sudden rise in serum creatinine. In addition, the patient might experience an increase in blood pressure, reduced urine output, or pain over the transplanted kidney. To confirm the diagnosis, a small sample of tissue from the new kidney is taken (tru-cut needle biopsy) which is examined microscopically for signs of rejection. Treatment is then started accordingly.
- Chronic — this is more correctly called chronic allograft failure. It occurs insidiously at least one year after the transplant operation. The mechanisms involved are not clearly understood and there is no treatment. Renal function deteriorates inexorably over a few months, resulting in a return to dialysis. This is the most common cause of transplant failure after the first year.

PREVENTING ACUTE REJECTION

Corticosteroids Most recipients receive glucocorticoids early after transplantation. A starting dose of around 20mg of prednisolone daily is typical in the United Kingdom. This is gradually reduced after a few weeks. The eventual maintenance dose depends largely upon events that occur after surgery (eg, infections, rejection episodes and adverse effects). The anti-inflammatory effects of steroids affect most of the cells associated with initiation of a rejection episode (eg, macrophages). At maintenance doses, steroids block the release and inhibit the action of cytokine interleukins, and interfere with T-cell activation. They inhibit macrophage function and prostaglandin production.[7,8]

The adverse effects of steroids are well known but are of great importance in a population in which graft survival depends on compliance. In addition to minimising the dose, many patients require further treatment to limit complications (ie, bisphosphonates to treat osteoporosis). All patients should carry a steroid card.

Antimetabolites Two purine antimetabolites are currently licensed for the prevention of renal transplant rejection in the UK — azathioprine and mycophenolate mofetil. Although the two drugs have different mechanisms, both achieve their primary effect by preventing activated lymphocytes from differentiating and proliferating and thereby limit clonal expansion.

Azathioprine Azathioprine has been a central component of most renal transplant immunosuppression regimens since its development in the late 1950s.

Oral forms of azathioprine are generally used at doses between 1 and 3mg/kg body weight per day. It can be given once daily, or in divided doses to minimise gastrointestinal effects. Intravenous formulations are only used when patients are temporarily unable to take the drug by mouth (most centres assume dose equivalence to the oral formulation). The abbreviation AZT should not be used, as it can be confused with the anti-viral zidovudine, which has the same abbreviation.

Azathioprine is well absorbed when given orally. It is extensively and rapidly metabolised to 6-mercaptopurine (6-MP). This is further metabolised within cells to thioguanine nucleotides, which interfere with RNA and DNA synthesis. The major route of elimination of 6-MP is via xanthine oxidase to produce thiouric acid. If drugs that inhibit this enzyme, such as allopurinol, are given concomittantly, a 75 per cent reduction in azathioprine dose is required. Penicillamine and other agents with myelosuppressive effects should generally be avoided in patients who are taking azathioprine. Azathioprine can reduce the anticoagulant effect of warfarin.

Azathioprine is associated with reversible, dose-dependent depression of bone marrow. This most frequently presents as leucopenia but it can also inhibit platelet formation and cause anaemia. Nausea is experienced by about one in five patients.[9,10] This can be relieved by taking a dose after food and separately from any concurrent steroids. Azathioprine can cause cholestasis and deterioration of liver function but these are generally reversible on withdrawal. More serious hepatic veno-occlusive disease has also been reported but is rare. Hair loss associated with azathioprine is uncommon.

Mycophenolate mofetil Licensed as the mofetil ester in 1995, mycophenolic acid (MPA) was first isolated from a penicillium culture almost 100 years earlier. It is available as a 250mg capsule, 500mg tablet and intravenous preparation for short-term use. The licensed dose for renal transplant is 1g twice daily, although some centres have used lower doses in their immunosuppression regimens.

When used at the licensed dose in regimens commonly chosen in the UK, mycophenolate mofetil has reduced the number of acute rejection episodes from 36 per cent to 20 per cent compared with azathioprine. However, more patients are unable to tolerate it and kidney survival one year post-transplant is no better than with azathioprine.[9]

Acute rejection episodes are considered a risk factor for poorer long-term graft survival,[11] and it had been hoped that using agents such as mycophenolate might result in improved long-term outcomes. A study of United States Renal Registry data shows a decreased incidence of chronic graft failure with mycophenolate.[12] In the UK, the drug has generally been used in selected patients who were considered to be at a higher risk of rejection than normal. Some centres are converting patients to mycophenolate to "spare" ciclosporin in patients with chronic graft dysfunction.

The addition of the ester moiety to mycophenolate mofetil greatly improves the bioavailability (94 per cent) of mycophenolic acid.[10] The active form inhibits inosine monophosphate dehydrogenase (IMPDH). This enzyme is the rate-limiting step in the synthesis of guanosine nucleotides. Lymphocytes are dependent upon IMPDH for these DNA building blocks and have no salvage pathway, unlike other cell lines. The result is prevention of their proliferation.[10]

Mycophenolate has significant gastrointestinal adverse effects but its absorption is decreased if it is administered with cholestyramine or magnesium- and aluminium-containing antacids.

Mycophenolic acid does not distribute well into cells and is mainly present in the plasma bound to albumin. It undergoes enterohepatic recirculation and its principal metabolite is an inactive glucuronide conjugate, which is excreted renally. Drugs that compete for tubular secretion (eg, aciclovir) could decrease clearance of the conjugate. Tacrolimus has been shown to increase the area under the curve of unconjugated mycophenolic acid and some centres will use lower doses of the latter when these two drugs are combined.[10]

Excluding infection, the most frequently observed adverse effects have been gastrointestinal complications and haematological reactions. Mycophenolate causes more vomiting, diarrhoea and anaemia than azathioprine but less nausea and leucopenia.[9,10]

Panel 1: Drugs that affect cytochrome P450

Drugs that inhibit cytochrome P450 can increase ciclosporin, tacrolimus and sirolimus blood levels. They include:

- Macrolide antibiotics (eg, erythromycin, clarithromycin)
- Imidazoles (eg, ketoconazole, fluconazole)
- Diltiazem
- Verapamil
- Cimetidine
- Danazol

Drugs that induce cytochrome P450 can reduce ciclosporin, tacrolimus and sirolimus levels. They include:

- Antiepileptics (eg, phenytoin, carbamazepine, phenobarbitone)
- Rifampicin
- St John's wort

Calcineurin inhibitors Ciclosporin and tacrolimus are calcineurin inhibitors that work early in T-cell activation. T-cell activation involves a series of cascades, and the enzyme calcineurin is one of the rate-limiting points.

Calcineurin is the target of both ciclosporin and tacrolimus complexes, which inhibit it and prevent transcription of the genes encoding interleukin-2 (IL-2) and other cytokines that cause early T-cell activation.

Ciclosporin binds to an immunophilin (a cytoplasmic protein) called cyclophilin A. Tacrolimus binds to another class of immunophilins known as FK binding proteins (FKBP), specifically FKBP-12.

Ciclosporin, tacrolimus and sirolimus are metabolised in the liver via the cytochrome P450 pathway (specifically the cytochrome P450 3A4 isoenzyme). Any drug that affects this system can have an impact on these immunosuppressants (see Panel 1).[13] Counselling points for patients taking these drugs are given in Panel 2.

Ciclosporin There are currently two brands of ciclosporin available in the UK — Sandimmun and Neoral — but generic formulations are being developed. Sandimmun is available only on a named-patient basis from Novartis, and patients carry an identity card stating their patient number. All new transplant patients who start on a ciclosporin-based regimen are now given Neoral.

The different ciclosporin preparations are not interchangeable without specialist supervision and monitoring. It is critical, therefore, that patients do not accidentally switch brands because this can lead to an unnecessary risk of graft rejection, graft loss or complication associated with drug toxicity. The British National Formulary recommends that prescribers should specify which ciclosporin brand is required on each prescription because of the differences in bioavailability.[14]

Doses of ciclosporin used vary according to local practice. However, a typical initial oral dose would be 4mg/kg twice daily. Doses are adjusted according to pre-dose (trough) whole-blood concentrations. After six months or so, target ranges are reduced to aim for lower-dose maintenance therapy. Ciclosporin levels are measured using an EMIT assay. Typical target levels would be:

- 0–6 months, 150–300ng/ml
- Over 6 months, 75–150ng/ml

Some units are now performing C_2 monitoring, ie, measuring blood concentrations two hours post-dose. C_2 is thought to predict more accurately individual patient absorption than traditional trough monitoring, and results in a reduced incidence of acute rejection episodes and acute renal dysfunction.15

Overall, the bioavailability of Neoral is 50 per cent (that of oral Sandimmun is 20 per cent).[16] If intravenous (IV) dosing is required, the total oral dose must be reduced to one-third and given as a divided dose 12-hourly, to provide an equivalent IV dose.

Ciclosporin is 50 per cent bound to erythrocytes, 10 per cent to leucocytes and 30–40 per cent to plasma proteins. Only 1–6 per cent exists in a free state,[17] with 80–90 per cent bound to lipoproteins in plasma.[18] Ciclosporin is extensively metabolised in the liver and bowel under the influence of cytochrome P450 3A4, so pharmacokinetic interactions are common (see Panel 1). It is primarily eliminated by biliary excretion with a median half-life of 6–8 hours.

The major adverse effects of ciclosporin are nephrotoxicity, hirsutism, hyperlipidaemia, glucose intolerance, hypertension, tremor, gingival hyperplasia, and hyperuricaemia. Although ciclosporin nephrotoxicity is largely dose-dependent, chronic toxicity also occurs, necessitating the drug's withdrawal (and possible change to sirolimus or mycophenolate-based regimens) to attenuate the decline in renal function.

Tacrolimus Most units start with an oral dose of 0.1mg/kg twice daily, either for use as primary immunosuppression or as rescue therapy.[19] Doses are adjusted according to trough blood levels and, after a few months, target ranges are reduced to aim for lower dose maintenance therapy. Tacrolimus whole blood trough levels are measured using an Abbott IMX assay and typical desired levels would be:

- 0–6 months, 10–15ng/ml
- After 6 months, 5–10ng/ml

Oral bioavailability of tacrolimus is about 20 to 25 per cent,[20] and food appears to reduce the rate and extent of absorption significantly. However, IV dosing is avoided, where possible, because the IV formulation is incompatible with PVC. If given IV, it should be given as a continuous infusion, and the dose administered should be one-third of the total oral dose.

Tacrolimus binds extensively to erythrocytes, so whole blood is necessary for therapeutic drug monitoring. In plasma, the drug is 99 per cent bound to plasma proteins. Like ciclosporin, tacrolimus is almost completely metabolised, primarily by the liver and to a lesser extent the intestinal mucosa, by cytochrome P450 3A4 isoenzyme (see Panel 1).[20] The reported elimination half-life is variable but the mean value for renal transplant recipients is 19 hours.[20]

The most common side effects of tacrolimus are nephrotoxicity, diabetes, tremor and headache.

Sirolimus and SDZ-RAD Sirolimus (formerly known as rapamycin), and its more water-soluble analogue SDZ-RAD, act later in T-cell activation than ciclosporin and tacrolimus. Sirolimus, like tacrolimus, binds to FKBP-12 but the complex formed has no effect on calcineurin. Instead, it binds to the

Panel 2: Counselling points for patients taking calcineurin inhibitors (ciclosporin and tacrolimus) or sirolimus

CICLOSPORIN ONLY

- It is important to maintain good dental hygiene by cleaning and flossing your teeth regularly, to avoid gum infections.

TACROLIMUS ONLY

- Take your tacrolimus one hour before or two hours after food (eg, at 10am and 10pm) because food can affect the oral absorption of tacrolimus.

SIROLIMUS ONLY

- Take your sirolimus 30 to 60 minutes before food, with water or orange juice
- If you are also taking ciclosporin, take your sirolimus about four hours after the morning dose of ciclosporin (ie, about midday, 30 to 60 minutes before lunch)
- Keep sirolimus liquid in a fridge and discard one month after first opening
- Only use the syringes provided with the liquid once
- The daily dose can be carried at room temperature in a syringe with a cap in the case provided
- You must not become pregnant or father a child while on sirolimus, and for three months after stopping the drug

POINTS COMMON TO ALL THREE DRUGS

- On clinic days, bring the morning dose to clinic and take after your blood test
- Avoid eating grapefruit or drinking grapefruit juice, as some of its components and can increase ciclosporin blood levels. This is likely to occur with tacrolimus and sirolimus, too.[32-34]
- Always check with a pharmacist, doctor or nurse before taking any new medicines (prescribed or over-the-counter) in case they interact with your calcineurin inhibitor or sirolimus.

TABLE 1: ADMINISTRATION REGIMENS OF MONOCLONAL ANTIBODIES

Drug	Dose	Dose interval	Number of doses
Basiliximab	20mg	At day 0 and day 4 only	Two
Daclizumab	1mg/kg bodyweight	At day 0 and then at 14 day intervals	Five

mammalian target of rapamycin (mTOR) and inhibits IL-2-mediated signal transduction pathways. Sirolimus is not nephrotoxic, which gives it an advantage over ciclosporin and tacrolimus. In clinical trials, sirolimus has been used both as an adjunct to calcineurin inhibitor-based immunosuppression and in place of calcineurin inhibitors to avoid nephrotoxicity.[21]

Wyeth-Ayerst Laboratories have recently launched sirolimus as Rapamune in the UK in spring 2001. It is available as an oral solution (1mg/ml). Rapamune is taken once a day and the dose can be adjusted according to trough blood levels.

Sirolimus has a mean elimination half-life of 60 hours.[22] It is poorly absorbed, with a reported bioavailability of 15 per cent.[23] It is primarily bound (95 per cent) to erythrocytes. In plasma, it is extensively bound (92 per cent) to plasma proteins. Sirolimus is metabolised in the liver by cytochrome P450 3A4 isoenzymes (see Panel 1). Its metabolites are excreted primarily via bile in the faeces.

The main adverse effects of sirolimus are hypercholesterolaemia, hypertriglyceridaemia, thrombocytopenia, hypertension and nosebleeds.

Interleukin-2 receptor antibodies Two very similar drugs — basiliximab and daclizumab — have recently been licensed in the UK for use at the time of renal transplant surgery. These monoclonal antibodies (mAbs) are given as infusions before surgery and then as in Table 1. They exert their immunosuppressant effect only over the first few weeks post-transplant. Both are licensed for use in combination with ciclosporin and steroids, which then form the base-line therapy.

Both mAbs work by binding specifically to part of the IL-2 receptor that is only expressed on activated T-lymphocytes. This sub-unit increases the sensitivity of the receptor to IL-2. Inactivating it helps to prevent proliferation of antigen-stimulated T-cells. Unlike older antibody preparations that have sometimes been used as induction therapy (ie, muromonab or anti-thymocyte globulin), neither of these drugs affects the resting T-lymphocyte population.

Basiliximab is a chimeric human/mouse mAb and daclizumab is a genetically engineered, humanised mAb (with less than 10 per cent mouse regions). These manipulations disguise the mouse portion, preventing recipient antibody formation and extending the half-lives. The changes might also account for the different affinities to CD25 demonstrated by their respective potency.[24]

Compared with placebo, basiliximab reduces biopsy-proven acute rejection episodes at six months by around 30 per cent.[25,26] Daclizumab reduces biopsy-confirmed acute rejection episodes by 37 per cent when used with ciclosporin, azathioprine and prednisolone.[27]

Neither mAb has any known drug interactions, but perhaps the most appealing characteristic of these drugs is that they do not appear to add to the adverse effects of concurrent therapies. In clinical trials, the incidence of adverse effects, malignancy and infection has not differed significantly between drug and placebo.

IMMUNOSUPPRESSION REGIMENS

For adult renal transplant recipients in the UK, the most common immunosuppression combination remains triple therapy with ciclosporin, azathioprine and prednisolone. However, with an ever-growing number of drugs available to prevent rejection and an increasing understanding of how these drugs work, the aim is to fit the immunosuppressive regimen used much more specifically to the clinical profile of the patient.

Patients who have received more than one transplant require more immunosuppression than those having their first, and might need ciclosporin, mycophenolate, steroids and IL-2 antibody.

Those identified by tissue typing as being at greatest risk of rejection could benefit from a more potent immunosuppressive regimen, such as tacrolimus with mycophenolate, corticosteroids and an IL-2 receptor antibody at the time of transplantation.

It is becoming increasingly possible to select immunosuppressive regimens for individual patients according to the adverse events that they are at risk of suffering. For instance, in patients at high risk of developing diabetes, the use of steroids should be minimised and tacrolimus used with care. There is still considerable potential to be unlocked in the use of the currently available immunosuppressive agents.

The problem of acute rejection has largely been resolved by the use of effective immunosuppression. The challenge now is to use emerging therapies, such as mAbs, along with non-nephrotoxic maintenance therapy to reduce the rate of chronic allograft failure.

TREATMENT OF ACUTE REJECTION

If a biopsy shows that acute rejection is taking place, or there is a strong suspicion that it might be, patients should be given high-dose intravenous corticosteroids. Methylprednisolone 500mg–1g is given as a slow IV infusion daily for at least three days. Often, this will suppress the rejection process and serum creatinine levels will fall towards baseline. If not, either a second course is given or stronger antibody therapy (eg, anti-T-cell antibodies derived from an animal source) could be considered.

There are three types of antibodies used and each, invariably, leads to resolution of rejection:

- ATG — anti-thymocyte globulin (rabbit)
- ALG — anti-lymphocyte globulin (horse)
- OKT3 — muromonab (mouse)

ATG and ALG are administered as slow infusions over 6–8 hours via a central line. OKT3 is given as a peripheral bolus injection. These antibodies are usually given daily for 10–14 days, depending on the patient's response. Some units administer them according to absolute T-cell or lymphocyte count, which results in intermittent dosing.[28]

All three agents can cause severe adverse effects, especially with the first dose (eg, rigors, fever and pulmonary oedema). This is associated with the release of cytokines and other intracellular inflammatory mediators from ablated T-cells. To lessen these first-dose effects, patients are given pre-medication consisting of IV corticosteroids, chlorpheniramine and oral paracetamol. In addition, with the horse and rabbit infusions, a test dose is given to identify possible allergic reactions to animal protein.

Any acute rejection episode is deemed a failure of the patient's immunosuppression, and their current regimen must be reviewed. Examples of changes that can be made are:

- After treatment of a second rejection episode, calcineurin inhibitors can be changed (eg, ciclosporin to tacrolimus). This is referred to as rescue therapy.
- Evidence of vascular changes on biopsy can provoke a change of antimetabolite (eg, azathioprine to mycophenolate).

COMMON PROBLEMS

Most of the drugs that suppress the immune system will, in addition to their particular adverse effect profile, increase the incidence and/or severity of infectious complications. Increased rates of malignancy have also been reported. These effects have a number of implications for those prescribing for renal transplant recipients.

Infection Infection is the most common problem in kidney transplant patients, particularly in the early weeks and months after surgery, when immunosuppressive doses are greatest.

Urinary tract infections (bacterial and fungal), re-emergence of dormant tuberculosis, cytomegalovirus disease and pneumonia caused by the protozoan *Pneumocystis carinii*, are complications that have organ- and life-threatening implications. Patients often receive oral prophylactic agents according to the unit protocol, such as antifungals and/or cotrimoxazole and/or antivirals (eg, aciclovir, valaciclovir or ganciclovir), for several months post-operatively.[29]

Malignancy One of the functions of the immune system is to fight cancer. Long-term immunosuppression, therefore, increases

the likelihood of developing some types of cancer. One UK study showed that the risk of developing neoplasia in the first 10 years after transplantation was 14 per cent, and, by 20 years, this had risen to 40 per cent, compared to a 6 per cent cumulative risk in an age-matched control population. More than half of the neoplasms were cutaneous lesions (mostly squamous cell carcinoma).[30]

Ultraviolet radiation is an important contributing factor to skin cancer and patients should be advised to protect their skin from excessive sun exposure. There is an increased risk of cervical cancer, and all women should be advised to have an annual cervical smear test. Post-transplant lymphoproliferative disease (lymphoma) occurs in about 3–4 per cent of renal transplant recipients and usually reflects a potent immunosuppressive regimen. There is no increased incidence of carcinoma of the lung, prostate, colon, rectum or breast.[31]

CONTRAINDICATED DRUGS

Some drug interactions have already been covered in Panel 1. Other relative contraindications to be aware of are:

- Non-steroidal anti-inflammatory drugs (including topical NSAIDs) should be avoided, unless prescribed by a specialist, with close monitoring of transplant renal function.
- Nephrotoxic drugs, such as amphotericin or gentamicin, should generally be avoided where possible in people who have had a transplant, particularly if the immunosuppression regimen is ciclosporin or tacrolimus-based.
- Any live vaccine (eg, yellow fever, mumps, measles and rubella [MMR], Bacillus Calmette-Guerin [BCG], oral polio, oral typhoid and smallpox) is contraindicated in patients taking immunosuppressive drugs.
- Some herbal remedies can boost the immune system and should be avoided in transplant recipients. Always check with a specialist transplant centre before advising a transplant patient.

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