Immunosuppression after Liver Transplantation

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The purpose of immunosuppression is to prevent the recipient's immune system from destroying or damaging the graft. Immunosuppression aims to balance under-immunosuppression leading to graft rejection and over-immunosuppression leading to sepsis and malignancy. There have been comparatively few studies on which to base a rational approach to immunosuppression. The types of immunosuppressants are 1) purine analogues such as 6-mercaptopurine (6-MP), 2) inhibitors of inosine monophosphate dehydrogenase such as myciphenolate mofetil (MMF), 3) glucocorticoids such as prednisone, 4) calcineurin binding drugs such as cyclosporin and tacrolimus, 5) TOR inhibitors such as sirolimus, and 6) mono- and polyclonal antibodies. There are five phases in the management of immunosuppression: 1) induction, 2) maintenance, 3) treatment of acute rejection, 4) treatment of chronic rejection, and 5) withdrawal of immunosuppression. Immunosuppression is complicated by intercurrent infection, usually viral or tubucular, and by pregnancy, breast feeding, diabetes mellitus, and renal impairment.

Keywords: liver transplantation; calicineurin inhibitors; anti-CD3

The purpose of immunosuppression is to prevent the body's immune system destroying or damaging the graft. Since currently available drugs are not specific for graft alloantigens, the clinician must maintain a balance between under-immunosuppression, leading to graft rejection, and over-immunosuppression, leading to the consequences of immunodeficiency such as sepsis and malignancy. The clinician should also be aware of, and attempt to minimize, the unwanted effects of long-term use of these agents.

In the early days of liver transplantation, the protocols for liver allograft recipients were derived by extrapolation from renal transplantation. It has become clear, however, that different approaches need to be adopted: for example, in liver allograft recipients, tolerance may develop and those strategies that aim to abolish early acute rejection may inhibit the development of tolerance. While acute rejection is associated with a poor outcome in renal transplantation, there is no evidence that acute cellular rejection, which is reversed by short periods of increased immunosuppression (so-called reversible acute cellular rejection), has any untoward effect on liver graft survival.

There have been comparatively few studies on which to base a rational approach to immunosuppression: the success of liver transplantation has meant that to demonstrate significant improvement in graft survival or a reduction in the immunosuppressive-related morbidity, a large number of patients need to be followed for long periods of time. In the present climate, this is usually difficult. Furthermore, the introduction of newer agents, or improved formulations of existing drugs, means that the conclusions of randomized trials may be superseded before results are available.

Most centers have adopted a common approach to the principles of immunosuppression but differ significantly in the details. Therefore, in this article, the principles of immunosuppression will be outlined together with a description of the conse-

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Table 1 | **PHYSICAL METHODS OF IMMUNOSUPPRESSION**

Types of physical immunosuppression include
Blood transfusion
Removal of lymphocytes:
Leucophoresis
UV or total body irradiation
Thoracic duct drainage
Thymectomy, splenectomy
Plasmaphoresis
Photophoresis after lymphocyte priming

quences of over-immunosuppression. Details of those drugs that are currently available and those shortly to be licensed will be described.

Drugs and Other Agents Used in Immunosuppression

The drugs and other agents and procedures used for immunosuppression are shown in Table 1, and details of those drugs and agents licensed for immunosuppression are shown in Tables 2 to 13.

Types of Immunosuppression

Immunosuppression may be physical or pharmacological. Physical methods, as shown in Table 1, are rarely used in liver transplantation.

Medications Used for Immunosuppression

Purine Analogues

Azathioprine has been used for many years in transplantation (see Table 3). It is metabolized by thiopurine methyltransferase to the active component 6-mercaptopurine (6-MP), an analogue of the natural purines hypoxanthine and adenine. 6-MP is then metabolized to thioinosine monophosphate, which inhibits synthesis of DNA precursor molecules and interferes with nucleic acid synthesis during clonal expansion of lymphocytes. People who have low levels of thiopurine methyltransferase are more susceptible to the side effects of azathioprine but may tolerate 6-MP.

The rationale for long-term use of azathioprine is not well established, although several studies have suggested an increased probability of chronic rejection in patients not taking azathioprine. Following the introduction of azathioprine (usually at a dose of 1-2 mg/kg/day), the white count should be monitored twice monthly for 3 months: if the white count falls below 4.0 × 10.9/l, the dose should be halved; if the white count falls below 3.0 × 10.9/l, azathioprine should be discontinued. Veno-occlusive disease and hepatitis are the most serious forms of liver dysfunction associated with azathioprine and usually develop within the first 6 months.

MMF

Mycophenolate mofetil

IMPDH

Inosine monophosphate dehydrogenase

6-MP

6-mercaptopurine

IMPDH Inhibitors (Table 4)

Mycophenolate mofetil acts by inhibition of inosine monophosphate dehydrogenase; it is colloquially referred to as MMF.

Glucocorticoids

These agents have both anti-inflammatory and immunosuppressive effects. The glucocorticoids bind to the glucocorticoid receptor, and the complex then translocates to the nucleus where, after binding to DNA, protein synthesis is affected. Among the intranuclear functions altered by glucocorticoids is synthesis of nuclear factor kappa B (NF-κB), resulting in apoptosis of lymphocytes. There are many different glucocorticoids used in transplantation, and the potency on a weight-for-weight basis varies and is summarized in Table 5.

There is increasing evidence that corticosteroids can be withdrawn by 3 months or earlier in most liver transplant recipients. In contrast, some centers maintain corticosteroids in patients grafted for autoimmune hepatitis to prevent recurrent disease in the allograft (see Table 6).

Table 2 | **Pharmacological Methods of Immunosuppression**

Types of pharmacological immunosuppression include
Depletion of lymphocytes
Polyclonal antibodies to lymphocytes (e.g., ALG, Thymoglobulin)
Monoclonal antibodies to lymphocytes (e.g., OKT3)
Inhibition of lymphocyte activation
Corticosteroids
Immunophilin-binding drugs
Calcineurin-inhibitors:
Cyclosporin
Tacrolimus
TOR inhibitors: Sirolimus (formerly known as rapamycin)
Inhibitors of de novo nucleotide synthesis
Purine synthesis inhibitors (IMPDH inhibition)
Mycophenolate mofetil
Mizoribine
Pyrimidine synthesis inhibitors (DHODH inhibition)
Leflunomide
Brequinar
Antimetabolites
Azathioprine
Cyclophosphamide
Inhibition of lymphocyte activation/trafficking/interaction
Inhibition of trafficking
FTY720
Inhibition of interactions
Antibodies to ICAM-1
Antibodies to IL2-R
CTLA-4 Ig

Table 3 | **Immunosuppressive Drugs: Azathioprine**

Drug Name	Azathioprine
Mechanism of action	Anti-metabolite; metabolized to 6-mercaptopurine and then active agent interferes with DNA and RNA synthesis so inhibits T and B lymphocyte differentiation and proliferation
Side effects	Leukopenia (significant 15%)
	Nausea and vomiting
	Hepatotoxicity (especially veno-occlusive disease)
	Pancreatitis
	Pneumonitis
	Megaloblastosis
Dosage	1-2 mg/kg/day
Drug interactions	Allopurinol (avoid) ACE inhibitors
Notes	Used as a second-line drug

CALCINEURIN INHIBITORS

Cyclosporin and tacrolimus

Calcineurin-Binding Drugs (Tables 7 and 8)

Both cyclosporin and tacrolimus bind to immunophilins, which are widely distributed intracellular proline isomerases. Cyclosporin binds to cyclophilin and tacrolimus to the FK-binding protein, which results in inhibition of calcineurin, which inhibits activation of transcription factors such as NFATc, a transcriptional factor responsible for the calcium activation of cytokine genes during the immune response. Other downstream effects

Table 4 | **Immunosuppressive Drugs: Mycophenolate Mofetil**

Drug Name	Mycophenolate Mofetil
Mechanism of action	Prevents T- and B-cell proliferation by inhibition of de novo purine synthesis by inhibition of inosine monophosphate dehydrogenase (IMPDH)
Side effects	Diarrhea (15%) Leucopenia (5%) anemia, thrombocytopenia, Rarely GI hemorrhage and perforation hematuria, hypertension, hyperglycemia, disturbances of electrolytes and blood lipids, peripheral edema, dyspnea, cough, dizziness, insomnia, tremor. Hypersensitivity reactions
Dosage	1 to 2 g/day in divided doses
Drug interactions	May compete with drugs that undergo active renal tubular secretion: Probenecid, Acyclovir Some antacids and cholestyramine reduce absorption
Notes	Teratogenic in animals. Used as alternative to azathiprine or in calcineurin-inhibitor sparing protocols

Table 5 | **Equivalence of Corticosteroids**

Prednisolone/Prednisone	5 mg
Betamethasone	750 μg
Cortisone acetate	25 mg
Deflazacort	6 mg
Dexamethasone	750 μg
Hydrocortisone	20 mg
Methylprednisolone	4 mg
Triamcinolone	4 mg

Derived from the British National Formulary (2000).

Table 6 | **Immunosuppressive Drugs: Corticosteroids**

Drug Name	Prednisolone/Prednisone
Mechanism of action	Anti-inflammatory; stimulates migration of T cells from intravascular tissue to lymph nodes; inhibits production of T-cell lymphokines
Side effects	Increased tendency to diabetes mellitus
	Osteoporosis
	Impaired wound healing and increased skin bruising
	Sodium and fluid retention, potassium depletion
	Hypertension
	Muscular weakness, myopathy, and muscle wasting
	Aseptic necrosis especially of femoral head
	Cataracts, glaucoma, raised intraocular pressure
	Cushingoid facies
	Retardation of growth
	Headaches, pseudotumor cerebri
	Mood change (euphoria, hypomanic psychosis, depression)
	Weight gain
	May increase risk of peptic ulceration or retard ulcer healing
Dosage	Maintenance up to 20 mg/day; treatment of rejection 200 mg/day for 3 dats or 3 days
Drug interactions	NSAIDs
Notes	Other forms of steroids—See Table 5

Table 7 | Immunosuppressive Drugs: Cyclosporin

Drug Name	Cyclosporin
Mechanism of action	Binds to immunophilins (cyclophilin). Inhibition of T cells; suppresses T-cell activation by inhibiting synthesis and release of IL-2 and other lymphokines
Side effects	Renal impairment (30%-40%); hepatotoxicity (10%); hypertension (30%); gum hypertrophy (10%); hirsutism (40%); tremor (40%)
	Convulsions (3%)
	Headaches (40%)
	Hyperkalemia
	Hyperuricemia
	Gout
Dosage	Adjust to maintain trough whole blood levels (measured by RIA) between 100 and 250 ng/ml (target levels vary between centers and according to time after transplantation and graft function)
Drug interactions	See Table 9
Notes	Several formulations available: as they have different absorption profiles, the different formulations may not be interchangeable

Table 8 | **Immunosuppressive Drugs: Tacrolimus**

Drug Name	Tacrolimus
Mechanism of action	Binds to FK-binding protein 12; inhibits synthesis and release of IL-2
Side effects	Diabetes mellitus
	Hypertension
	Headaches
	Tremor
	Convulsions
	Nephrotoxicity
	Renal impairment
	Myocardial hypertrophy
Dosage	Maintain trough whole blood levels measured by RIA between 5 and 15 ng/ml. Target levels vary between centers, time after transplantation and renal and hepatic function
Drug interactions	See Table 9
Notes	Not licensed for use in pregnancy (although no evidence of increased teratogenicity compared with cyclosporin)

are thought to relate to some of the side effects of this class of drugs including diabetes and renal impairment.

Tacrolimus is well absorbed from the upper GI tract. Consequently, there is rarely an indication to give tacrolimus intravenously. The starting dose is 0.1 mg/kg/day in two divided doses: target levels for the first 3 months lie between 10 and 15 ng/ml (trough whole blood levels measured by RIA) and between 5 and 10 ng/ml thereafter.

Cyclosporin is fat soluble, and absorption is variable from the gut, especially in the early postoperative period when bile production and flow may be compromised. The microemulsion form is absorbed in a more consistent fashion, and there is rarely a need to administer cyclosporin intravenously. The starting dose is 8 mg/kg/day and the dose adjusted to trough whole blood levels between 150 and 200 ng/ml for the first 3 months and 100-150 ng/ml thereafter. However, measurement of blood levels taken 2 hours postdose (otherwise called C-2) may provide a better assessment of drug monitoring.

Tacrolimus and cyclosporin are metabolized by oxidation through the cytochrome P450 system. The liver is the main site of metabolism, although minor metabolism occurs in the gut. Drugs that induce or inhibit cytochromes P450, such as erythro-

Table 9 | **Drugs That Affect Levels and Toxicity of the Calcineurin Inhibitors and Sirolimus**

Increase levels (usually by inhibition of cytochrome P450 3A4 or reduced clearance)	Bromocryptine
	Cimetidine
	Cisapride
	Clarithromycin
	Danazol
	Diltiazem
	Erythromycin
	Fluconazole
	Grapefruit juice
	Itraconazole
	Ketoconazole
	Methylprednisolone
	Metoclopramide
	Nicardepine
	Statins (HMG CoA reductase inhibitors)
	Verapamil
	Protease inhibitors
Decrease levels (usually induction of cytochrome P450 3A4)	Barbiturates
	Carbamazepine
	Phenytoin
	Rifampicin
	St. John's wort (Hypericum)
Increase toxicity	Amphotericin B
	Cimetidine
	Gentamicin
	NSAIDs
	Ranitidine
	Tobramycin
	Vancomycin
Decrease toxicity	—

TARGET OF RAPAMYCIN (TOR) INHIBITORS

Sirolimus

mycin, ketoconazole, or rifampicin, interact with tacrolimus and cyclosporin and may affect drug levels. Drug interactions are listed in Table 9.

Calcineurin inhibitors (cyclosporin and tacrolimus) are the current mainstays of maintenance immunosuppression. Both agents are associated with significant side effects in the long term. There are several studies comparing the two drugs, and these suggest that tacrolimus may be superior. For both drugs, target levels have been derived from clinical experience, although the dose should be adjusted in the light of complications (such as renal impairment or symptoms such as headaches or tremors) and liver function.

TOR Inhibitors (Table 10)

Sirolimus (previously known as rapamycin) inhibits lymphocyte proliferation mediated by cytokines such as IL-2 and IL-4. Sirolimus, like tacrolimus, binds to the immunophilin called FK binding protein (FKBP), but it does not inhibit the calcineurin pathway. The sirolimus-immunophilin complex interacts with a protein kinase called TOR ("target of rapamycin") that is integral to a signal transduction pathway regulating the synthesis of proteins required for cell-cycle progression in both lymphoid and nonlymphoid cells.

Sirolimus is poorly absorbed from the gut. It is widely distributed in many tissues. The liver is the principal organ of metabolism, via the cytochrome P450 3A4 system. The half-life is approximately 50-70 hours in healthy subjects and renal transplant recipients and is considerably lengthened in patients with chronic liver dysfunction. The most frequently reported adverse effects in subjects receiving sirolimus are mild dose-related thrombocy-

Table 10 | **Immunosuppressive Drugs: Sirolimus**

Drug Name	Sirolimus (aka Rapamycin)
Mechanism of action	Inhibits T-cell activation
Side effects	Hyperlipidemia (40%)
	Hypercholesterolemia (40%)
	Thrombocytopenia
	Gastrointestinal disturbances
	Interstitial pneumonitis
	Hepatic artery thrombosis
	May impair wound healing
Dosage	2 mg/day
	Should be taken 4 hours after cyclosporin
	Monitoring of drug levels is not required in most patients (except in children, renal or hepatic impairment, with concurrent administration of enzyme inducers/inhibitors of CYP 3A4 or if cyclosporine discontinued)
Drug interactions	As for calcineurin inhibitors
Notes	Antiproliferative in vitro. May be effective in reducing malignant cell proliferation and in intimal call proliferation

Table 11 | **Immunosuppressive Drugs: Polyclonal Antibody Preparations**

Drug Name	Antithymocyte Globulin (ATG), Antilymphocyte Globulin (ATGAM)
Mechanism of action	Polyclonal antibodies raised in mammals against human lymphocytes or lymphocyte subsets
Side effects	Hypersensitivity; anaphylaxis; headache, dizziness, muscle pain, lymphopenia, leukopenia, thrombocytopenia (usually transient); nephrotoxicity
Dosage	Different preparations vary in their activity. See manufacturers instructions
Drug interactions	
Notes	Test for sensitivity before administration of first dose; Increases the risk of CMV. Use CMV prophylaxis in selected patients

topenia and leukopenia, and hyperlipidemia, affecting both serum triglycerides and cholesterol. Among the other effects reported include nausea, vomiting, hypertension, elevations in serum creatinine, elevations in liver-associated enzymes, and acne. Isolated cases of interstitial pneumonitis or hepatic arterial thrombosis have also been observed in patients receiving sirolimus.

Immunosuppressive Antibodies (Tables 11-13)

Antibodies may be mono- or polyclonal. Some preparations react with epitopes expressed by all lymphocytes, whereas others recognize epitopes expressed by subsets of lymphocytes only. All are profoundly immunosuppressive. Some centers use polyclonal antibodies to lymphocytes (e.g., ALG, Thymoglobulin) for induction (see Table 9).

Principles of Immunosuppression

The management of immunosuppression can be considered in five phases:

- Induction
- Maintenance
- Treatment of acute rejection
- Treatment of chronic rejection
- Withdrawal of immunosuppression

Induction of Immunosuppression

There is no consensus for the optimal method for induction of immunosuppression. Some centers use mono- or polyclonal antibodies, in combination with other immunosuppressive agents. Other centers use intraoperative corticosteroids.

Table 12 | **Immunosuppressive Drugs: Monoclonal Antibodies to T Lymphocytes**

Drug Name	Anti-CD3
Mechanism of action	Binds to and blocks the CD3 receptor on T cells and prevents signal transduction
Side effects	Treatment is associated with a cytokine release reaction ("shake and bake syndrome") which may be severe. Pretreatment with methylprednisolone may prevent the syndrome. Other side effects include profound lymphopenia, seizures, encephalopathy, aseptic meningitis, cerebral edema, and anaphylactic responses (such as wheezing, rigors, and hypertension)
Dosage	5 mg/day intravenously for 10-14 days
Drug interactions	Avoid the concomitant use of NSAI s and cyclosporin (increased CNS side effects), corticosteroids (increased risk of psychosis)
Notes	Muromonab-CD3 is a monoclonal antibody; should be avoided in patients with anti-murine antibody titers > 1:1000, uncompensated fluid overload, or patients with heart failure or with a history of seizures. Avoid in pregnancy or breastfeeding

Table 13 | **Immunosuppressive Drugs: Antibodies to IL-2 Receptor**

Drug Name	Basiliximab; Daclizumab (Antibodies to IL-2 Receptor)
Mechanism of action	These bind to and block the alpha unit of the IL-2 receptor on activated T cells and so inhibit IL-2 binding and inhibit IL-2 activation
Side effects	Anaphylaxis
Dosage	See below
Drug interactions	None known
Notes	There are two preparations: Basiliximab is a chimeric monoclonal antibody and is given at a dose of 20 mg within 2 hours of surgery and at 4 days (children below 15 years have a smaller dose). Daclizumab is a humanized monoclonal antibody: the dose is 1 mg/kg/dose for 5 doses, the first within 24 hours of transplantation. The initial dose required for liver transplants may be greater than for other solid organ recipients due to loss of antibody in ascites drained at laparotomy, and in ascitic or pleural fluid drained during the perioperative period

ANTIBODIES TO IL-2 RECEPTOR

Basiliximab and daclizumab

Maintenance of Immunosuppression

Currently most centers use a combination of corticosteroids, azathioprine, and a calcineurin inhibitor, although some use monotherapy (calcineurin inhibitor alone) or dual therapy (calcineurin inhibitor with azathioprine or mycophenolate), but there are few data to define the optimal regime. The introduction into clinical practice of newer drugs such as sirolimus will allow the clinician to tailor the immunosuppressive regime more closely to the patient.

Treatment of Acute Rejection

Acute rejection should, whenever possible, be confirmed prior to treatment using histology obtained by liver biopsy; fine needle aspiration biopsy is used occasionally. Although many serological markers in blood and bile have been described, none has been shown to be of adequate sensitivity and specificity to confirm rejection. It is rarely possible to distinguish reliably between rejection and infection without histology.

The mainstay of immunosuppression for early acute rejection is high-dose corticosteroids: regimes vary between centers, and there are no good data to demonstrate superiority of any one regime. Typical regimes are

- Prednisolone 200 mg/day for 3 days
- Methyl prednisolone 0.5-1 g/day for 3 days

The rate of reduction of corticosteroid pulses to maintenance steroids varies from center to center.

Treatment of Chronic Rejection

Chronic rejection of the liver allograft has many names: chronic ductopenic rejection, vanishing bile duct syndrome, chronic rejection. Chronic ductopenic rejection may lead to loss of the graft. It is treated by increased immunosuppression, including conversion to tacrolimus from cyclosporin or switching to sirolimus.

Withdrawal of Immunosuppression

The observation that some patients have maintained long-term good graft function after discontinuing immunosuppression has led some centers to embark on carefully controlled trials of withdrawal of all immunosuppression in long-term (>5 years) survivors with good graft function, or in subjects with major impediments to continued use of immunosuppressants, such as malignant disease. These studies have demonstrated that it is possible to withdraw all immunosuppression in about 20% of carefully selected patients. The remainder required maintenance immunosuppressants or their reintroduction if they had been stopped. The usual reason for failure to withdraw immunosuppressants was late onset acute cellular rejection, which was then controlled by adjusted phamacotherapy. Those recipients grafted for non-autoimmune diseases, without episodes of acute rejection and with a good HLA match, are more likely to be able to withdraw immunosuppression.

Side Effects of Immunosuppression

The side effects of immunosuppression may be due either to

- The effect of immunosuppression itself (especially infection and malignancy)
- The effects of individual drugs

Tailoring the Immunosuppression to the Individual

Since different drugs have differing effects and side effects both on the patient and the disease, it is important not to adopt one regime for all patients but to tailor the drug regime for the individual. The probability of developing acute rejection is, in part, dependent on the indication for transplantation so that patients grafted for viral hepatitis (especially B) and alcohol-associated liver disease have a much lower probability of developing early rejection than those grafted for autoimmune diseases such as PBC or AIH.

Intercurrent Bacterial Infections

Currently available immunosuppressants will not only reduce the risk of rejection but also predispose the patient to infection. The balance between over- and under-immunosuppression is even more difficult to maintain in the presence of active sepsis. The general approach is to reduce the immunosuppression but the onset of graft rejection may not only herald the need for high-dose immunosuppression but hepatic impairment is associated with a further reduction in the host defenses against infection. In the presence of bacterial infection, early detection and vigorous treatment with appropriate antimicrobials is clearly required; depending on liver function, steroids should be reduced initially. Remember, however, in maintaining the balance between rejection and infection, with rejection the graft will be lost, but with infection the patient will be lost.

Intercurrent Viral Infection

The most common viral infection during the early postoperative period is cytomegalovirus (CMV). CMV is associated with chronic rejection: this may be related to a direct effect of CMV on the biliary epithelial cells and, in part, to the reduction in immunosuppression. It is important, therefore, to reduce the immunosuppressive therapy in association with active antiviral treatment. A common practice is to stop azathioprine and reduce the calcineurin inhibitor.

Tuberculosis

Because of the severe course of reactivation of tuberculosis in the patient on immunosuppression, most centers use prophylactic treatment with isoniazid 100 mg/day in those at risk. Isoniazid should be given with pyridoxine. Treatment should be for at least 1 year.

Retransplantation for Chronic Rejection, Late Acute Rejection, and Early Ductopenic Rejection

These are associated with an increased risk of developing graft loss, and therefore many centers are

using a combination of corticosteroids, tacrolimus, and mycophenolate or sirolimus.

Comorbid Conditions

Pregnancy and Breast Feeding

If the recipient is likely to become pregnant after transplantation, consideration should be given to the appropriate choice of drugs.

Diabetes Mellitus

The tendency of calcineurin inhibitors to induce diabetes mellitus is controversial. Tacrolimus may be more diabetogenic than cyclosporin. Most transplant programs do not switch from tacrolimus to cyclosporin, on account of diabetes mellitus. Those diabetics given corticosteroids may have an increased requirement for insulin or oral agents.

Renal Impairment

Renal impairment may occur following transplantation for many reasons (such as IgA nephropathy, HCV-associated glomerulonephritis, diabetic nephropathy, or associated with the inappropriate prescription of nonsteroidal anti-inflammatory drugs or nephrotoxic drugs such as gentamicin). In the presence of perioperative renal failure, some centers avoid the use of calcineurin inhibitors. If renal impairment develops in association with calcineurin inhibitor use, most centers will reduce or discontinue the calcineurin inhibitor.

Development of Lymphoma and Other Malignancy

Lymphoma posttransplantation may be associated with EBV infection. Treatment is with aggressive therapy of the lymphoma and a reduction in the immunosuppressive regime; some centers discontinue all immunosuppression during chemotherapy.

Suggested Reading

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