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MEDICATION GUIDELINES FOR SOLID ORGAN TRANSPLANTS

BC TRANSPLANT
Provincial Health Services Authority

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Introduction

Patients who undergo solid organ transplant require lifelong immunosuppression to prevent organ rejection. In organ transplantation, the ideal form of immunosuppression is to induce donor specific tolerance without impairing the host defences or increasing the susceptibility to infection from all types of organisms.

The most common immunosuppressants prescribed for solid organ transplant recipients are:

- ***Calcineurin Inhibitors:***
  - ***Cyclosporine***
  - ***Tacrolimus***
- ***Mycophenolic Acids:***
  - ***Mycophenolate Mofetil***
  - ***Mycophenolate Sodium***
- ***Azathioprine***
- ***Sirolimus***
- ***Prednisone***
- ***Basiliximab***
- ***Anti-thymocyte Globulin***

Each of these drugs has its own adverse effect and toxicity profile that may result in serious morbidity or mortality. Careful management of these complications by the patient and the transplant team is critical to transplant success.

BC Transplant funds the following outpatient immunosuppressants for solid organ and pancreatic islet cell transplant recipients who have BC Medical Services Plan coverage and are registered with BC Transplant, when the guidelines are followed:

Outpatient Immunosuppression:

- Calcineurin Inhibitors:
  - Cyclosporine
  - Tacrolimus IMMEDIATE Release
  - Tacrolimus EXTENDED Release
- Mycophenolic Acids:
  - Mycophenolate Mofetil
  - Mycophenolate Sodium
- Azathioprine
- Sirolimus
- Prednisone

Inpatient Immunosuppression

BC Transplant funds the inpatient immunosuppressant basiliximab and etanercept for pancreatic islet cell transplant when the guidelines are followed.

Special Outpatient Medications Required to Maintain Transplant

In addition to immunosuppressants, solid organ transplant recipients often require other outpatient medications which are needed to maintain the integrity of the transplant and are very important in a patient's medication regimen. BC Transplant covers the cost of the following medications if the guidelines are met:

Erythropoiesis - Stimulating Agents:

- Epoetin
- Darbepoetin

Granulocyte Colony Stimulating Factor – Hematopoietic Agents:

- Filgrastim

Anti-Viral Agents:

- Valganciclovir
- Lamivudine
- Tenofovir
- Entecavir
- Leflunomide
- Letermovir
- Maribavir

Anti-thymocyte globulin (ATG)

INTRODUCTION

Anti-thymocyte globulin (ATG) is a pasteurized solution of rabbit-derived polyclonal IgG antibodies directed against human T cells, produced by immunization of rabbits with human lymphocytes.
This monograph will focus on its use in solid organ transplants. ATG is funded by the inpatient pharmacy drug budget and not covered by BC Transplant.

MECHANISM OF ACTION

ATG is a potent immunosuppressant and immunomodulator whose mechanisms of action are not fully understood.

The mixture of antibodies recognizes key receptors on T-cells, resulting in complement-dependent T-cell lysis and opsonisation of T-cells with subsequent phagocytosis by macrophages. Thymopoiesis is also impaired, resulting in a decrease in the number of newly formed T-cells. This causes a substantial drop in the number of circulating T-cells, hence reducing the risk of organ rejection.

The usual magnitude is a greater than 90% reduction in the number of circulating T-cells. The duration of lymphopenia lasts around 3 months for most patients, though some have had sustained lymphopenia for over 1 year post-ATG.

ATG has shown benefits for patients at high risk of delayed graft function (DGF), potentially due to reducing ischemia-reperfusion injury by inflammatory mediators produced from T-lymphocytes.

PHARMACOKINETICS

Absorption / Onset:

T-cell depletion is usually noted within 1 day of the first ATG dose.

Distribution:

The volume of distribution of ATG is approximately 2 times plasma volume.

Distribution into breast milk is unknown, though other immunoglobulins do enter breast milk.

Metabolism:

Likely removed via opsonisation by the reticuloendothelial system if bound to T-cells, or via human antibody production.

Elimination:

Plasma half-life is variable (1.5 to 30 days[5], usually 2 to 3 days).

ATG remains active for days to weeks post-treatment.

The primary route of elimination is via cellular uptake with subsequent proteolytic degradation. Hence, no dosage adjustment is required in renal or hepatic impairment.

THERAPEUTIC USE

ATG is used at induction of immunosuppression to prevent transplant rejection in patients:

- at high immunological risk of rejection (i.e. recipients with greater than 80% calculated panel-reactive antibodies (cPRA), or those who have previously rejected one or more transplants within 1 year post-transplant)
- at high risk of delayed graft function due to DCC or ECD donors.
    - DCC: donation after death by circulatory criteria, ECD: expanded criteria donor (donor age greater than 60 years old, or donors aged 50 to 59 with 2 of the 3 features: hypertension, diabetes, terminal SCr >132 umol/L, or death resulting from stroke)
- Low and intermediate immunological risk patients are generally treated with basiliximab for induction.

ATG is also administered for the treatment of acute rejection.

CONTRAINDICATIONS

Known hypersensitivity to rabbit proteins or any ingredient of the formulation, history of anaphylaxis with ATG, Epstein-Barr Virus mismatch, and acute infections which contraindicate further immunosuppression.

DRUG INTERACTIONS

Live vaccinations should not be administered to patients taking ATG or within 6 weeks of their scheduled transplant.
ATG has additive risks of infection and malignancy when used in combination with other immunosuppressants.

ADVERSE DRUG REACTIONS

Cytokine release syndrome associated with ATG administration frequently causes high grade fevers (over 39º C), chills and possibly rigors during or shortly after infusion. In severe cases, cardiorespiratory depression and death may rarely occur. To prevent or minimize febrile reactions, patients should be pre-treated with antipyretics (acetaminophen 650mg to 1000mg) and/or antihistamines (diphenhydramine 25mg to 50mg), and / or corticosteroids (methylprednisolone). Slowing the infusion rate may also be of benefit. For pediatric patients, acetaminophen 15 mg/kg/dose, diphenhydramine 1 mg/kg/dose.

Anaphylaxis occurs in less than 1% of patients. It may occur at any time during therapy and may present as hypotension, respiratory distress, or pain in the chest, flank, or back. If anaphylaxis occurs, the preparation should be discontinued immediately and standard treatments started (e.g. epinephrine).

Serum sickness has been reported in 5 to 10% of patients, which presents as fever, rash, arthralgias and / or myalgias. This usually occurs within 5 to 15 days of ATG therapy.

Thrombocytopenia and leukopenia occur in about 14% and 30% of patients respectively. Severe and prolonged lymphocytopenia may last over 1 year.

Due to the substantial drop in the number of circulating T-cells, infection and malignancy risk are significantly increased. Infections include bacterial, fungal, and viral infections with potential reactivation of latent infections (e.g. CMV); infections can be severe and may present as sepsis, so prophylaxis against certain infections such as CMV and PCP is essential if clinically indicated. Malignancies such as lymphoma and post-transplant lymphoproliferative disorder (PTLD) are significantly more common than basiliximab.

Other frequently reported adverse effects (incidence >25%) include fever, chills, diarrhea, headache, myalgias, nausea, peripheral edema, shortness of breath, weakness, tachycardia, and hypertension.

Area of Effect	Adverse Effect
CNS	Chills (55-57%), fever (46%), headache (27-40%), pain (26%), insomnia (12-20%), malaise (9-13%), serum sickness (2%)
CV	Hypertension (27-37%), tachycardia (23%), peripheral edema (20%), hypotension (10-16%)
Resp	Dyspnea (15-26%)
GI	Abdominal pain (17-38%), nausea (29-37%), diarrhea (20%), vomiting (20%), constipation (15%)
GU	None
Endo	None
Derm	Rash (7-13%), diaphoresis (6-13%), acne (12%) Injection site reactions (pain, erythema, swelling)
MSK	Myalgia (11-20%), arthralgia (15%), weakness (13%)
Heme	Leukopenia (49-57%) Neutropenia Lymphopenia (>90%) Thrombocytopenia (29-37%) Anemia (12%) Malignancy (e.g. PTLD, lymphoma) (4%)
ID	Infections (bacterial, fungal, viral, protozoal) (17%) Reactivation of latent infections (e.g. CMV – 13%) Sepsis (12%)
Other	Hypersensitivity reactions Infusion reactions / cytokine release syndrome

DOSE AND ADMINISTRATION

Most studies using ATG have based dosing calculations on actual body weight. Some preliminary studies have suggested that using ideal body weight results in similarly low rates of acute rejection with lower cost and fewer adverse effects, but this strategy requires further evaluation before it should become a new standard of practice.

Prophylactic antiviral therapy (e.g. valganciclovir) and antimicrobial therapy (e.g. nystatin mouth wash, sulfamethoxazole-trimethoprim) should be given during ATG therapy, if indicated.

Doses should always be rounded down to the nearest 25 mg increment in adult patients.

The degree of lymphopenia may be helpful to assess the degree of T-cell depletion.

Dose reductions:

Reduce ATG dose by 50% if white blood cells (WBCs) are between 2 to $3x10^9$ cells/L or if platelets are between 50 to $75x10^9$ cells/L.

Consider holding or discontinuing ATG if WBCs are less than $2x10^9$ cells/L or platelets are less than $50x10^9$ cells/L.

Kidney Transplant Recipients (Adult and Pediatric):

Induction for high immunologic risk transplant candidates (i.e. cPRA ≥80%):

ATG 1.5 mg/kg/dose IV once daily for 4 days, ideally given intra-operatively
Total cumulative ATG dose of 6 mg/kg.

Induction for high donor risk (high risk for delayed graft function):

ATG 1 mg/kg/dose IV once daily for 3 days, ideally given intraoperatively
Total cumulative ATG dose of 3 to 4.5 mg/kg as per patient clinical status

Treatment of acute rejection:

ATG 1.5 mg/kg/dose IV once daily. Total cumulative ATG dose of 6.0 to 7.5 mg/kg.

Administration

Refer to hospital's IV manual for detailed administration guidelines.

Safety is not established for peripheral line administration, and there is an increased risk of deep vein thrombosis and thrombophlebitis. If there is no alternative other than a peripheral line, "administration via peripheral line" must be written as a component of the order, so that pharmacy can add hydrocortisone 20 mg and heparin 1000 units to the IV solution of saline (dextrose may cause precipitant and is no longer recommended). If peripheral line is not specified, hydrocortisone and heparin will NOT be added, risking complications.

AVAILABILITY

Antithymocyte globulin rabbit (Thymoglobulin® Genzyme Corporation) is available in 25 mg/5 mL vials for injection.

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Azathioprine

INTRODUCTION

Azathioprine is an immunosuppressant antimetabolite that belongs to the thiopurine drug class and may be used in combination protocols. In the past azathioprine was used routinely for maintenance therapy to prevent rejection following solid organ transplantation. Azathioprine is no longer used routinely in post-transplant immunosuppression protocols but may be used in certain circumstances.

MECHANISM OF ACTION

Azathioprine is a purine analog that is incorporated into cellular DNA, where it inhibits purine nucleotide synthesis and interferes with the synthesis and metabolism of RNA.

PHARMACOKINETICS

Azathioprine is well absorbed from the gastrointestinal tract. Azathioprine is a prodrug for mercaptopurine. The thiopurine S-methyltransferase (TPMT) is involved in the metabolism of all thiopurines and is one of the main enzymes that inactivates mercaptopurine. Azathioprine is primarily metabolized to two active metabolites: 6-mercatopurine and 6-thionosinic acid. Only one to two percent of the drug is eliminated unchanged by the kidneys.

THERAPEUTIC USE

Azathioprine may be used as maintenance therapy in conjunction with other immunosuppressive agents to prevent organ transplant rejection in patients who are unable to tolerate the gastrointestinal effects of mycophenolic acids, have an increased incidence of infection while on mycophenolic acids or in female transplant recipients who are considering pregnancy.

Prior to initiating azathioprine therapy, it is recommended thiopurine S-methyltransferase (TPMT) genotyping be determined. This allows for patients at increased risk for myelosuppression to be identified, for starting dose of azathioprine to be reduced, or an alternative therapy to be prescribed. TPMT testing must receive Health Insurance of BC approval. Refer to LifeLabs website

Kidney and Kidney/Pancreas Transplant Recipients

Physicians must consult the patient's primary transplant centre if azathioprine is being considered. Azathioprine may be used in patients who cannot tolerate the gastrointestinal toxicity of mycophenolate mofetil, have an increased incidence of infection while on mycophenolate mofetil, or in female transplant recipients who are considering pregnancy. Azathioprine is not a preferred immunosuppressant in a patient who is on a steroid-free protocol.

Lung Transplant Recipients

Mycophenolate mofetil has replaced azathioprine post-transplant. There are some patients currently receiving azathioprine who have an intolerance to mycophenolate. If patients are stable on azathioprine there is no benefit to switching them to mycophenolate mofetil.

Heart Transplant Recipients

Mycophenolate mofetil has replaced azathioprine post-transplant. There are some patients currently receiving azathioprine who have an intolerance to mycophenolate. If patients are stable on azathioprine there is no benefit to switching them to mycophenolate mofetil.

Liver Transplant Recipients

TPMT genotyping will not be done in liver transplant recipients.

ADVERSE DRUG REACTIONS

Azathioprine Adverse Drug Reactions

Area of Effect	Adverse Effect	Symptoms
Hematologic	***Bone marrow depression Infection	Leukopenia Megaloblastic anemia Pancytopenia Thrombocytopenia
Gastrointestinal	Nausea and vomiting Anorexia Diarrhea Ulceration of oral mucosa Esophagitis with possible ulceration Steatorrhea	
Hepatic	Hepatotoxicity Hepatic veno-occlusive disease	Increased alkaline phosphatase Increased bilirubin
Other	Alopecia Retinopathy Hypersensitivity reaction Rash, fever Serum sickness Arthralgias Cutaneous effects Pulmonary effects Hypotension Pancreatitis	

*** Bone marrow suppression is dose dependent and may be reversed by reducing the dose of azathioprine. However, people who inherit two non-functional TPMT alleles universally experience life-threatening myelosuppression. For this reason, it is recommended that TPMT genotyping or phenotyping be done prior to starting

azathioprine. Dean L. Azathioprine therapy and TPMT genotype. Medical Genetics Summaries, Bethesda: National Center for Biotechnology

DRUG INTERACTIONS

Xanthine oxidase inhibitors (allopurinol and febuxostat (Uloric®) :
Azathioprine is metabolized by xanthine oxidase. Xanthine oxidase inhibitors (allopurinol and febuxostat) may inhibit azathioprine metabolism, thus resulting in increased azathioprine activity and toxicity when administered concurrently. If possible, concurrent use of xanthine oxidase inhibitors and azathioprine should be avoided. If concurrent use is required, the azathioprine dose should be reduced and the patient carefully monitored for bone marrow suppression.

Concurrent use of angiotensin-converting enzyme inhibitors (i.e., captopril, enalapril) may induce anemia as well as severe leukopenia.

Azathioprine may inhibit the anticoagulant effect of warfarin.

DOSE AND ADMINISTRATION

ADULT Kidney Transplant Recipients
If azathioprine is to be used, a maintenance adult dose of approximately 1.5 mg/kg/day PO is given once daily. Dosages are adjusted according to the white blood cell count. Decrease dose for white blood cell count less than 3.0 x 10^9/L.

PEDIATRIC Kidney Transplant Recipients
Pediatric azathioprine dosing is 1.5 to 3 mg/kg/day PO once daily.

ADULT Liver Transplant Recipients
If azathioprine is to be used, initial adult dosage of azathioprine is 1 mg/kg/day PO given once daily, rounded off to the nearest 25 mg. Dosages are adjusted according to the white blood cell count.

ADULT Lung Transplant Recipients
If azathioprine is used, the maintenance adult dose is approximately 1.5 to 2 mg/kg/day PO, rounded off to the nearest 25 mg. Consider reducing the dose if the patient has gastrointestinal intolerance or adjust the dose according to the white blood cell count.

ADULT Heart Transplant Recipients
If azathioprine is used, the maintenance adult dose is 25 to 100 mg PO daily.

AVAILABILITY

Azathioprine is available for oral use as a 50 mg tablet. Azathioprine tablets are available from several drug manufacturers.

Basiliximab

INTRODUCTION

Basiliximab is a monoclonal antibody, which is produced by recombinant DNA technology. It is a chimeric antibody in which the murine constant region of the immunoglobulin is replaced by human amino acid sequences. Mouse variable regions are combined with the constant region of human IgG1 immunoglobulin. Basiliximab is less immunogenic and has a much longer half-life than the murine monoclonal antibodies [1].

Basiliximab inhibits T-cell proliferation by inhibition of a portion of the interleukin-2 (IL-2) receptor. IL-2 receptor antagonists have been shown to reduce the incidence of acute graft rejection in renal transplant recipients without increasing the incidence of opportunistic infections or malignancy [1-3].

Basiliximab has been shown to reduce renal transplant rejection within 6 months of transplant in low-risk patients [4-9].

MECHANISM OF ACTION

Basiliximab binds to the alpha chain of the IL-2 receptor on the surface of activated T-lymphocytes. It functions as a competitive inhibitor of IL-2, inhibiting CD25 mediated stimulation of lymphocytes, a critical event in the process of allograft rejection. By binding specifically to activated T-lymphocytes, inactive T-lymphocytes are not affected [1,5,7].

PHARMACOKINETICS

The mean initial concentration of basiliximab ranges from 5 to 10 microgram/mL. Basiliximab volume of distribution in the central compartment is reported to be 3.1 or 4.9 L in adults and 1.7 L in children, consistent with blood and plasma distribution [5, 8]. The terminal elimination half-life is estimated to be between 7 and 14 days [2, 5, 8]. Body weight or gender does not affect clearance. Among adult patients, elimination half-life is not influenced by gender, age (20 to 69 years) or race. Compared to adults, children (2 to 15 years old) have a lower clearance and longer half-life (11.5 days [5, 8]). The plasma concentration necessary to saturate IL-2 receptors is approximately 0.2 microgram/mL. After two doses of basiliximab, the duration of saturation of IL-2 receptors was four to six weeks in adult kidney transplant recipients [4-8].

THERAPEUTIC USE

Basiliximab is indicated for the prophylaxis of acute renal transplant rejection as part of an induction immunosuppressive regimen. The safety and efficacy of basiliximab has been investigated in kidney transplant clinical trials that have compared it to placebo in patients receiving cyclosporine and steroids [2, 4, 6, 8, 9].

The safety and efficacy of basiliximab has been reported in liver transplant recipients. Several clinical trials comparing basiliximab to placebo have demonstrated a lower rate of rejection in patients receiving cyclosporine, azathioprine and steroids [10-12].
The trials have concluded that the addition of basiliximab result in a reduction in the number of rejection episodes compared with a placebo or historical control with no increased of malignancies, infections, or other side effects [2, 4, 6, 8-12].

Kidney and Kidney-Pancreas Transplant Recipients
Basiliximab is indicated for prophylaxis of kidney transplant rejection in the following patients immediately post-transplant:

- Kidney and kidney-pancreas recipients from deceased or living donors with one or more HLA mismatch.
- Kidney and kidney-pancreas recipients who are defined as "low" and "intermediate" risk. "Intermediate risk" recipients are those patients who have received a previous transplant, or are a multi-organ recipient.
- Basiliximab is usually not indicated for kidney and kidney-pancreas recipients who are considered "high-risk" as defined by a PRA of 80 or greater and/or previous transplant lost within one-year post transplant. Basiliximab may be prescribed in high risk patients at the discretion of the nephrologist. If basiliximab is not indicated, high-risk patients should receive anti-thymocyte globulin as induction therapy.

Basiliximab is indicated for prophylaxis of kidney transplant rejection in the following patients for calcineurin inhibitor (CNI) replacement therapy. Prior to beginning basiliximab for CNI replacement, physician must submit in writing to BC Transplant, patient criteria for use. Each case will be considered on a case-by-case basis.
Patient must have:

- confirmed CNI nephrotoxicity (biopsy-proven)
- serum creatinine does not decrease in response to a decrease in CNI dose
- an increase of serum creatinine greater than 50% over baseline
- patient's glomerular filtration rate must be less than 40 mL/min
- patient must not be in a clinical trial

Liver Transplant Recipients
Basiliximab is for standard induction therapy in liver transplant recipients with impaired renal function, in patients with a risk of developing renal dysfunction, and in patients whom are not able to tolerate calcineurin inhibitors early post-transplant. Impaired renal function is defined as a creatinine clearance of less than 50 mL/min or a serum creatinine greater than 150 micromole/L at time of transplant. The use of calcineurin inhibitors can be delayed until renal function has recovered after transplantation.

Lung Transplant Recipients
Basiliximab is indicated for prophylaxis of transplant rejection in all lung transplant recipients.

Basiliximab may be considered under exceptional circumstances in patients with calcineurin inhibitor (CNI) toxicity. Prior to beginning basiliximab for CNI replacement, physician must submit in writing to BC Transplant, patient criteria for use. Each case will be considered on a case-by-case basis.

Adult Heart Transplant Recipients

Basiliximab is indicated for prophylaxis of transplant rejection in all adult heart transplant recipients immediately post-transplant.

The heart transplant team does use basiliximab for other indications which include calcineurin inhibitor sparing pre and post-surgery to prevent nephrotoxicity. The use of basiliximab in these cases is not currently funded by BC Transplant.

ADVERSE DRUG REACTIONS

Although data is limited, basiliximab is well tolerated. Administration of this agent has not been associated with significant clinical toxicity or cytokine release syndrome (fever, chills, headache, and pulmonary edema), which is commonly observed with muromonab-CD3 therapy. Adverse effects observed among patients treated with basiliximab are similar to those treated with placebo [5, 6]. However, hypersensitivity reactions can occur. Medications for hypersensitivity reactions should be available for immediate use during the administration of these agents [7].

Administration of basiliximab does not appear to influence the frequency or severity of known immunosuppressive effects. Incidence of infection and frequency of malignancy, including lymphoproliferative disorders, was not increased when compared to placebo [5-8]. No clinically relevant changes in leukocyte counts or absolute lymphocyte counts have been noted during treatment [5, 6]. A small percentage (1.4%) of patients have developed anti-idiotype antibodies when treated with basiliximab. Detection of anti-idiotype antibodies was not associated with increased rejection or adverse reactions [5, 6, 8].

The effects of basiliximab on fertility and fetal harm are unknown. Basiliximab cannot be recommended for use in pregnancy unless the potential benefits outweigh potential risk to the fetus [7].

DRUG INTERACTIONS

No drug interactions have been reported. Basiliximab does not appear to interact pharmacokinetically with cyclosporine or tacrolimus. No significant increase in adverse reactions has been reported with basiliximab in combination with corticosteroids, azathioprine, acyclovir or ganciclovir [5-8].

DOSE AND ADMINISTRATION

ADULT Kidney and Kidney-Pancreas Transplant Recipients

For adults and adolescents 15 years old and older: 20 mg IV given on day 0, prior to transplant surgery (ideally intra-operatively), followed by 20 mg IV given on day 4 after transplantation [7].

PEDIATRIC Kidney Transplant Recipients
For adolescents and children 2 to 15 years old: <35 kg: 10 mg IV given on day 0 prior to transplant surgery, followed by 10 mg IV given on day 4 after transplantation. >35 kg: 20 mg IV given on day 0 prior to transplant surgery, followed by 20 mg IV given on day 4 after transplantation.

ADULT Liver Transplant Recipients
20 mg IV given on day 0, either intra-operatively or immediately after transplant surgery, followed by the second dose, 20 mg IV given on day 4 after transplantation.

ADULT Lung Transplant Recipients
20 mg IV given on day 0, intra-operatively or immediately after transplant surgery, followed by the second dose, 20 mg IV given on day 4 after transplantation.

ADULT Heart Transplant Recipients
20 mg IV given on day 0, intra-operatively, followed by the second dose, 20 mg IV given on day 4 post transplantation.

AVAILABILITY

Basiliximab (Simulect® Novartis Pharmaceuticals) is available as a powder for reconstitution for IV use in 20 mg/5 mL vials [7].

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Cyclosporine

INTRODUCTION

Cyclosporine is a potent immunosuppressant used for the prophylaxis and treatment of graft rejection following solid organ transplantation. The narrow therapeutic range and variability of the pharmacokinetics of cyclosporine requires monitoring of blood concentrations in the management of transplant recipients.

MECHANISM OF ACTION

The immunosuppressive effect of cyclosporine is mediated through inhibition of T-lymphocyte function with minimal activity against B-cells. It is known that cyclosporine inhibits the production and release of interleukin 2 (IL-2) (T-cell growth factor) from activated T-helper cells. IL-2 is necessary for the proliferation of cytotoxic T-lymphocytes in response to antigen challenge. The expression of IL-2 receptors on precursor cytotoxic T-cells are also inhibited. This inhibition results in decreased proliferation of activated cytotoxic T-cells, the cells responsible for the rejection of transplanted tissue.

In contrast, cyclosporine has little effect on the activation and proliferation of suppressor T-cells. B-cell differentiation and function, required for normal antibacterial defences, appear to be resistant to cyclosporine. As a result of the selectivity of cyclosporine, it is possible to suppress T-cell mediated cellular immunity without adversely affecting the B-cell mediated humoral immunity.

PHARMACOKINETICS

Cyclosporine Neoral® is a microemulsion formulation. The absorption phase for cyclosporine occurs over the first 4 hours after oral administration. This phase is characterized by rapid changes in blood cyclosporine concentrations and a high degree of inter- and intra-patient variability. This phase demonstrates the individual patient's capacity to absorb cyclosporine from the gastrointestinal tract, which is dependent on concurrent medications, integrity of the gastrointestinal tract and other patient-specific factors. Cyclosporine Neoral® is distributed largely outside the blood volume. In the blood, 33 to 47% is present in plasma, 4 to 9% in lymphocytes, and 41 to 58% in erythrocytes. In plasma, approximately 90% is bound to proteins, mostly lipoproteins. Cyclosporine Neoral® is extensively metabolized to approximately 15 metabolites. There is no single metabolic pathway. Elimination is primarily biliary, with only 6% of the oral dose excreted in the urine; only 0.1% is excreted in the urine as unchanged drug. The half-life of cyclosporine is approximately 18 hours (range 7.7 to 26.9 hours) with a high variability reported on depending on the assay used and type of transplant patient has received.

THERAPEUTIC USE

Cyclosporine is approved for solid organ transplant rejection prophylaxis and treatment. Cyclosporine may be used alone or in combination with other immunosuppressants.

CONTRAINDICATIONS

Cyclosporine is contraindicated in all patients with a hypersensitivity to cyclosporine.

ADVERSE DRUG REACTIONS

Nephrotoxicity

The most frequently reported adverse effect of cyclosporine is reversible nephrotoxicity. Elevated cyclosporine blood concentrations are thought to increase the risk of nephrotoxicity. Cyclosporine nephrotoxicity is particularly troublesome in renal transplant recipients as it may be difficult to differentiate from graft rejection. The incidence of nephrotoxicity increases when cyclosporine is administered with other nephrotoxic agents, including amphotericin B and aminoglycosides.

Other Side Effects

Other frequently observed side effects include hypertension, hirsutism, tremors, gingival hyperplasia and hepatotoxicity. Hypertension may be difficult to control in these patients and is seen most frequently in cardiac transplant recipients (53% versus 13 to 26% in renal transplant recipients). Hirsutism may be treated with depilatory creams, electrolysis, or shaving. Gingival hyperplasia may be controlled by proper oral hygiene and regular dental check-ups. Both hirsutism and gingival hyperplasia are reversible upon discontinuation of cyclosporine. Hepatotoxicity, manifested by an increase in direct and total bilirubin, is also reversible upon dose reduction or discontinuation of the drug.

Hypersensitivity

Hypersensitivity reactions have been reported in patients receiving intravenous cyclosporine. Symptoms include flushing, shortness of breath, hypotension and anaphylaxis. The reaction is believed to be due to poly-oxyethylated castor oil (cremophor-E), a surfactant present in the IV solution. Patients who have experienced a hypersensitivity reaction while on IV cyclosporine have subsequently received oral cyclosporine without a reaction.

Cyclosporine Adverse Drug Reactions

Area of Effect	Adverse Effect
Renal	Nephrotoxicity
Cardiovascular	Hypertension
Nervous System	Tremors Seizures * Headache Paresthesia * Confusion *
Dermatologic	Hirsutism Gingival hyperplasia Acne
Hepatic	Hepatotoxicity
Gastrointestinal	Diarrhea Nausea and vomiting Anorexia Abdominal discomfort Gastritis Hiccups Peptic ulcer
Infectious	Pneumonia Septicemia Abscesses Urinary tract, viral, local and systemic fungal infections Skin and wound infections
Hematologic	Leukopenia Anemia Thrombocytopenia Lymphoproliferative diseases
Sensitivity Reactions	Anaphylactic response to IV Cyclosporine*
Other	Hyperlipidemia Sinusitis Gynecomastia Edema Fever Hearing loss

* Rare

DRUG INTERACTIONS

Cyclosporine interacts with many drugs. Refer to Appendix A for significant drug-drug and pharmacodynamic interactions. Drugs that inhibit liver microsomal enzyme function can impair the metabolism of cyclosporine, leading to increased cyclosporine blood concentrations and toxicity. Alternatively, enzyme-inducing drugs increase the metabolism of cyclosporine and may result in lowered cyclosporine blood levels and increased risk of transplant rejection.

DOSE AND ADMINISTRATION

The cyclosporine dose will vary according to the dosage form, type of transplant, patient factors, time post-transplant and hospital protocols. Dosage must be individualized for the best therapeutic effect with minimal toxicity.

Cyclosporine is not prescribed in liver transplant recipients with hepatitis C or renal dysfunction.

The route of cyclosporine **administration** depends on the type of transplant received and the patient status. Immediately post-transplant heart, pancreas and kidney transplant patients receive intravenous cyclosporine. Oral cyclosporine is administered as soon as oral intake is tolerated. Patients with malabsorption syndromes or liver transplants should receive intravenous cyclosporine therapy until adequate absorption can be ensured. The intravenous dose of cyclosporine (Sandimmune IV®) is one third the oral cyclosporine (Neoral®) dose.

Oral cyclosporine (Neoral®) is available both in capsule and liquid form. The solution should be used within two months of opening the amber glass container. Once the solution has been measured with an oral syringe, the dose may be mixed with milk, apple juice or orange juice to mask the bitter taste (in a glass or ceramic cup only). ***Do not*** use grapefruit juice as the drink, as grapefruit juice has been shown to inhibit cyclosporine metabolism, thus increasing cyclosporine concentrations. The same drink should be mixed with the cyclosporine each time. Once mixed, the solution should be taken immediately.

For patients requiring a switch from cyclosporine to tacrolimus, an estimated conversion of 40:1 (cyclosporine dose to tacrolimus) can be used a starting point.

Therapeutic Drug Monitoring

Cyclosporine has a narrow therapeutic index; thus, therapeutic drug monitoring is required.

Cyclosporine exposure as determined by the area under the concentration time curve (AUC_{0-12}) has been shown to correlate with clinical events.

Studies demonstrate that the AUC in transplant patients is ideal for minimizing cyclosporine toxicity and promoting its efficacy. However, full AUC measurements are impractical for use as a monitoring tool in a clinical setting.

Evidence shows that the monitoring of cyclosporine at the 2-hour concentration point (C_2) is the most accurate single time point for assessment of cyclosporine absorption and immunosuppressive effect. By monitoring C_2 target concentrations in renal and liver transplant recipients one can more accurately adjust the patients' cyclosporine dose to minimize toxicity and rejection rates. However C_2's are not done in all patients, some program use cyclosporine trough concentration measurements.

In British Columbia, the tandem mass spectrometry is the assay used for the determination of cyclosporine blood concentrations due to its high specificity. The assay is done at Vancouver General Hospital, St. Paul's Hospital, Victoria General Hospital, and LifeLabs®. Blood for cyclosporine assays from Northern Health and Interior Health are sent to Vancouver General Hospital. Note that IH switched from the Siemens Immunoassay at Royal Inland Hospital to the mass spectrometry assay at Vancouver General Hospital on April 22, 2024. When reviewing the literature and results, it is important to know which assay was used as the results are not comparable.

Target Cyclosporine Blood Concentrations for Solid Organ Transplant Recipients

Time Post Transplant (Months)	Cyclosporine Trough Concentration (ng/mL) Tandem Mass Spectrometry Assay	Cyclosporine C_2 Concentration (ng/mL) Tandem Mass Spectrometry Assay
ADULT Kidney and Kidney Pancreas Transplant Recipients (Oct 2014)		
Less than 1 months	300 to 350	1300
1 to 2 months	250 to 300	1100
3 to 6 months	150 to 250	800 to 900
7 to 12 months	125 to 200	700
Greater than 12 months	75 to 125	450-600
ADULT Liver Transplant Recipients (May 2021)**		
0 to 3 months	200 to 250	Not used
3 to 12 months	150 to 200	Not used
Greater than 12 months	100 to 125	Not used
** **Cyclosporine C_2** is not routinely used in liver transplant recipients		
ADULT Lung Transplant Recipients (Oct 2022)		
0 to 6 months	300 to 350	Not used
6 to 12 months	200 to 300	Not used
Greater than 12 months	100 to 200	Not used

Target Cyclosporine Blood Concentrations for Solid Organ Transplant Recipients cont'd

Time Post Transplant (Months)	Cyclosporine Trough Concentration (ng/mL) Tandem Mass Spectrometry Assay	Cyclosporine C_2 Concentration (ng/mL) Tandem Mass Spectrometry Assay
ADULT Heart Transplant * (Nov 2014)**		
C_2 targets when eGFR is greater than 45 mL/min/1.73 m^2		
Less than 1 month	Not used	1200 to 1400
2 to 3 months	Not used	1000 to 1200
4 to 5 months	Not used	800 to 1100
6 to 12 months	Not used	700 to 1000
12 to 24 months	Not used	600 to 800
Greater than 24 months	Not used	400 to 600
C_2 targets when eGFR is less than 45 mL/min/1.73 m^2		
Less than 1 month	Not used	1000 to 1200
2 to 3 months	Not used	800 to 1100
4 to 5 months	Not used	700 to 900
6 to 12 months	Not used	600 to 800
12 to 24 months	Not used	400 to 600
Greater than 24 months	Not used	300 to 400
Cyclosporine trough targets		
0 to 3 months	300 to 350	Not used
3 to 6 months	200 to 300	Not used
6 to 12 months	150 to 250	Not used
Greater than 12 months	100 to 150	Not used
*** MOTOWN study used immunoassay not tandem mass spectrometry assay to analyze cyclosporine concentrations		

Dose Adjustments for Adult Patients
For C_2 levels to be useful they must be taken exactly 2 hours after the cyclosporine dose. If the level is not taken at exactly the correct time with respect to the dose, cyclosporine doses may be adjusted to the detriment of the patient.

For patients who have been stable, a dosage change is rarely recommended based on a single cyclosporine C_2 or trough level.

To ensure correct dose adjustment use the following guidelines:

1. Ensure that the following measurements have been done within one month prior to any dose adjustment: blood pressure, serum creatinine, serum urea and lipid levels.

2. If the patient is stable, had no rejections and no transplant complications continue with the current cyclosporine dose and continue to monitor the patient.

3. If the patient has suspected problems with the absorption of cyclosporine, has cyclosporine nephrotoxicity, or has had a rejection, measure the C_2 concentration:

   a) If the **C_2 concentration is consistently lower** than the target (at two consecutive concentrations), and the patient is stable (i.e. no history of multiple or recent rejections), the dosage may be left unchanged or increased carefully based on clinical criteria.

   b) If the **C_2 concentration is consistently higher** than the target (at two consecutive concentrations), and the patient is not stable (i.e. history of recent or recurrent rejection) the dosage may be left unchanged or decreased carefully based on clinical criteria.

Be cautious that the change in dosage is reasonable; normally a dosage change is not greater than 50 mg/day increments.

AVAILABILITY

Oral cyclosporine (Neoral® Novartis Pharmaceuticals) is available both in capsule and liquid form. The capsules are supplied in 10 mg, 25 mg, 50 mg and 100 mg strengths. The solution contains 100 mg/mL cyclosporine microemulsion. The solution should be used within two months of opening the container.

Cyclosporine (Sandimmune® Novartis Pharmaceuticals) is available as a concentrate for intravenous use 50 mg/mL, in 1 mL and 5 mL ampules.

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Erythropoiesis-Stimulating Agents Darbepoetin/Epoetin

INTRODUCTION

Darbepoetin alpha is a hyper glycosylated erythropoiesis-stimulating protein, produced by recombinant DNA technology. It is indicated for the treatment of anemia associated with chronic renal failure, including patients on dialysis and not on dialysis. Darbepoetin has a longer terminal half-life than epoetin which allows for less frequent dosing [(1)].

MECHANISM OF ACTION

Darbepoetin stimulates erythropoiesis by the same mechanism as endogenous erythropoietin. Erythropoietin is a glycoprotein that is the primary regulator of erythropoiesis with specific interaction with the erythroid receptor on the erythroid progenitor cells in the bone marrow. The production of erythropoietin primarily occurs in and is regulated by the kidney in response to changes in tissue oxygenation. Darbepoetin binds to the erythropoietin receptors on burst forming units erythroid (BFU-e) and colony forming units erythroid (CFU-e), which divide and eventually differentiate into mature circulating red blood cells [(1)].

PHARMACOKINETICS

Following intravenous (IV) administration to adult chronic renal failure patients, darbepoetin serum concentration-time profiles are biphasic, with a distribution half-life of approximately 1.4 hours and mean terminal half-life of approximately 21 hours. Following subcutaneous administration, the absorption is slow and rate limiting, and the terminal half-life is 49 hours (range: 27 to 89 hours), which reflects the absorption half-life. The peak concentration occurs at 34 hours (range: 24 to 72 hours) post subcutaneous administration in adult chronic renal failure patients, and bioavailability is approximately 37% (range: 30% to 50%). The distribution of darbepoetin in adult CRF patients is predominantly confined to the vascular space (approximately 60 mL/kg). The pharmacokinetics of darbepoetin does not change as a function of time/dose. Steady state levels are achieved within 4 weeks [(1)].

A single dose, randomized, double blind study was conducted to compare the pharmacokinetics of IV epoetin to IV darbepoetin. Eleven patients receiving chronic ambulatory peritoneal dialysis (CAPD) received a single IV dose of either epoetin (100 units/kg) or an equivalent dose of darbepoetin based on peptide mass. After a 28-day washout period, patients received a single IV injection of the alternate drug. The half-life of IV darbepoetin was three-fold longer than IV epoetin, 25.3 hours vs. 8.5 hours, respectively ($p=0.0008$). In the second phase of this study, the half-life of SC darbepoetin was determined to be 48.8 hours. In comparison to epoetin, the area under the curve was greater and the clearance lower for darbepoetin. There was no significant difference in the volume of distribution of these two drugs and the bioavailability of SC injection is very similar [(2)]. Other evaluations indicate that the pharmacokinetics of darbepoetin are similar in adult and pediatric patients with chronic renal failure [(3)].

THERAPEUTIC USE

The erythropoiesis stimulating agents (ESA; darbepoetin and epoetin) are indicated for the following kidney and kidney-pancreas transplant recipients:

Criteria for ESA: (based on BC Renal CKD non-dialysis anemia recommendations)
Patients NOT on dialysis who have a failing kidney transplant,

- Have at least one symptom of anemia (fatigue, excessive intolerance, angina, impaired cognition)
- Must meet all the following lab criteria:
  - GFR less than 50 mL/min by eGFR (eGFR based on CKD-EPI equation for adults, CKiD-U25 equation for children)
  - Hemoglobin (Hgb) less than 95 g/L
  - Transferrin saturation (TSAT) 22% or greater

See BCCH Pediatric Chronic Kidney Disease Anemia Management Protocol for pediatric specific Hgb & TSAT targets.

ESAs are not indicated for patients who have anemia due to causes other than anemia associated with chronic renal failure. This includes gastrointestinal bleeding, folate and iron deficiencies, hemolysis or underlying hematologic disease [1]. BC Transplant does not fund darbepoetin for these patients.

Darbepoetin or epoetin are not intended for patients who require immediate correction of severe anemia or emergency transfusions. Blood pressure should be adequately controlled prior to initiation of darbepoetin therapy and must be closely monitored and controlled during treatment.

Therapeutic End Goal: Target Hgb 95-115 g/L

Target TSAT 22% or greater: Suggest iron studies 1 month after ESA start, then every 3 months (refer to page 2 on BC Renal Agency anemia protocol)

- If Hgb is between 85-94 g/L, check iron studies. For TSAT less than 22% consider iron therapy. If no dose increase of ESA in past 5 week, increase ESA dose per BC Renal protocol and monitor at regular blood work cycle.
- If Hgb is between 95-115 g/L, maintain ESA and monitor at regular blood work cycle
- If Hgb is between 116-125 g/L, if no dosage reduction of ESA in past 5 weeks, reduce ESA dose per BC Renal protocol and monitor at regular blood work cycle.
- If Hgb is between 126-139 g/L, hold ESA. Measure Hgb every 2 weeks. If Hgb is above 126 g/L after 12 weeks off ESA, discontinue ESA.

ADVERSE DRUG REACTIONS

The safety profile of darbepoetin was assessed in 1578 chronic renal failure patients treated with this drug and compared to 591 patients treated with epoetin[4]. Adverse events were

comparable in incidence, type and severity between the two treatments and the majority of these were due to the underlying disease process. There was no evidence that the safety profile of darbepoetin differed in patient subgroups or changed with time [1, 4].

Darbepoetin Adverse Drug Reactions

Area of Effect	Adverse Effects
Cardiac	Congestive heart failure, cardiac arrhythmia, hypertension, hypotension
Body	Sepsis, headache
Gastrointestinal	Diarrhea, nausea
Musculoskeletal	Myalgia
Other	Vascular access thrombosis

Despite the longer half-life of darbepoetin no drug accumulation was observed over time. [6] Compared to epoetin, there was no difference in the rate of decline in Hgb following cessation of therapy due to higher than target hemoglobin levels [7,9].

Darbepoetin is contraindicated in patients with: uncontrolled hypertension, development of Pure Red Cell Aplasia (PRCA) following treatment with any ESAs, known hypersensitivity to the active substance or any of the excipients or sensitivity to mammalian cell-derived products [1].

Drug Interactions

No formal drug interaction studies of darbepoetin with other medications commonly used in chronic renal failure patients have been performed; however, there are no known drug interactions reported [1].

Dose and Administration

Starting Dose

The recommended starting dose of darbepoetin for the correction of anemia in patients with chronic renal failure is 0.45 mcg/kg administered as a single IV or subcutaneous injection once weekly [1]. Because of individual variability, doses should be titrated to a target not to exceed a Hgb concentration of 120 g/L [1]. In a study by Toto et al, 608 epoetin naïve, pre-dialysis patients were successfully managed with darbepoetin given subcutaneously every 2 weeks at a starting dose of 0.75 mcg/kg rounded to the nearest available fixed dose [8].

Due to the possibility of ESA's causing an increase in blood pressure and adverse cardiac events in patients with a Hgb greater than 130 g/L, use the lowest dose to maintain an upper Hgb target of 100 g/L. Dosage reduction is required if Hgb is above 130 g/L.

Dosing When Switching to Darbepoetin from Epoetin

Clinical studies demonstrated that the relationship between baseline epoetin and maintenance darbepoetin is nonlinear across the dosing spectrum [1, 9]. Consequently, the starting weekly dose of darbepoetin should be estimated on the basis of the weekly epoetin

dose at the time of substitution. Due to the longer serum half-life, darbepoetin should be administered less frequently than epoetin. Patients receiving epoetin 2 or 3 times a week should change to once weekly darbepoetin at a dose equivalent to their total weekly dose of epoetin. Patients receiving epoetin once per week should change to darbepoetin once every 2 weeks at a dose that is equivalent to the sum of 2 weekly doses of epoetin. The same route of administration should be used. For patients prescribed prefilled syringes, the calculated dose should be rounded upward to the next available syringe strength [(1)]. In darbepoetin clinical trials, a dose conversion of 200 units of epoetin for 1 mcg of darbepoetin was used and was shown to be an appropriate starting dose for darbepoetin. The following chart shows a conservative approach to starting darbepoetin when switching from epoetin and in most instances, the darbepoetin dose will likely need to be titrated upwards to achieve target Hgb levels.

Estimated Darbepoetin (Aranesp®) Starting Dose (mcg/week)
Based on Previous Epoetin (Eprex®) (units/week) [(1)]

Previous Weekly Epoetin Dose (units/week)	Weekly Darbepoetin Dose (mcg/week)
less than 2,500	6.25
2,500 to 4,999	12.5
5,000 to 10,999	25
11,000 to 17,999	40
18,000 to 33,999	60
34,000 to 89,999	100
90,000 and greater	200

Administration
Darbepoetin can be administered by either the intravenous (IV) or subcutaneous route [(1)].

Monitoring
When darbepoetin therapy is initiated or adjusted, the Hgb should be followed weekly until stabilized and monitored at least monthly thereafter [(1)].

Availability
Darbepoetin (Aranesp® Amgen Inc.) is available as a human serum albumin free formulation in single use prefilled syringes (PFS) in the following doses: 10, 20, 30, 40, 50, 60, 80, 100, 130, 150, 200, 300, 500mcg/syringe [(1)].

Epoetin (Eprex, Janssen) is available in for following strengths: 1000, 2000, 3000, 4000, 5000, 6000, 8000, 10000, 20000, 30000 and 40000 unit/syringe

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Filgrastim (G-CSF)

MANAGEMENT OF POST-TRANSPLANT LEUKOPENIA/NEUTROPENIA

Background:
Solid organ transplant recipients commonly experience low white blood cell counts (neutropenia) post-transplant. The cause of neutropenia is usually due to bone marrow suppression effects of anti-rejection and antiviral transplant medications or infections such as cytomegalovirus (CMV) related to transplantation. Patients with very low neutrophil counts are at very high risk for severe infections which require hospital admission, antibiotics and therapy with filgrastim.

The management of neutropenia post-transplant involves a careful assessment of the cause(s) of neutropenia and adjustments in immunosuppressive regimens and/or anti-viral therapies if CMV is suspected as the cause of the neutropenia. The most common medication adjustment includes reduction in the anti-metabolite (mycophenolate/azathioprine) dose to allow for neutrophil count recovery. However, there are many cases where a reduction in anti-metabolite dose is not the optimal choice as it can pose an increased risk of graft rejection. Clinicians are challenged with balancing neutropenia and the risk of infection versus immunosuppression reduction and risk of graft rejection. In some clinical situations where the risk of rejection and the consequences of rejection are extreme, the use of filgrastim will allow the continuation of anti-rejection treatment.

Evidence for filgrastim use in solid organ transplants:

Although not extensively studied, filgrastim has been used to increase neutrophil counts in solid organ transplant patients. Schmaldienst et al studied 19 renal transplant patients that experienced leukopenia in the 2 weeks to 24 months after transplantation (1). In comparison to an age-matched historical control group, patients receiving filgrastim had shorter duration of leukopenia (1.29 versus 7 days), with fewer infections; in addition, there were no episodes of rejection 2 weeks following administration.

Turgeon et al retrospectively reviewed 50 renal or liver transplant patients (2). Of the 50 patients, 43 patients had a rise in the leukocyte count to greater than 5.0 X 10^9/L following filgrastim. In 81.6% of cases, filgrastim therapy allowed for recommended dosing of ganciclovir or valganciclovir for treatment of CMV-induced neutropenia. Most recently, an abstract presented by Poon et al at the American Transplant Congress 2016 demonstrated effective reversal of neutropenia in kidney transplant recipients without increasing the risk of rejection (3).

Protocol:
With the support of the various organ group specialists/clinicians, the Management of Neutropenia Post Transplant protocol has been developed below.

Since September 4, 2023, it has been optional for clinicians to complete the Filgrastim Prescription/Worksheet (Appendix B). One of the designated BC Transplant Pharmacies will dispense the filgrastim. If a patient requires more than 2 courses in a 12-month period, please contact the pharmacy manager at BC Transplant.

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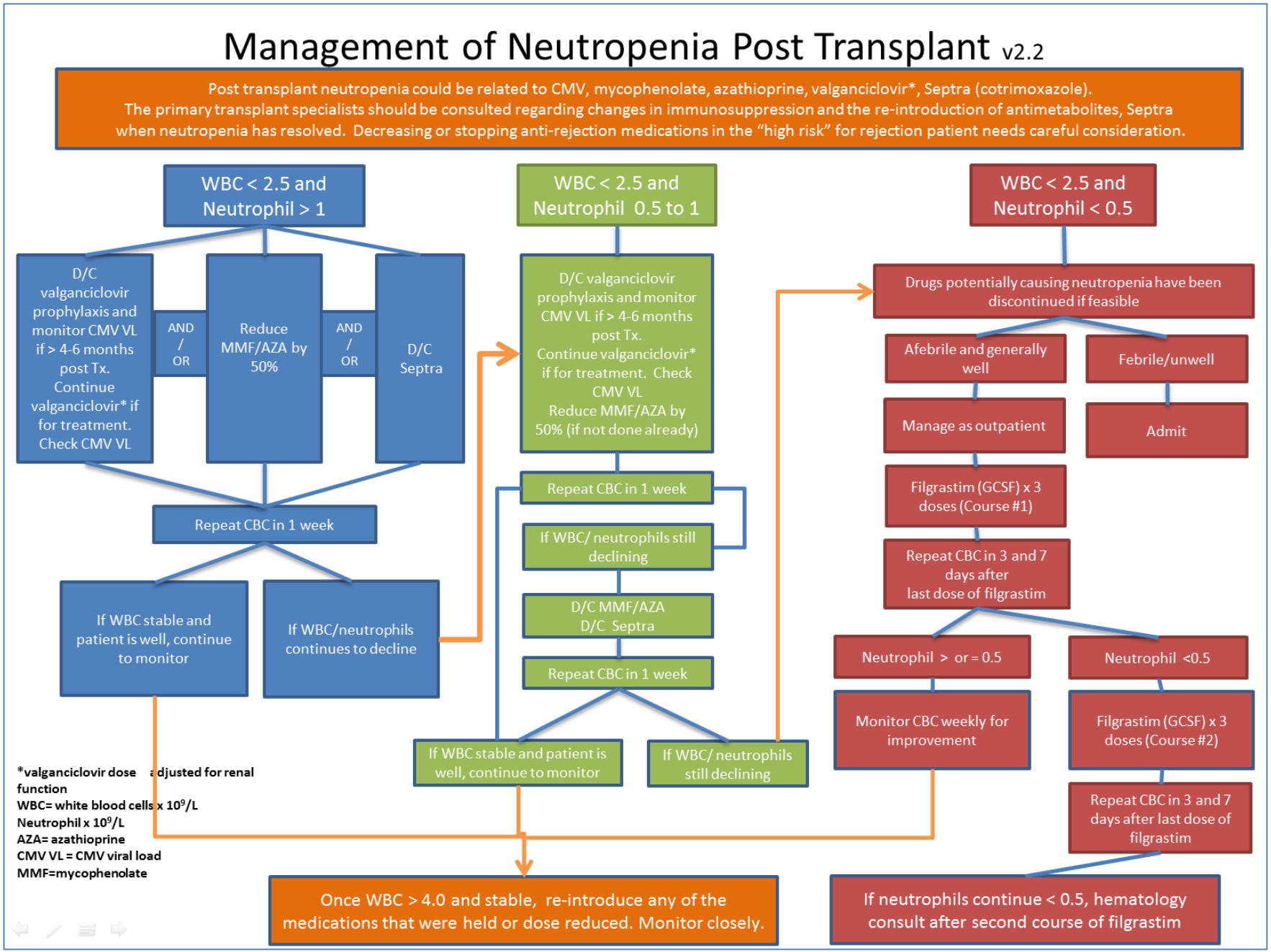
Management of Neutropenia Post Transplant v2.2



Hepatitis B Antiviral Agents: Entecavir, Tenofovir#, and Lamivudine

INTRODUCTION

Patients undergoing liver transplantation for hepatitis B virus (HBV) infection require ongoing antiviral therapy post transplantation. In the absence of HBV prophylaxis, recurrence of HBV occurs in approximately 80% of liver transplant recipients within four years post-liver transplant. Current treatments do not eradicate the virus. The aim of therapy for chronic hepatitis B is to achieve long-term continued suppression of the HBV DNA to prevent disease progression leading to cirrhosis and hepatocellular carcinoma. Effective therapy for the liver transplant recipient with chronic HBV infection includes administration of life-long oral antiviral agents in combination with short-term Hepatitis B Immunoglobulin (HBIG).

Due to the high risk of reactivation in solid organ transplant (SOT) recipients with chronic HBV (i.e HBsAg positive), appropriate antiviral therapy should be initiated post transplant. Non-liver SOT patients with evidence of resolved HBV infection (i.e HBsAg negative, HBcAb reactive) have a varying risk of reactivation that increases with increased degree of immunosuppression. Lung transplant recipients are generally on profound and prolonged immunosuppression with a lifelong risk of reactivation, warranting antiviral prophylaxis. Other non-liver SOT transplant recipients can generally be monitored for reactivation.

Currently entecavir and tenofovir disoproxil fumarate (TDF) are considered first line antiviral agents for the treatment of chronic HBV infection due to their excellent efficacy and high barrier to resistance. Lamivudine and adefovir are no longer recommended due to high incidence of resistance with continued use. Patient adherence to medication is critical to achieve adequate HBV DNA suppression and prevent resistance.

NOTE: #Tenofovir disoproxil fumarate (TDF) – currently funded by BC Transplant
Tenofovir alafenamide (TAF) is only available through BC Transplant Compassionate Funding approval process.

ANTIVIRAL USE GUIDELINES

A. Chronic Hepatitis B Virus Infection

Liver Transplant Recipients
BC Transplant covers the cost of outpatient HBV antiviral agents for patients **following liver transplant**.

HBV Antiviral Indications for Liver Transplant Program

HBV Antiviral Agent	Post-transplant indications
Entecavir	• first line therapy in HBV treatment - naïve patient • on entecavir prior to transplant • contraindicated if patient has a history of lamivudine resistance
Tenofovir	• first line agent in patients with lamivudine resistance • on tenofovir prior to transplant • caution when used in patients with renal dysfunction
Lamivudine	• no longer recommended unless there are exceptional circumstances

Non-Liver Transplant Recipients with chronic HBV infection

- BC Transplant will cover the cost of outpatient HBV antiviral agents for patients who have confirmed chronic HBV (HBsAg positive for at least 6 months) infection following **non-liver transplant** (regardless of HBV viral load) to avoid HBV reactivation with immunosuppressive therapy.

HBV Antiviral Indications for Non-Liver Transplant Program

HBV Antiviral Agent	Post-transplant indications
Entecavir	• on entecavir prior to transplant • recommended first line agent in HBV treatment-naïve patient • NOT recommended if history of lamivudine resistance
Tenofovir	• first line agent in patients with lamivudine resistance • on tenofovir prior to transplant • caution when used in patients with renal dysfunction
Lamivudine	• no longer recommended unless there are exceptional circumstances

B. Hepatitis B Core Antibody Positive Donors and Recipients

BC Transplant covers the cost of **post-transplant** HBV antiviral agents for some recipients of liver and non-liver solid organ transplants depending on donor and recipient HBV core antibody status (in patients without active HBV replication) to avoid HBV reactivation with immunosuppressive therapy. In general, liver transplant and lung transplant recipients require prophylaxis and other recipients can be monitored.

This table refers to donors and recipients who are **HBsAg negative**. HBV DNA testing should be done on all donors with HBV core antibody positive status. Generally, donors who are HBsAg positive would not be suitable donors, and recipients who are HBsAg positive would require life-long anti-viral therapy.

For organ recipients, confirming immunity or immunizing to Hepatitis B is recommended prior to transplant.

Organ Transplanted	Donor HBV Status	Recipient HBV Status	Anti-Viral Therapy Post Transplant
Liver	HBV core positive	HBV core positive or negative	Entecavir for life (preferred) or alternative agent
	HBV core negative	HBV core positive	Monitor for HBV reactivation* No prophylaxis
Kidney, kidney-pancreas, heart transplants	HBV core positive	HBV core negative Regardless of anti-HBs status	Monitor for HBV reactivation* No prophylaxis
	HBV core negative	HBV core positive	Monitor for HBV reactivation*,+ May consider a referral to a hepatologist for ongoing monitoring
Lung transplant	HBV core positive	HBV core negative Regardless of anti-HBs status	Monitor for HBV reactivation* No prophylaxis
	HBV core negative	HBV core positive	Entecavir for life (preferred) or alternative agent

*Monitor for HBV reactivation at every 3 months for one year then every 6 months. If patient being treated for acute rejection, monitor for HBV reactivation every 3 months for 6 months. Tests to be done: liver enzymes, hepatitis B surface antigen, hepatitis B core antibody, hepatitis B surface antibody and hepatitis B DNA. If Hep B DNA detectable or HBsAg positive, consult transplant hepatology or infectious disease specialist.
+Recipients who receive rituximab for any reason require HBV cAb testing and prophylaxis

ADVERSE DRUG REACTIONS

Nucleos(t)ide analogues for hepatitis B are well tolerated. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues.

Severe exacerbations of hepatitis have been reported in patients who have discontinued HBV antiviral therapy.

HBV Antiviral Agent	Adverse Drug Reactions
Entecavir	• Most common (greater than and equal to 3%): headache, fatigue, dizziness, and nausea
Tenofovir	• Nephrotoxicity: Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia) • Metabolic bone disease especially in children

DRUG INTERACTIONS

Entecavir

Entecavir is primarily eliminated by the kidneys; therefore, co-administration of entecavir with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of either entecavir or the co-administered drug. In clinical trials, co-administration of entecavir with lamivudine, adefovir dipivoxil or tenofovir disoproxil fumarate did not result in significant drug interactions. The effects of co-administration of entecavir with other drugs which are renally eliminated or are known to affect renal function have not been evaluated, and patients should be monitored closely for adverse events.

Entecavir is not a substrate, inhibitor or inducer of the CYP450 enzyme system; therefore, the pharmacokinetics of entecavir are unlikely to be affected by co-administration with drugs that affect the CYP450 system.

Tenofovir

The potential for CYP450 mediated interactions involving tenofovir and other medications is low. Co-administration of tenofovir with drugs which are eliminated by active tubular secretion may increase serum concentrations of either tenofovir or the co-administered drug, due to competition for this elimination pathway. Drugs which decrease renal function may also increase serum concentrations of tenofovir.

DOSE AND ADMINISTRATION

Liver Transplant Patients

Entecavir and tenofovir are administered orally once a day. Dosages must be adjusted in patients who have impaired renal function as these drugs are eliminated by renal excretion. HBV antiviral therapy should be continued indefinitely in all patients post-transplant. The relationship between treatment with HBV antivirals and long-term outcomes (hepatocellular carcinoma, decompensated cirrhosis) is not known in transplant recipients.

Entecavir

Adult dose: 0.5 mg PO once daily on an empty stomach. To be used in treatment naïve patients or in those with lamivudine sensitive disease
1 mg PO daily for decompensated liver disease
Pediatric dose: limited data for use, consult pediatric transplant pharmacist

Adult Dosage Adjustment of Entecavir in Renal Impairment

Creatinine Clearance (mL/min)	Entecavir Dose in Patients with Lamivudine Sensitive HBV Disease
Greater than and equal to 50	0.5 mg once daily
30 to 49	0.5 mg three times a week on Monday, Wednesday and Friday or q48hrs
10 to 29	0.5 mg twice a week on Monday and Thursday or q72hrs
Less than 10 (hemodialysis or chronic peritoneal dialysis patients)	0.5 mg every seven days. Give after hemodialysis

Tenofovir

Adult dose: 300 mg PO once daily with or without food.
Pediatric dose: not established

Adult Dosage Adjustment of Tenofovir in Renal Impairment

Creatinine Clearance (mL/min)	Tenofovir Dose
Greater than 50	300 mg once daily
30 to 49	300 mg three times a week on Monday, Wednesday and Friday or q48hrs
10 to 29	300 mg every Monday and Thursday
Less than 10	Not recommended
On hemodialysis	300 mg once weekly after dialysis (assume thrice weekly dialysis)

DOSE AND ADMINISTRATION, ADVERSE DRUG REACTIONS, AND DRUG INTERACTIONS FOR LAMIVUDINE (FOR PATIENTS REMAINING ON LAMIVUDINE):

Adult dose: 100 mg PO once daily with or without food
Pediatric dose: greater than two years of age, 3 mg/kg/dose once daily to a maximum of 100 mg PO daily

Lamivudine is generally well tolerated. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues. Severe exacerbations of hepatitis have been reported in patients who have discontinued HBV antiviral therapy.

HBV Antiviral Agent	Adverse Drug Reactions
Lamivudine	• Most common adverse events (greater than 10%): malaise, fatigue, respiratory tract infections, abdominal discomfort and pain, nausea, vomiting and diarrhea • ALT elevations more common in patients treated with lamivudine than placebo

The likelihood of metabolic interactions with lamivudine is low due to limited metabolism, limited plasma protein binding, and almost complete renal elimination of unchanged drug. Lamivudine is primarily eliminated by active organic cationic secretion. The possibility of interactions with other drugs administered concurrently should be considered when their main route of elimination is active renal secretion via the organic cationic transport system (e.g. trimethoprim).

There have been no observed clinically significant interactions in patients taking lamivudine concurrently with commonly used transplant immunosuppressants.

Adult Dosage Adjustment of Lamivudine in Adults with Renal Impairment

Creatinine Clearance (mL/min)	Lamivudine Dose
greater than 30	100 mg once daily
15 to 29	100 mg three times a week on Monday, Wednesday and Friday
Less than 15	100 mg twice a week on Monday and Thursday
on hemodialysis	100 mg twice weekly on Monday and Wednesday. On dialysis days, dose post dialysis

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Letermovir in Solid Organ Transplants

Background:

Letermovir (Prevymis[R], Merck Canada Inc.) was launched in Canada in Dec 2017, and marketed for CMV prophylaxis for allogeneic hematopoietic stem cell transplant HSCT (bone marrow transplant) based a double-blind, randomized placebo-controlled trial (Study P001, n=570). Its novel mechanism of action, inhibition of CMV DNA terminase complex results in the inhibition of viral maturation.[1] Letermovir's spectrum of activity is specific to human CMV with no activity against HSV or VZV. Its favourable side effect profile suggests it does not have the same bone marrow suppressive activity as ganciclovir/valganciclovir, nor the renal toxicity of foscarnet/cidofovir.

The CDA (Canada's Drug Agency) review has recommended Provincial funding agencies consider reimbursement for prophylaxis of CMV for adult CMV R+ recipients for HSCT[2]. BC Pharmacare provides special authority support for letermovir for HSCT CMV prophylaxis based on the CDA recommendation.[2]

Evidence for letermovir use in solid organ transplants (SOT):

The evidence for letermovir use in SOT is limited to a single RCT. The CDA began reviewing letermovir for primary prophylaxis of CMV in adult kidney transplant recipients at high-risk D+/R-, but the review was withdrawn by the manufacturer in May 2024.[6] The renal transplant group in Vancouver has participated in the randomized controlled trial of letermovir vs valganciclovir for primary prophylaxis of CMV in high risk D+/R- kidney transplant recipients (NCT3443869)[5]. Letermovir was non-inferior to valganciclovir with similar rates of CMV disease at 52 weeks. Valganciclovir continues to be the drug of choice for both prophylaxis and treatment for ambulatory patients.[3]

There has been a Phase II study looking at using letermovir for pre-emptive therapy for CMV viremia, however, the doses used in that study were much lower than those currently used for the prophylaxis indication.[4] Letermovir is currently not approved for pre-emptive therapy or treatment of CMV disease.

Recommendation:

Letermovir's novel mechanism of action and favourable side effect profile may offer advantages over traditional antivirals. However, due to the similarity of rates in CMV disease compared with traditional antivirals for primary prophylaxis, its low genetic barrier for resistance, and its high cost, BC Transplant Drug Strategy Advisory Committee supports the addition of letermovir to the BC Transplant Drug Formulary on a ***restricted basis.***

Clinicians are required to consult the Transplant Infectious Disease specialist to review therapeutic options for CMV prophylaxis. Letermovir is ***reserved for CMV primary/secondary prophylaxis*** (CMV viral load less than 200 IU/mL prior to starting letermovir):

- CMV resistance to ganciclovir/valganciclovir
- Allergy to ganciclovir or valganciclovir
- Significant neutropenia (persistently less than 0.5 10^9/L) despite filgrastim/G-CSF support and unable to reduce immunosuppression

If CMV viral load is above 500 IU/mL while on letermovir prophylaxis, discontinue letermovir and treat viremia using alternate CMV antivirals. Due to letermovir's lack of activity against HSV/VZV, additional antiviral therapy may be necessary.

A **Letermovir Authorization and Request Form** must be completed and authorized prior to use. See Appendix B

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Maribavir

Introduction

Maribavir is an orally bioavailable antiviral drug approved by Health Canada to treat refractory/resistant forms of post-transplant cytomegalovirus (CMV) infection[1].

Mechanism of Action

Maribavir competitively inhibits the CMV UL97 protein kinase, which inhibits the phosphorylation of proteins[2] needed for DNA replication, encapsidation, and nuclear egress of viral capsids[3].

Therapeutic use

Maribavir is approved for the treatment of adults with post-transplant CMV infection/disease who are refractory (with or without genotypic resistance) to one or more prior antiviral therapies including cidofovir, foscarnet, ganciclovir or valganciclovir[3, 4]. It is available on the BC Transplant formulary on a restricted basis - please see authorization form in Appendix D for criteria and approval process. Maribavir should be discontinued if there is no change or an increase in CMV viral load after at least 2 weeks of maribavir treatment, or if there is confirmed CMV genetic mutation associated with resistance to maribavir[5].

Maribavir has not been studied for central nervous system (CNS) infections with CMV and is expected to have poor blood-brain barrier penetration based on the results from the whole-body autoradiography study in rats. Therefore, it is not expected to be effective in treating CNS infections with CMV. If this type of infection is suspected, coverage with another CMV anti-viral agent is recommended[6].

Due to maribavir's lack of activity against herpes simplex virus (HSV) or varicella-zoster virus (VZV), additional antiviral therapy may be necessary to prevent these infections[7].

Contraindications

Maribavir is contraindicated for co-administration with ganciclovir or valganciclovir[3], since these two medications need the UL97 kinase to be active.

Warnings/precautions

Virologic failure with maribavir can occur during and after treatment due to resistance in the UL97 enzyme. Recurrence may happen within 4 to 8 weeks after discontinuing treatment. Cross-resistance with ganciclovir and valganciclovir has been observed in some cases, but emerging CMV resistance to maribavir is more common[8]. Regular monitoring of CMV levels is recommended to ensure the patient responds to treatment[9].

Dose and Administration

400 mg (two 200 mg tablets) orally twice daily with or without food[3]. If patients miss a dose and the next dose is due within the next 3 hours, they should skip the missed dose and continue with the regular schedule[3]. Patients are not to double their next dose or take more than the prescribed dose[3].

Pharmacokinetics

Maribavir is rapidly absorbed following oral administration with peak plasma concentrations (Cmax) occurring 1 to 3 hours post-dose. Plasma exposure (Cmax and AUC) increases dose-proportionally between 50 mg and 1600 mg, reaching steady state within 2 days when taken twice daily. Its pharmacokinetics are time independent. A moderate-fat meal decreases the AUC by 13.6% and Cmax by 27.8%. The approved 400 mg twice-daily dosing achieves a steady-state AUC of 128 h*µg/mL and a trough concentration of 4.90 µg/mL[1, 3, 9].

Maribavir is 40% bioavailable[3], 98% bound to plasma proteins, and has a volume of distribution of 27.3 L. It is primarily metabolized by CYP3A4, with some involvement of CYP1A2, and its inactive metabolite (VP44669) is excreted in urine and feces. Following oral administration, 61% is excreted in urine (<2% unchanged) and 14% in feces (5.7% unchanged). In transplant patients, it has a clearance of 2.85 L/h, and an elimination half-life of 4.32 hours[1, 3, 9].

Special Populations

Pregnancy: There is insufficient human data to determine the risk of maribavir on pregnancy outcomes. In animal studies, decreased embryo-fetal survival was observed in rats at maribavir exposures lower than those seen in humans at the recommended dose, while no such effects were noted in rabbits. Maribavir is not recommended during pregnancy and in women of childbearing potential not using contraception[3, 4, 6, 9].

Lactation: It is unknown if maribavir or its metabolites are present in human or animal milk, or if they affect milk production or the breastfed infant. A risk to the breastfeeding child cannot be excluded; Breastfeeding should be discontinued during treatment[3].

Pediatric use (< 18 years): Health Canada has not authorized an indication for pediatric use due to lack of data[3].

Geriatric Use: No dosage adjustment is needed for patients over 65. Clinical studies showed similar safety, effectiveness, and pharmacokinetics in elderly (≥65 years) and younger patients[3, 4, 9].

Impaired Renal Function: No dose adjustment is required for patients with mild to severe renal impairment. However, maribavir has not been studied in patients with end-stage renal disease (ESRD) or those on dialysis[3, 4, 9].

Impaired Hepatic Function: No dose adjustment is needed for mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, but maribavir has not been studied in patients with severe hepatic impairment (Child-Pugh Class C)[3, 4, 9].

Adverse Drug Reactions

Side Effects (>10%)[3, 10]

Area of Effect	Adverse Effects
Nervous system	Fatigue & **taste disturbance**
Gastrointestinal	Nausea, vomiting, diarrhea, abdominal pain
Hematologic & oncologic	Decreased hemoglobin, platelets, neutrophils
Infection	Infection including CMV
Renal	Increased serum creatinine

Drug Interactions

Maribavir is metabolized by CYP-3A4 (70-85%) and CYP-1A2 (15-30%). It is also a substrate of P-glycoprotein (P-gp) and uridine diphosphate glucuronosyltransferases (UGTs). Maribavir is a weak inhibitor of CYP3A4, and an inhibitor of P-gp and breast cancer resistance protein (BCRP).

The table below outlines major drug interactions[3, 9, 12] only and is not all-inclusive. For a complete list of drug interactions and management, refer to tertiary references or consult the transplant clinic.

Drug	Possible mechanism, onset, and severity	Adverse effects	Management
Pharmacodynamic interactions with maribavir			
Immunosuppressants:			
tacrolimus (tacrolimus stable daily dose between 1.5 and 16 mg, maribavir 400 mg twice daily)	CYP3A/P-gp inhibition: ↑ tacrolimus C_{max} 38% and AUC 51%[12]	↑ toxicity including renal impairment and neurotoxicity[12]	Frequently monitor immunosuppressant levels throughout treatment with maribavir, especially following initiation and after discontinuation up to 48 hours of maribavir and adjust dose, as needed.
cyclosporine, everolimus, sirolimus	CYP3A/P-gp inhibition: interactions not studied	Expected: ↑ cyclosporine, everolimus, sirolimus	

Antivirals:			
ganciclovir, valganciclovir	CMV pUL97 kinase inhibition: interactions not studied	Expected: ↓ ganciclovir ↓ valganciclovir	Co-administration of maribavir with ganciclovir or valganciclovir is contraindicated.
HMG-CoA reductase inhibitors:			
rosuvastatin	BCRP inhibition: interaction not studied	Expected: ↑ rosuvastatin	The patient should be closely monitored for rosuvastatin-related events, especially the occurrence of myopathy and rhabdomyolysis. A rosuvastatin dose reduction may be necessary.
Antiarrhythmics:			
digoxin (0.5 mg single dose, 400 mg twice daily maribavir)	P-gp inhibition: ↑digoxin C_{max} 26% and AUC 22%[14]	↑ digoxin	Monitor serum digoxin concentrations. The dose of digoxin may need to be reduced when co-administered with maribavir
Drugs that DECREASE maribavir levels			
Anticonvulsants:			
carbamazepine	CYP3A induction: ↓ maribavir C_{max}23% and AUC 29%[12]	↓ maribavir levels: reduced virologic response	Adjust maribavir dose to 800 mg BID.
phenobarbital	CYP3A induction: ↓ maribavir C_{max}27% and AUC 39%[12]		Adjust maribavir dose to 1200 mg BID and caution in phenobarbital doses higher than 100 mg due to potential decreased efficacy of maribavir.
phenytoin	CYP3A induction: ↓ maribavir C_{max}31% and AUC 42%[12]		Adjust maribavir dose to 1200 mg BID.

Antimycobacterials:			
rifampin	CYP3A and CYP1A2 induction: ↓ maribavir C_{max} and AUC 61%[12]	↓ maribavir levels: reduced virologic response	Co-administration is not recommended due to potential decreased efficacy of maribavir.
rifabutin	CYP3A induction: interaction not studied	Expected: ↓ maribavir	
Herbal products:			
St. John's wort (hypericum perforatum)	CYP3A induction: interaction not studied	Expected: ↓ maribavir	Co-administration is not recommended due to potential decreased efficacy of maribavir.
Drugs that INCREASE maribavir levels			
Antifungals:			
ketoconazole (400 mg single dose, maribavir 400 mg single dose)	CYP3A/P-gp inhibition: ↑ maribavir C_{max} 17% and AUC 54%	↑ maribavir	No dose adjustment is required.
Calcium-channel blockers:			
diltiazem	CYP3A/P-gp inhibition: ↑maribavir C_{max} 6% and AUC 9%	↑ maribavir	No dose adjustment is required.
Macrolide antibiotics:			
erythromycin	CYP34A inhibition: ↑maribavir C_{max}26% and AUC 44%	↑ maribavir	No dose adjustment is required.
Protease inhibitors:			
Ritonavir	CYP3A/P-gp inhibition: ↑ maribavir C_{max} 37% and AUC 63%	↑ maribavir	No dose adjustment is required.

No clinically significant interactions were observed in clinical drug-drug interaction studies of maribavir and voriconazole, antacids, caffeine, warfarin, dextromethorphan, or midazolam[9, 12, 13].

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Mycophenolate Mofetil and Mycophenolate Sodium

INTRODUCTION

Mycophenolate mofetil and mycophenolate sodium are immunosuppressants used in combination with cyclosporine or tacrolimus and corticosteroids, as well as in steroid-free regimens. Mycophenolate mofetil significantly reduces acute rejection rates following renal transplantation [1-3]. Mycophenolate sodium is therapeutically equivalent to mycophenolate mofetil in renal transplant recipients [4-6].

MECHANISM OF ACTION

Mycophenolate mofetil is a semi synthetic prodrug that is rapidly hydrolyzed *in vivo* to form the active metabolite, mycophenolic acid (MPA) [7].

Mycophenolate sodium is an enteric-coated formulation which allows delayed release of MPA into the small intestine.

The active immunosuppressant agent of mycophenolate mofetil and mycophenolate sodium, MPA, is a potent, non-competitive, reversible inhibitor of inosine monophosphate dehydrogenase resulting in blockage of *de novo*, guanosine synthesis, selectively suppressing proliferation of T- and B-lymphocytes [8].

PHARMACOKINETICS

Mycophenolate mofetil is rapidly absorbed following oral administration and completely hydrolyzed to yield MPA, the active metabolite [7].

Mycophenolate sodium is an enteric-coated formulation which allows delayed release of MPA into the small intestine [8].

MPA is metabolized in the liver to form an inactive mycophenolic acid glucuronide (MPAG). MPAG undergoes enterohepatic recirculation giving rise to a secondary MPA peak concentration six to twelve hours after oral administration of mycophenolate mofetil. This helps to maintain sustained plasma concentrations of the drug.

Less than one percent of the dose is excreted as MPA in the urine. Approximately 87% of the administered dose is excreted in the urine as MPAG [7]. The time to reach peak concentrations of MPA is delayed (1.5 to 2.5 hours) with mycophenolate sodium compared to mycophenolate mofetil (1 hour), consistent with the release of MPA in the small intestine [8]. Mycophenolate mofetil and mycophenolate sodium are not interchangeable because the rate of absorption following oral administration of the two medications is not equivalent. The half-life of MPA is approximately 11.7 to 17.9 hours [7, 8].

Mycophenolate sodium 720 mg and mycophenolate mofetil 1,000 mg can be considered equimolar in terms of mycophenolic acid [6, 8].

THERAPEUTIC USE

Mycophenolic acids are used in combination post-transplant immunosuppressive regimens to prevent solid organ transplant rejection.

Mycophenolate mofetil may be used in adults pre-kidney transplant in combination with tacrolimus, plasma exchange and rituximab for ABO incompatible recipients who may receive a living donor transplant.

Mycophenolate mofetil may be used pre-transplant in pediatric recipients who may receive a living donor transplant.

The safety and efficacy of mycophenolate sodium and mycophenolate mofetil when used in combination with cyclosporine and steroids in renal and heart transplant recipients is comparable for at least one year post transplant in terms of outcomes [5][13-15].

CONTRAINDICATION

Pregnant Women: Mycophenolic acids are associated with an increased risk of first trimester pregnancy loss and congenital malformations if taken during pregnancy. Unplanned pregnancies in patients taking mycophenolic acids should be avoided to minimize fetal exposure. Mycophenolic acids should not be used in pregnant women unless the potential benefit to the fetus justifies the risk. Effective contraception should be used before beginning mycophenolic acids, during therapy and for six weeks following discontinuation of therapy, even when there has been a history of infertility [16, 18].

ADVERSE DRUG REACTIONS

Overall frequencies of adverse effects are similar between mycophenolate mofetil (2 gram/day) and mycophenolate sodium (1.44 gram/day) in both *de novo* and maintenance adult renal transplant recipients when used in combination with cyclosporine and corticosteroids [7, 8, 9].

Most Common Mycophenolic Acid Adverse Drug Reactions

Area of Affect	Adverse Effect
Gastrointestinal	Constipation* Diarrhea** refer to Management of Post -Transplant Diarrhea, page 45 Dyspepsia Nausea** Vomiting* Abdominal pain*
General	Edema Pain** Fever*
Hematologic	Bone marrow suppression Anemia*** Leukopenia**refer to Management of Post -Transplant Leukopenia, page 46
Infectious	Sepsis* Opportunistic (CMV) Urinary tract infection**
Nervous System Disorder	Insomnia* Tremor Headache

* Most common adverse effects (greater than and equal to 10%)

** Most common adverse effects (greater than and equal to 25%)

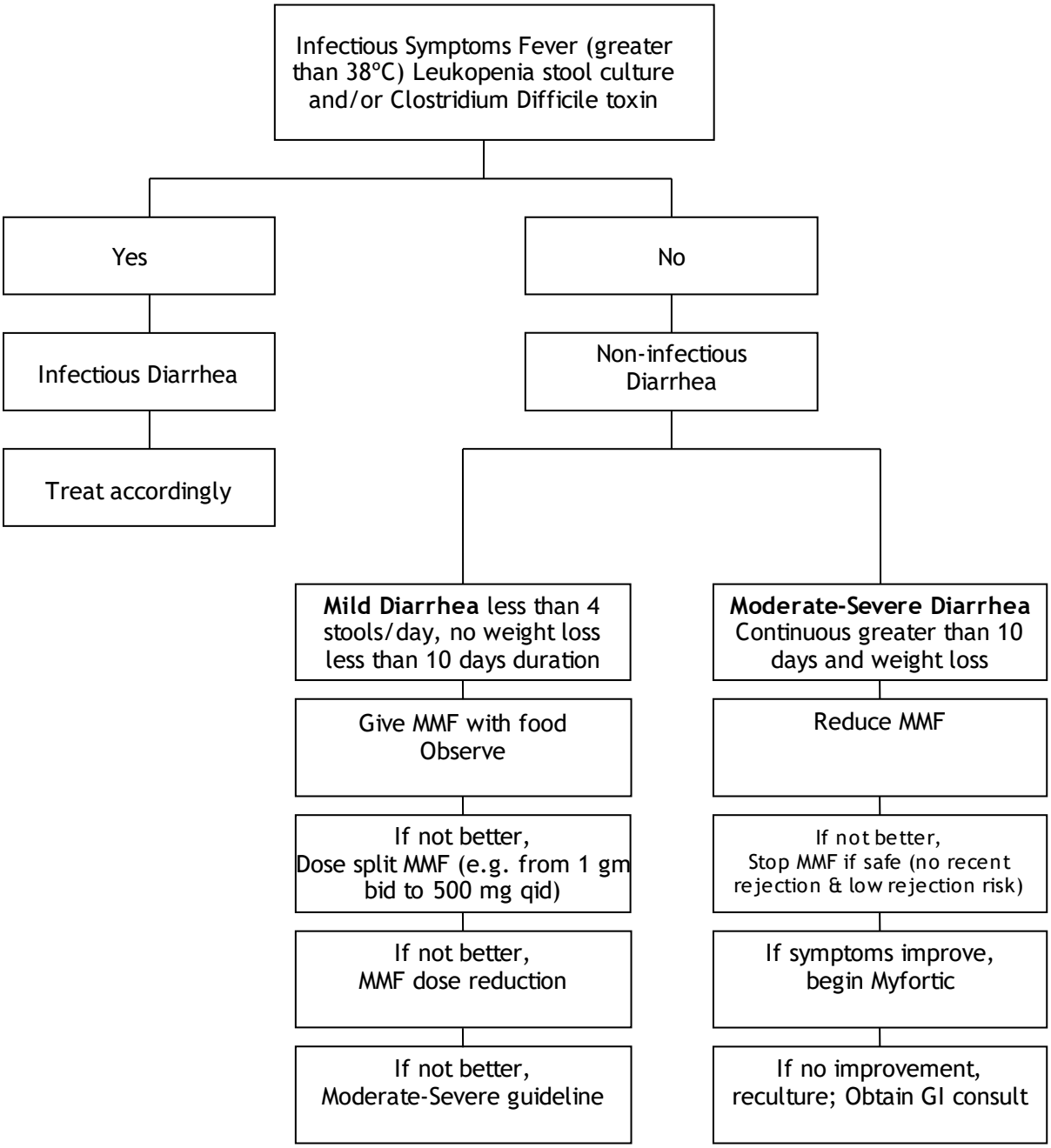
*** Cases of pure red cell aplasia (PRCA) type of anemia that develops secondary to failure of erythropoiesis have been reported in patients treated with mycophenolate in combination with other immunosuppressive agents. The mechanism for mycophenolate mofetil induced PRCA is not known. In some cases, PRCA was found to be reversible with dose reduction or discontinuation of mycophenolate. In transplant recipients reduced immunosuppression may place the graft at risk [17].

Many of the common side effects are dose dependent and can be ameliorated by reducing or discontinuing the mycophenolate mofetil or mycophenolate sodium dose temporarily. However, this may leave the transplant recipient at increased risk of allograft acute rejection as a result of suboptimal immunosuppression [10, 11].

MANAGEMENT OF POST-TRANSPLANT DIARRHEA

Diarrhea is a frequent problem in post-transplant patients. One must make a distinction between medication induced and infectious diarrhea.

Treatment of Post-Transplant Diarrhea



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DRUG INTERACTIONS

Magnesium and aluminum containing antacids may decrease the absorption of mycophenolate mofetil and mycophenolate sodium and should not be taken at the same time [8].

Cholestyramine (Questran®) and other medications that interfere with enterohepatic recirculation may decrease the absorption of the mycophenolate mofetil and should not be administered concurrently [8].

When mycophenolic acids are administered with acyclovir, ganciclovir, and valganciclovir, increased plasma concentrations of acyclovir, ganciclovir, and valganciclovir may occur due to competition for tubular secretion in the presence of renal failure [8]. Monitor carefully.

Azathioprine and mycophenolate mofetil inhibit purine synthesis. Azathioprine and mycophenolic acids should not be administered concomitantly [8].

There is a potential interaction between proton-pump inhibitors and mycophenolate sodium. Proton-pump inhibitors lower the gastric PH and increase the probability of early release of MPA in the stomach.

DOSE AND ADMINISTRATION

Mycophenolate mofetil is the standard mycophenolic acid used in the BC Transplant immunosuppressant protocols.

Mycophenolate Mofetil (generic brands)

ADULT Kidney and Kidney-Pancreas Transplant Recipients

The initial adult post-transplant dose of mycophenolate mofetil is 1 gram PO bid.
For adult patients requiring desensitization prior to a renal transplant, mycophenolate mofetil may be administered up to 14 days prior to transplant at a dose of 500 mg PO bid.

PEDIATRIC Kidney Transplant Recipients

The initial pediatric dose of mycophenolate mofetil is 600 mg/m^2/dose PO bid (up to a maximum total daily dose 2 gram daily). With pharmacokinetic monitoring, doses are individualized to optimize therapy for each patient.

- Body surface area of 1.25 to 1.5 m^2: mycophenolate mofetil 750 mg PO bid.
- Body surface area greater than 1.5 m^2: mycophenolate mofetil 1 gram PO bid [7].

Dose may be adjusted downwards if a patient has gastrointestinal intolerance.

For pediatric patients receiving a living donor transplant mycophenolate mofetil may be administered up to 14 days prior to transplant at a dose of 300 mg/m^2/dose PO bid (up to a maximum total daily dose of 1 gram daily), and adjusted to 600 mg/m^2/dose PO bid (up to a maximum total daily dose of 2 grams daily) on the day of transplant.

ADULT Liver Transplant Recipients
For adults the initial mycophenolate dosage is 1 gram PO bid. Mycophenolate mofetil will be tapered with a view to discontinuing after three to five years post-transplant in select patients.

ADULT Lung Transplant Recipients
Initial immunosuppression will include mycophenolate mofetil. For adults the initial dose is 1 gram PO every 12 hours.

ADULT Heart Transplant Recipients
Initial immunosuppression will include mycophenolate mofetil 1 gram PO bid for all patients. Patients will remain on mycophenolate mofetil.

ADULT Pancreatic Islet Transplant Recipients
Standard immunosuppression for all adult pancreatic islet transplant recipients includes mycophenolate mofetil 1 gram PO bid.

Mycophenolate Sodium (generic brands)

In terms of mycophenolate sodium provided, 180 mg is equivalent to mycophenolate mofetil 250 mg, and mycophenolate sodium 360 mg is equivalent mycophenolate mofetil 500 mg [8].

ADULT Kidney and Kidney-Pancreas Transplant Recipients
Mycophenolate sodium may be prescribed for patients at the discretion of the physician or patients who are following out-of-province protocols.
The initial adult dose of mycophenolate sodium is 720 mg PO bid. Total daily dose is 1.44 gram [8].

PEDIATRIC Kidney Transplant Recipients
The initial pediatric dose of mycophenolate sodium is 432 mg/m^2 PO bid, rounded to the nearest capsule or tablet strength (maximum 720 mg/dose) [12].

Tablets should not be crushed, chewed or cut prior to ingesting. Tablets must be swallowed whole to maintain integrity of enteric coating [8].

ADULT Liver Transplant Recipients
Mycophenolate sodium may be prescribed for patients who are following out of province protocols or at the discretion of a physician.

ADULT Lung Transplant Recipients
Mycophenolate sodium may be prescribed for patients who are following out-of-province protocols and at the discretion of the physician. The initial adult dose of mycophenolate sodium is 720 mg PO bid. Total daily dose is 1.44 gram [8].

ADULT Heart Transplant Recipients
Mycophenolate sodium may be prescribed at the discretion of the physician, in patients who are intolerant of mycophenolate mofetil. The initial adult dose of mycophenolate sodium is 720 mg PO bid. Total daily dose is 1.44 gram [8].

Therapeutic Drug Monitoring

Mycophenolic acid (MPA) blood concentrations are not done routinely at adult transplant centres.

For pediatric transplant recipients, MPA limited-sampling AUC pharmacokinetic testing is routinely done to assess individual patient's drug exposure.

For adult heart transplant patients, although not routinely done, if a patient shows signs of MPA gastrointestinal side effects or rejection, a follow up level may be obtained four to eight weeks after the initial level to ensure appropriate dosage.

Target Mycophenolic Acid Blood Concentrations for Heart Transplant Recipients (Nov 2014)

Patient Status	Mycophenolic Acid Trough Blood Concentrations (mg/L) 12 hours Post Dose Tandem Mass Spectrometry Assay*
Stable and no transplant rejection	1.7 to 4
Has transplant rejection	2.5 to 4
Has MPA side effects and is stable	1.7

*Assay done at Vancouver General Hospital Special Chemistry Lab

AVAILABILITY

Mycophenolate mofetil (brand name: CellCept; various generic brands) is available as 250 mg capsules and 500 mg tablets. Mycophenolate mofetil (CellCept® liquid) is available as a powder for oral suspension which must be reconstituted before dispensing. When reconstituted the oral suspension contains 200 mg/mL mycophenolate mofetil [7]. Mycophenolate mofetil is also available as a lyophilized powder for solution for intravenous infusion, resulting in a 500 mg/20 mL vial after reconstitution.

Mycophenolate mofetil capsules and tablets are contained in a blister pack, which should not be opened until the dose is to be administered. Mycophenolate mofetil has demonstrated teratogenic effects in rats and rabbits; therefore, tablets should not be crushed and capsules should not be opened or crushed. Avoid inhalation or direct contact with skin and mucous membranes of the powder contained in the capsules or suspension [7].

Mycophenolate sodium (brand name: Myfortic®; various generic brands) is available in two strengths of enteric-coated tablets for oral use containing 180 mg mycophenolic acid as mycophenolate sodium and 360 mg mycophenolic acid as mycophenolate sodium. Tablets are provided in blister packs. The tablets should not be crushed or cut [8].

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Prednisone

Introduction

Prednisone is a synthetic corticosteroid used for its anti-inflammatory and non-specific immunosuppressive effects.

Mechanism of Action

Prednisone acts by stabilizing the cell wall and suppressing the body's inflammatory response to foreign proteins. Prednisone:

- reduces activity and volume of lymphatic system (lymphocytopenia)
- decreases immunoglobulin concentrations
- decreases passage of immune complexes through basement membranes
- possibly depresses reactivity of tissue to antigen antibody interactions

Pharmacokinetics

Prednisone is readily absorbed from the gastrointestinal tract and is bound to plasma proteins. It is primarily metabolized by the liver to inactive metabolites, which are excreted by the kidney.

Therapeutic Use

Prednisone is used in conjunction with other immunosuppressive medications for transplant rejection prophylaxis and treatment.

Contraindications and Precautions

One large morning dose or alternate day therapy is less likely to suppress the hypothalamic/pituitary axis than divided daily doses.

Blood pressure, weight, serum glucose, and electrolytes should be monitored routinely while patients are on corticosteroids, Patients on prolonged prednisone may require additional steroid coverage during a stressful period (i.e., infection, trauma, surgical procedure). Chronic use of steroids may suppress growth in pediatric and adolescent patients and should be used with caution.

Use with caution in the elderly and patients with: chronic renal failure, peptic ulcers, cirrhosis, psychoses, congestive heart failure, uremia, diabetes mellitus, glaucoma, hypothyroidism, infection, osteoporosis.

ADVERSE DRUG REACTIONS

Prednisone Adverse Drug Reactions

Area of Effect	Adverse Effects
Nervous system	Headache, vertigo, convulsions, paresthesia, psychoses, pseudotumor cerebri
Dermatologic	Impaired wound healing, petechiae, ecchymoses, striae, hyperpigmentation, hirsutism, acne, dermatitis, urticaria, alopecia, brittle hair
Endocrine/ metabolic	Menstrual irregularities, Cushing's syndrome, growth suppression in children, diabetes mellitus, protein catabolism, hyperglycemia, glycosuria, hypernatremia, hypokalemia, hypocalcemia
Gastrointestinal	Nausea, vomiting, increased appetite, weight gain, peptic ulcer, pancreatitis
Neuromuscular	Myopathy, osteoporosis, aseptic necrosis of femoral and humoral heads, spontaneous fractures
Ocular	Posterior subcapsular cataracts, increased intraocular pressure, glaucoma
Other	Hypersensitivity reactions

DRUG INTERACTIONS

Prednisone Drug Interactions

Drug	Effect	Mechanism	Importance
Alcohol, Anti-inflammatory drugs	Enhanced ulcerogenic effect	Additive	Caution
Amphotericin B, Potassium - depleting diuretics	Enhanced potassium depletion	Additive	Caution
ASA	Increased renal excretion of ASA	Unknown	Caution
Barbiturates, Phenytoin, Rifampin	Reduced steroid effect	Increased steroid metabolism	Caution
Digoxin	Increased arrhythmia associated with hypokalemia	Additive	Caution
Isoniazid	Decreased isoniazid plasma levels	Increased hepatic metabolism or renal excretion of Isoniazid	Caution
Insulin or Antidiabetics	Decreased hypoglycemia response	Steroids increase blood glucose	Caution
Oral contraceptives	Increased corticosteroid effect	Decreased Corticosteroid metabolism	Caution
Vaccines	Decreased antibody response	Steroid effect	Caution

DOSE AND ADMINISTRATION

Following transplant, the patient may be prescribed methylprednisolone IV. When the patient can tolerate oral medications, prednisone may be started. Give prednisone with food or milk to reduce gastric irritation.

Adult Kidney Transplant Recipients

The administration of prednisone varies in kidney transplant recipients. Patients may be on one of the following regimens:

Rapid steroid elimination: Prednisone is withdrawn quickly post-transplant over a maximum of 7 days.

Early Steroid Withdrawal: Prednisone is tapered and withdrawn over the first few weeks to months, post-transplant. This approach has risks, and the primary transplant center should be contacted as these patients are at high risk for acute rejection.

Late Steroid Withdrawal: Prednisone is withdrawn later than 6 months post-transplant. This is generally unsafe and has little benefit. Therefore, patients who have been on steroids for over the first six months post-transplant should continue on prednisone indefinitely. The prednisone maintenance dose should be the lowest possible dose, down to a minimum of 7.5 mg on alternate days or 5 mg daily. Consultation with the transplant nephrologist is highly recommended before steroids are withdrawn.

PEDIATRIC Kidney Transplant Recipients

The administration of prednisone varies in pediatric kidney transplant recipients. Patients may be on one of the following regimens:

Steroid Minimization: methylprednisolone IV (300 mg/m^2) with induction treatment only.

Prolonged Steroid Taper for select high-risk patients:

Days Post Transplant	Pediatric Drug and Dose
Day 0, 1	**MethylpredniSOLONE** 300 mg/m^2 IV daily (Maximum 500 mg)
Day 2-7	**PredNISone** 40 mg/m^2 PO daily (Maximum 60 mg daily)
Day 8-14	30 mg/m^2 PO daily (Maximum 45 mg daily)
Day 15-28	20 mg/m^2 PO daily (Maximum 30 mg daily)
Week 5-8	10 mg/m^2 PO daily (Maximum 15 mg daily)
Week 9-12	5 mg/m^2 PO daily (Maximum 7.5 mg daily)
Week 13-16	3 mg/m^2 PO daily (Maximum 5 mg daily)
Week 17 onwards	3 mg/m^2 PO THREE times weekly on MON, WED, FRI (Maximum 5 mg THREE times weekly)

ADULT Liver Transplant Recipients
Prednisone 20 mg (0.3 mg/kg) PO daily is usually begun on day six post - transplant. Dosage is tapered so patient is usually steroid-free by four to six months.

ADULT Lung Transplant Recipients
Methylprednisolone is given for the first 24 hours post - transplant. Prednisone is then begun at a dose of 1 mg/kg/day PO, tapering by 5 mg/day until 0.2 mg/kg/day PO is reached. Hold dosage at 0.2 mg/kg/day for 3 months post transplant, then decrease to 0.15 mg/kg/day PO until one year, then, decrease to 0.1 mg/kg/day PO. Continue prednisone 0.1 mg/kg/day PO indefinitely.

ADULT Heart Transplant Recipients
Methylprednisolone is given for the first 24 hours post-transplant or until the patient is receiving oral intake. Prednisone is then begun at a dose of 0.5 mg/kg/day PO, tapering by 5 mg/day until 20 mg PO daily is reached. If there is no transplant rejection, the goal is to have patients taper off prednisone over the first three to four months post-transplant.

If a patient develops severe transplant rejection methylprednisolone 1 gram IV for 3 days is given, or, if the patient with severe transplant rejection is hemodynamically stable prednisone 100 mg PO daily for 3 days is given. After the three days return to previous prednisone dose, or as prescribed by the physician and then continue to taper

AVAILABILITY

Prednisone is available in oral tablets of 1 mg, 5 mg, and 50 mg strengths. Prednisone is available from several drug manufacturers.

Prednisolone suspension (Pediapred® Sanofi-Aventis Canada Inc.) is available in 1 mg/mL strength. Prednisone 5 mg/mL suspension is prepared at B.C.'s Children's Hospital and other BC Transplant pharmacies.

Sirolimus

INTRODUCTION

Sirolimus is a potent immunosuppressive agent. The pharmacokinetic and drug interaction profile of sirolimus is similar to cyclosporine and tacrolimus, but it has a unique mechanism of action and adverse effect profile [1, 2]. Sirolimus has demonstrated efficacy and safety in two large clinical trials in kidney transplantation when used in combination with cyclosporine and prednisone. Acute rejection episodes were significantly decreased compared with azathioprine or placebo. However, there was no change in graft survival over the first two years post-transplant [3, 4].

MECHANISM OF ACTION

Sirolimus is a macrolide antibiotic, structurally related to tacrolimus, with immunosuppressive, antitumor, and antifungal properties. Sirolimus acts during both co-stimulatory activation and cytokine-driven pathways via a unique mechanism: inhibition of a multifunctional serine-threonine kinase, mammalian target of rapamycin (mTOR). Sirolimus blocks the response of T- and B-cell activation by cytokines, which prevents cell-cycle progression and proliferation. In contrast, tacrolimus and cyclosporine inhibit the production of cytokines [5, 6, 7].

Transplant patients are at particular risk of skin tumors including squamous cell carcinoma, Kaposi sarcoma and the group of post-transplant lymphoproliferative diseases. Preliminary clinical studies have reported a lower incidence of skin malignancy in patients treated with sirolimus compared with cyclosporine at the time of transplantation [8]. Patients receiving sirolimus without cyclosporine or sirolimus maintenance therapy after early cyclosporine withdrawal have lower rates of malignancy in the first 2 years after renal transplantation [9].

PHARMACOKINETICS

Most of the available pharmacokinetic data for sirolimus has been obtained from stable renal transplant patients [1]. Sirolimus appears to exhibit much of the same pharmacokinetic variability that occurs with cyclosporine and tacrolimus.

Following oral administration, sirolimus is rapidly, but poorly, absorbed with peak concentrations occurring at about 0.5 to 2 hours.

The systemic bioavailability is approximately 14% after administration of sirolimus oral solution. The mean bioavailability of sirolimus after administration of the tablet is about 27% higher relative to the oral solution. Sirolimus oral tablets are not bioequivalent to the oral solution in kidney transplant recipients. Fatty meals reduce the maximum concentration (Cmax) of sirolimus obtained and increase the time to peak sirolimus concentration (Tmax).

To minimize variability, sirolimus oral solution and tablets should be taken consistently with or without food.

The mean volume of distribution is about 12 L/kg, with approximately 92% plasma protein binding. Sirolimus is metabolized by both cytochrome P450 IIIA4 (CYP3A4) and P-glycoprotein into more than seven metabolites that do not contribute to the immunosuppressive activity. The mean half-life is about 57 to 62 hours. Large inter-patient variability exists in the clearance of sirolimus. Liver disease significantly increases sirolimus bioavailability, reducing its clearance and prolonging its elimination half-life. In renal transplant patients, whole blood trough concentrations are significantly correlated with AUC (r^2=0.96), and trough concentrations of sirolimus appear to be related to the immunosuppressive effects and toxicity of the drug [1, 2, 5, 6, 10].

THERAPEUTIC USE

ADULT and PEDIATRIC Kidney and Kidney-Pancreas Transplant Recipients

Sirolimus is indicated for the prophylaxis of renal transplant rejection in the following patients:

- Patients who were enrolled in a sirolimus clinical trial
- Patients who have developed severe calcineurin inhibitor toxicity (nephrotoxicity or neurotoxicity [11]. Definition of severe nephrotoxicity: Biopsy-proven calcineurin inhibitor nephrotoxicity despite therapeutic concentrations of cyclosporine or tacrolimus. Increase in serum creatinine must be at least 50% above baseline. In this case sirolimus would be used as a substitute for cyclosporine or tacrolimus, in combination with mycophenolate mofetil or azathioprine.
- Patients who have developed severe refractory BK virus-induced nephropathy while on a calcineurin inhibitor. The calcineurin inhibitor would be replaced with sirolimus.
- Patient has recurrent skin cancer or has renal cell cancer [8, 9]. **Prior to beginning sirolimus for cancer indication, the patient must be discussed with the primary transplant centre** to be assessed by dermatology and the renal transplant team.
- For other cancers, sirolimus must be approved by a transplant nephrologist at the patient's primary transplant centre, either Vancouver General Hospital, St. Paul's Hospital or B.C.'s Children's Hospital.
- Refractory rejection in pediatric transplant recipients.

Liver Transplant Recipients

Sirolimus is only indicated for prophylaxis of liver transplant rejection under special circumstances for the following patients. It is not to be used as first line therapy and should be used with caution in the first three months post-transplant as its use has been associated with thrombotic events including DVT's [14-19]. **If sirolimus is to be used in a patient, the prescribing physician must discuss the risk/benefit of sirolimus in liver transplantation with the liver team and patient.**

- Patient has developed calcineurin inhibitor nephrotoxicity or neurotoxicity despite calcineurin inhibitor blood concentrations within the therapeutic range.
- Patient has hepatocellular carcinoma, skin or other types of cancers.
- Patient has developed refractory transplant rejection, and not responding to other immunosuppressants
- Patients with intolerance to calcineurin inhibitors that is potentially life threatening or has significant morbidity including hypersensitivity reactions or microangiopathy.

Lung Transplant Recipients

Sirolimus is not indicated for lung transplant recipients. However, in exceptional circumstances on a case- by- case basis sirolimus may be prescribed by the lung transplant physician at Vancouver General Hospital. Sirolimus is not to be given for the first three months after transplant due to the interference with wound healing.

Sirolimus may be considered as a 4th line agent in the following patient situations:

- Recurrent rejection on standard therapy
- Bronchiolitis obliterans syndrome (BOS)
- Renal dysfunction
    - May be added in patients with marginal renal function when higher doses of tacrolimus cannot be used
    - Must check proteinuria, if moderate to high proteinuria do NOT start sirolimus
    - Must follow albumin creatinine ratio
- Add to therapy in patients who cannot tolerate tacrolimus, use in combination with mycophenolate and prednisone
- Lymphangioleiomyomatosis (LAM)
- Recurrent squamous cell carcinoma
- MMF or azathioprine intolerance

Cardiac Transplant Recipients

Sirolimus is only indicated for prophylaxis of heart transplant rejection in the following patients. It is NOT to be used within the first three months post-transplant

- In addition to a calcineurin inhibitor in patients who have recurrent or persistent transplant rejection within the first-year post transplant
- Patient has developed cardiac allograft vasculopathy (CAV)
- Patient has developed calcineurin inhibitor toxicity
- Patient is following an out-of-province protocol
- Patient has developed cancer

ADVERSE DRUG REACTIONS

Sirolimus exhibits a unique adverse effect profile compared with other immunosuppressive agents. Most adverse effects are dose/concentration dependent. The incidence of adverse reactions was determined in two randomized, double-blind, multi-center, controlled trials in which patients received sirolimus or azathioprine or placebo [3, 4]. In the trials all patients received cyclosporine and prednisone.

Adverse reactions associated with the administration of sirolimus that occur at a significantly higher frequency than patients receiving azathioprine or placebo include arthralgia, hirsutism, diarrhea, hypertension, hypokalemia, lymphocele, peripheral edema, rash, tachycardia and some infections. Dose related increases in triglycerides and cholesterol and decreases in platelets and hemoglobin have occurred in patients receiving sirolimus [1, 2, 6, 10, 20, 21].

Sirolimus Adverse Drug Reactions

Area of Affect	Adverse Effect
Common:	
Body (as a whole)	Abdominal pain Asthenia Headache Lymphocele Pain
Cardiovascular	Hypertension
Digestive System	Constipation Diarrhea Nausea
Hematologic (bone marrow suppression)	Anemia Leukopenia Thrombocytopenia
Hepatic	Hepatic artery thrombosis (HAT)***
Infectious	Increased risk**
Metabolic	Hypercholesterolemia Hyperlipidemia* (50% of patients) Peripheral Edema
Skin/mucous membranes	Oral ulceration Acne Rash Bronchial anastomotic dehiscence
Respiratory	Interstitial Pneumonitis** Upper respiratory infections
CNS	Insomnia
Rare:	
Lymphoma	Increased risk
Nephrotoxicity	Increased risk in combination with Cyclosporine

* **Hyperlipidemia** is a major complication of sirolimus therapy. In Phase III trials, treatment of new onset hyperlipidemia was reported in 42 to 52% of patients treated with sirolimus. All patients receiving sirolimus should be closely monitored for hyperlipidemia and treated as required for any unexplained muscle weakness or pain, especially if associated with malaise or fever. Patients treated with a statin should be made aware of and monitored for rhabdomyolysis [1, 22].

** **Antimicrobial prophylaxis against PCP** for 12 months and **CMV antiviral prophylaxis** as per guidelines is essential [23].

*** **Hepatic artery thrombosis** (HAT) is a clinical diagnosis, which depends on a strong index of suspicion. An angiogram is the only specific test, which can confirm that the hepatic artery is not patent [24].

DRUG INTERACTIONS

Sirolimus like tacrolimus and cyclosporine is metabolized by the cytochrome P450 3A4 enzyme system. Therefore, medications known to affect this system will likely alter sirolimus metabolism, resulting in changes to sirolimus blood concentration. Refer to Appendix A for significant drug-drug and pharmacodynamic interactions.

DOSE AND ADMINISTRATION

ADULT Kidney and Kidney-Pancreas Transplant Recipients

Prior to beginning sirolimus, the primary transplant centre must be consulted due to the high rate of sirolimus toxicity. Caution is advised for patients on steroid free protocols.

When sirolimus is used in a patient with recurrent skin cancer or renal cell cancer, the patient **must be discussed with** the primary transplant centre before initiating sirolimus therapy. The patient will be assessed by both the dermatology and renal transplant teams. At the time sirolimus therapy is begun, other immunosuppressive therapy will be evaluated [25]. Sirolimus is not to be used in *de novo* adult renal transplant recipients, nor is a loading dose administered. Most centres will overlap the current immunosuppressants until their sirolimus levels is at therapeutic levels. This can take 2-3 weeks due to its long pharmacokinetic half-life.

The initial oral maintenance dose of sirolimus is 2 to 5 mg daily. Subsequent doses are based on the achievement of therapeutic trough concentrations [1].

PEDIATRIC Kidney Transplant Recipients

Children and Adolescents: 1 to 3 mg/m^2/day PO divided every twelve hours or once daily. Adjust dose to achieve target sirolimus blood concentration.

ADULT Liver Transplant Recipients

The use of sirolimus is not recommended to be used within the first three months post liver transplant due to an increased risk of thrombotic events including hepatic artery thrombosis and delayed wound healing. The safety and efficacy of sirolimus has not been established in liver transplant recipients. The risk/benefit ratio of sirolimus in any liver transplant recipient must be discussed with patient.

When sirolimus is used in combination with mycophenolate mofetil or azathioprine and corticosteroids for maintenance therapy in liver transplant recipients, a sirolimus dosage of 2 to 3 mg PO daily (0.05 mg/kg/day) is prescribed and then dosage is adjusted to achieve therapeutic target concentrations [14-19].

ADULT Heart Transplant Recipients

Sirolimus is not to be used within the first three months post- heart transplant. Sirolimus dosages are adjusted based on sirolimus blood concentrations.

ADULT Lung Transplant Recipients

Sirolimus may be used in exceptional circumstances on a case-by-case basis when prescribed by the transplant physician.

Administration

Sirolimus should be taken consistently either with or without food [1,2,10]. Cyclosporine increases absorption of sirolimus, and their administration should be separated by four hours (sirolimus should be taken four hours after the cyclosporine dose). Concomitant administration may increase the risk of sirolimus-associated adverse effects [1, 2, 6]. However, the combination of sirolimus and tacrolimus can be taken at the same time.

The dose of sirolimus solution should be added to at least 60 mL of water or orange juice in a glass or plastic container (not a Styrofoam or paper container), stirred vigorously and drunk at once. Grapefruit juice should be avoided since it can unpredictably alter sirolimus pharmacokinetics. The sirolimus container should be rinsed with an additional volume of 120 mL of water or orange juice, stirred vigorously, and drunk at once [1,2,10,22]. Swish mouth with water and spit after liquid, to help reduce mouth sores.

Monitoring

It is recommended that blood sirolimus trough blood concentrations be monitored in all patients, with particular attention to the following patient groups [23]:

- Pediatric patients
- Patients greater than and equal to 13 years old and weighing less than 40 kg
- Patients with significant liver disease
- Patients receiving medications that inhibit Cytochrome P_{450} 3A4 or P-glycoprotein (i.e. diltiazem, ketoconazole, fluconazole, verapamil) or induce Cytochrome P_{450} 3A4 (rifampin, phenytoin, carbamazepine)
- Patients whose cyclosporine or tacrolimus dose has been markedly reduced or discontinued
- Patients receiving sirolimus plus low-dose tacrolimus
- Patients who are at high risk for acute rejection
- Patients whom are on sirolimus monotherapy

Sirolimus serum concentrations are to be obtained once weekly until therapeutic range is achieved and then monthly.

The high-performance liquid chromatography - tandem mass spectrometry assay (HPLC-TMS) to determine sirolimus concentrations is only done at Vancouver General Hospital and Victoria General Hospital. Samples must be sent to Vancouver General Hospital or Victoria General Hospital for analysis.

Target Sirolimus Whole - Blood Concentrations for Transplant Recipients

Table 1: Renal Transplants

Time Post Transplant (Months)	Sirolimus Trough Concentration (mcg/L)* (When sirolimus is used with mycophenolic acid and steroids)	Sirolimus Trough Concentration (mcg/L)* (When sirolimus is used as a single agent +/- steroids)
ADULT Kidney Transplants (May 2017)		
Greater than 3 months	5 to 10	8 to 10
PEDIATRIC Kidney Transplants (May 2025)		
Greater than 3 months	5 to 8	6 to 10

***Tandem Mass Spectrometry Assay**

Table 2 Liver, Lung and Heart Transplants

Time Post Transplant (Months)	Sirolimus Trough Concentration (mcg/L)* (When sirolimus is used with tacrolimus or cyclosporine +/- mycophenolic acid and steroids)	Sirolimus Trough Concentration (mcg/L)* (When sirolimus is used as a single agent +/- steroids)
ADULT Liver Transplants (May 2021)		
1 to 3 months	8 to 12	10 to 15
Greater than 3 months	5 to 10	8 to 12
ADULT Lung Transplants (Dec 2020)		
contact lung transplant clinic for patient specific targets		
ADULT Heart Transplants (Nov 2014)		
All	4 to 8	8 to 12

***Tandem Mass Spectrometry Assay**

AVAILABILITY

Sirolimus (Rapamune® Pfizer) is available for oral administration both in solution and tablet formulations. It is supplied as oral solution at a concentration of 1 mg/mL in glass bottles of 60 mL and as a 1 mg white triangular tablet. Solutions should be stored in the refrigerator and protected from light [(1)]. Once opened the solution should be used within one month.

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Tacrolimus: IMMEDIATE Release and EXTENDED Release

INTRODUCTION

Tacrolimus is an immunosuppressant used in combination with other immunosuppressants to prevent transplant rejection.

In BC, tacrolimus is available in FOUR different formulations **(non-interchangeable formulations**):

- Tacrolimus IMMEDIATE release (**Sandoz tacrolimus** or **Prograf® tacrolimus)** a twice daily formulation.
- Tacrolimus EXTENDED release (**Advagraf® tacrolimus or Envarsus PA® tacrolimus)** a once a day formulation.

MECHANISM OF ACTION

The mechanism of action of tacrolimus is similar to that of cyclosporine, even though their chemical structures differ greatly. Tacrolimus inhibits T-lymphocyte activation. Experimental evidence suggests tacrolimus becomes activated only when complexes with intracellular receptors or cytosine binding proteins known as immunophilins. The immunophilin - drug complex binds competitively to and inhibits calcineurin. Inhibition of calcineurin blocks the transcription factor NFAT from entering the nucleus leading to inhibition of transcription of IL-2 and other related genes; this is believed to mediate the immunosuppressive activity of both tacrolimus and cyclosporine [1].

PHARMACOKINETICS

Tacrolimus is a hydrophobic molecule with poor absorption from the gastrointestinal tract. The oral bioavailability of tacrolimus ranges from 5 to 67%, with a mean bioavailability of 29% in patients who have undergone liver, small bowel, or kidney transplantation. The presence of food reduces the absorption of tacrolimus. Maximum absorption occurs when the medication is taken on an empty stomach. Bile does not appear to influence tacrolimus absorption.

Tacrolimus undergoes extensive tissue distribution, as evidenced by its large volume of distribution (V_{ss} in plasma ranges from 5.6 to 65 L) [1, 2].

Tacrolimus EXTENDED release a once-a-day formulation has prolonged release characteristics [2]. There is a marked reduction of intra-subject variability for exposure (AUC 0-24) in black kidney transplant recipients at steady state after converting from tacrolimus IMMEDIATE release [% coefficient of variation (% CV) 25.4%] to tacrolimus EXTENDED release (% CV 12.2%). In white kidney transplant recipients, the intra-subject variability for exposure at steady state was similar after converting from tacrolimus, IMMEDIATE release (% CV 12.2%) to tacrolimus EXTENDED release (% CV 14.1%). Black patients require higher tacrolimus EXTENDED release doses to attain comparable trough concentrations compared to white patients [2].

Tacrolimus is extensively metabolized primarily by the hepatic P_{450} enzyme system. Less than one percent of the administered dose is excreted unchanged in urine, bile, and feces [1].

Pediatric transplant patients appear to eliminate tacrolimus from the body more rapidly than adult transplant patients on a body-weight basis. Therefore, pediatric patients often require higher doses of tacrolimus based on mg/kg body weight than adults do to maintain similar plasma tacrolimus concentrations. Elimination half-life from whole blood is approximately 12 hours in adult liver transplant patients and 21 hours in healthy adult volunteers.

THERAPEUTIC USE

Tacrolimus IMMEDIATE release is indicated for prophylaxis and treatment of rejection following renal, liver, heart, lung and pancreas transplantation when used in combination with other immunosuppressants.[1].

Tacrolimus may be used in adults, pre-transplant in combination with mycophenolate mofetil, plasma exchange and rituximab for ABO incompatible recipients who may receive a living donor kidney transplant.

Tacrolimus may be used pre-transplant in pediatric patients in combination with mycophenolate mofetil for recipients who may receive a living donor transplant.

It is important to note several international safety alerts have been sent out regarding prescribing, dispensing and administration errors of tacrolimus EXTENDED release.

Tacrolimus IMMEDIATE release and tacrolimus EXTENDED release **are not interchangeable** and should not be substituted without careful therapeutic monitoring as both have a very narrow therapeutic index. Tacrolimus IMMEDIATE release is dosed every 12 hours and tacrolimus EXTENDED release is dosed every 24 hours. Care must be taken when converting a patient from tacrolimus IMMEDIATE release to tacrolimus EXTENDED release.

Patients and health care providers must understand the once-a-day dosage regimen and which drug formulation (ie brand name) they are receiving as they are not interchangeable. Clinicians (providers) must always specify which brand name (eg. Sandoz tacrolimus, Prograf tacrolimus, Advagraf tacrolimus, Envarsus PA tacrolimus) is being prescribed. Any changes in brand and dose should done under the close supervision of the patient's transplant team [4-7].

ADVERSE DRUG REACTIONS

Adverse effects experienced by patients receiving tacrolimus are similar to those experienced by patients receiving cyclosporine. The principal adverse effects of tacrolimus are tremor, headache, nausea, diarrhea, hypertension, and renal impairment. Adverse reactions experienced by patients receiving with tacrolimus EXTENDED release are comparable to those patients receiving tacrolimus IMMEDIATE release [2].

Anaphylactic reactions have been reported in animals and humans following intravenous administration, most likely due to the polyoxyl-60-hydrogenated castor oil vehicle. All patients should be carefully observed for evidence of possible hypersensitivity and medications for the treatment of anaphylaxis must be available at the bedside.

Tacrolimus Adverse Drug Reactions

Area of Affect	Side Effect
Nervous system	Headache Tremor Insomnia Paresthesia
Gastrointestinal	Diarrhea Nausea Constipation LFT abnormal Anorexia Vomiting
Cardiac	Hypertension
Dermatologic	Pruritis Rash Alopecia
Endocrine	Hyperglycemia
Hematologic	Lymphoproliferative diseases Anemia Leukocytosis Thrombocytopenia
Infectious	CMV
Musculoskeletal	Abdominal pain Pain Fever Asthenia Back pain Ascites
Renal	Nephrotoxicity

DRUG INTERACTIONS

Tacrolimus, sirolimus and cyclosporine are metabolized primarily by the hepatic P450 system. Therefore, medications known to affect cyclosporine and sirolimus metabolism are also likely to alter tacrolimus metabolism, resulting in changes in tacrolimus blood concentrations. Refer to Appendix A for significant drug-drug and pharmacodynamic interactions.

DOSE AND ADMINISTRATION

Tacrolimus IMMEDIATE release (PROgraf® or Sandoz tacrolimus) is the standard tacrolimus product used in BC Transplant protocols.

ADULT Kidney and Kidney-Pancreas Transplant Recipients

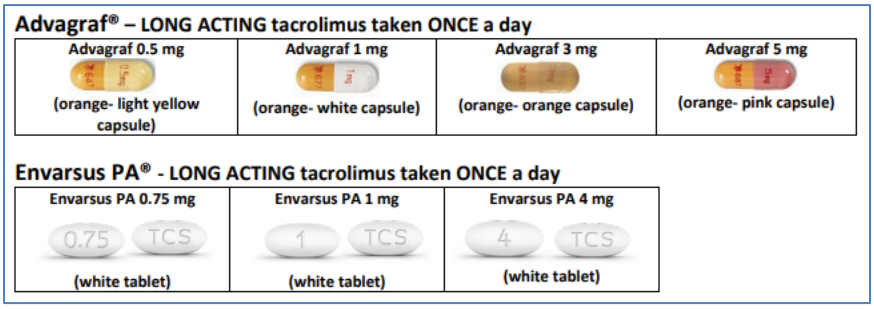
The post-transplant initial adult oral dose of tacrolimus IMMEDIATE release is 0.12 to 0.15 mg/kg/day divided every 12 hours.

The pre-transplant adult dose of tacrolimus IMMEDIATE release is 0.15 mg/kg/day PO divided every 12 hours for 14 days. This is for ABO incompatible recipients who can receive a living donor transplant.

If IV tacrolimus is required, it should be given at ¼ total daily adult oral dose (divided Q12H) over 4 hours or 1/3rd of total daily adult oral dose once a day IV over 3 to 4 hours. Alternatively, it may be given as a continuous 24 hour infusion.

Tacrolimus EXTENDED release may be prescribed on a case-by-case basis at the discretion of the transplant physician/pharmacist in patients in whom once daily dosing would be beneficial. BC Transplant has **2 non-interchangeable** formulations of EXTENDED release tacrolimus available:

- Advagraf tacrolimus 0.5 mg, 1 mg, 3 mg and 5 mg capsules – manufacturer Astellas
- Envarsus PA tacrolimus 0.75 mg, 1 mg and 4 mg tablets – manufacturer Paladin/Endo Ventures



Patients converting from tacrolimus IMMEDIATE release to tacrolimus EXTENDED release should be administered a single morning dose of tacrolimus EXTENDED release equivalent to patients' previous stable total daily dose of tacrolimus IMMEDIATE release. Initial conversion ratio:

- Immediate release tacrolimus to Advagraf tacrolimus: **1 mg: 1.2 mg basis***
- Immediate release tacrolimus to Envarsus PA tacrolimus: **1 mg: 0.7 mg basis***

***NOTE:** Recommend consultation with transplant centre clinical pharmacist for conversion protocol.

Subsequent tacrolimus EXTENDED release (Advagraf or Envarsus PA) dosages should be adjusted to maintain trough concentrations similar to those prior to conversion [2]. Data indicates de novo black kidney transplant recipients require higher tacrolimus EXTENDED release dosages to attain comparable trough concentrations to Caucasian patients [2].

For patients requiring a switch from tacrolimus to cyclosporine, an estimated conversion of 1:40 (tacrolimus dose to cyclosporine) can be used a starting point.

PEDIATRIC Kidney Transplant Recipients
The initial post-transplant pediatric oral dose of tacrolimus IMMEDIATE release is as follows:

- Children **<12 years:** 0.2 mg/kg/dose every 12 hours
- Children **≥12 years**: 0.1 mg/kg/dose every 12 hours

For recipients who can receive a living donor transplant, a pre-transplant pediatric dose of tacrolimus IMMEDIATE release (<12yrs: 0.2mg/kg/dose orally every 12 hours, or ≥12yrs: 0.1 mg/kg/dose orally every 12 hours) can be given for up to 14 days before transplant date.

If IV tacrolimus is required, it should be given at 1/3 total daily oral dose (divided Q12H) as a continuous 24 hr infusion, or alternatively, every 12 hours.

For pediatric patients, when converting between immediate release tacrolimus to an extended release formulation (Prograf/Sandoz tacrolimus to Advagraf), the ratio is usually 1:1.2[8]. Tacrolimus pre-dose levels to be monitored to ensure target range is maintained. There is no data currently on use of Envarsus PA tacrolimus in pediatric patients.

ADULT Liver Transplant Recipients
The initial adult oral dose of tacrolimus IMMEDIATE release is 0.03 mg/kg/dose given every 12 hours (approximately 1 mg PO Q12H) for the first few days post-transplant. This dose helps to ensure the patient does not experience tacrolimus toxicity in case the medication is not being metabolized efficiently. Further dosages are based on therapeutic blood concentrations.

Tacrolimus EXTENDED release may be considered on a case-by-case basis for patients with stable immunosuppression in whom once daily administration would be beneficial as a late change for tacrolimus IMMEDIATE release. Patients converting from tacrolimus IMMEDIATE release to tacrolimus EXTENDED release should be administered a single morning dose of tacrolimus EXTENDED release equivalent to patient's previous stable total daily dosage of tacrolimus IMMEDIATE release on a 1 mg:1 mg basis. Subsequent tacrolimus EXTENDED release doses should be adjusted in order to maintain trough concentrations similar to those prior to conversion [2].

ADULT Lung Transplant Recipients
The adult oral dose of tacrolimus IMMEDIATE release is 0.03 to 0.05 mg/kg/dose PO/NG every 12 hours. Adjust dose if patient is on interacting medications (i.e., fluconazole).

IV tacrolimus is generally not recommended, however if IV tacrolimus is to be used, ¼ total daily adult oral dose per day (divided Q12H) is to be given IV over 4 hours.

ADULT Heart Transplant Recipients

The initial adult oral dose of tacrolimus IMMEDIATE release is 0.1 mg/kg/day divided every 12 hours. Dosage is based on tacrolimus blood concentrations.

Therapeutic Drug Monitoring

In British Columbia the tandem mass spectrometry is the assay used for the determination of cyclosporine blood concentrations. The assay is done at Vancouver General Hospital, St. Paul's Hospital, Victoria General Hospital, and LifeLabs®. Blood for cyclosporine assays from Northem Health and Interior Health are sent to Vancouver General Hospital. Note that IH switched from the Siemens Immunoassay at Royal Inland Hospital to the mass spectrometry assay at Vancouver General Hospital in April 2024. When reviewing the literature and results it is important to know whether a mass spectrometry based assay was used. Immunoassay results tend to be impacted by accumulation of metabolites and other changes like hematocrit and total protein levels, thus results are not comparable. Contact your local lab for further information

Target Tacrolimus Blood Concentrations for Solid Organ Transplant Recipients

Time Post-Transplant (Months)	Tacrolimus Trough Blood Concentration (ng/mL) Tandem Mass Spectrometry Assay	
ADULT Kidney and Kidney/Pancreas Transplants (March 2025)		
Less than 1 month	9 to 12	
1 month to 3 months	8 to 10	
3 months to 12 months	6 to 8	
Greater than 12 months	5 to 7	
PEDIATRIC Kidney Transplants (May 2025) ***Targets may be adjusted based on pharmacokinetic testing**		
Month 1	10 to 15	
Month 2 and 3	8 to 12	
Month 4, 5 and 6	6 to 10	
After Month 6	5 to 8	
ADULT Liver Transplants* (May 2021) **Please contact Vancouver General Hospital Transplant Clinic if you have any questions.**		
	Standard Dosing	**Low Target/Kidney Sparing**
Dosing	0.05 mg/kg PO BID	0.03 mg/kg PO BID with basiliximab induction
Less than 1 month	8 to 10	6 to 8
1 to 3 months	7 to 9	6
Greater than 3 months	6 to 8	4 to 6
Greater than 12 months	4 to 6	3 to 5
ADULT Lung Transplants (Dec 2020)		
0 to 6 months	10 to 12	
6 to 12 months	8 to 10	
Greater than 12 months	6 to 8	
*For severe AKI or temporary dialysis with hopes of renal recovery contact transplant clinic for tacrolimus target		
ADULT Heart Transplants (Nov 2014)		
Less than 3 months	9 to 12	
3 to 6 months	8 to 9	
6 to 12 months	6 to 8	
Greater than 12 months	4 to 8	
PEDIATRIC Heart Transplants (Dec 2020)		
0 to 6 months	10 to 12	
6 to 12	8 to 10	
Year 2 and 3	6 to 8	
>3 years (No rejection)	4 to 6	

AVAILABILITY

- Tacrolimus IMMEDIATE release (**PROgraf® tacrolimus or Sandoz tacrolimus**) is available a 0.5 mg, 1 mg and 5 mg capsules.
- Tacrolimus EXTENDED release (**ADVAgraf® tacrolimus,** Astellas) is available as 0.5 mg, 1 mg, 3mg, and 5 mg capsules.
- Tacrolimus EXTENDED release **(Envarsus PA tacrolimus**, Paladin/Endo Ventures) is available as 0.75 mg, 1 mg and 4 mg tablets.

No oral liquid dosage formulation is commercially available. In British Columbia, pharmacies dispensing tacrolimus suspension prepare a 1 mg/mL suspension [7]. Contact B.C. Children's Hospital Pharmacy at 604-875-2059 for suspension preparation instructions.

Tacrolimus is supplied in ampules containing 5 mg tacrolimus IMMEDIATE release (PROgraf® Astellas) per mL for intravenous administration. The intravenous route should only be used if the patient is not able to tolerate oral tacrolimus [1].

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Valganciclovir

INTRODUCTION

Valganciclovir hydrochloride is the salt of the L-valyl ester of Ganciclovir, which is a synthetic 2'-deoxy-guanosine analogue used for the prevention and treatment of cytomegalovirus (CMV) infections in immuno-compromised or immunosuppressed patients [1,2].

MECHANISM OF ACTION

Valganciclovir is a prodrug of ganciclovir. Following oral administration, Valganciclovir is rapidly converted to ganciclovir by intestinal and hepatic esterases. Ganciclovir inhibits replication of herpes viruses and *in vitro* and *in vivo*. The virustatic activity of ganciclovir against CMV is due to the inhibition of viral DNA synthesis [1, 2].

PHARMACOKINETICS

Most reports of the pharmacokinetics of valganciclovir have been in HIV/CMV seropositive and HIV positive patients with CMV retinitis [1-3].

Following oral administration, valganciclovir is rapidly hydrolyzed to ganciclovir by esterases in the intestinal and hepatic cells. After administration of valganciclovir, ganciclovir bioavailability was 60% when taken with food. The bioavailability of valganciclovir is significantly higher than oral ganciclovir. When taken with food, steady state ganciclovir AUC increased by 30% and the Cmax increased by 14%, without any change in the time to peak plasma concentrations (Tmax). When taken with food, a 900 mg dose of valganciclovir is essentially equivalent to an IV ganciclovir dose of 5 mg/kg [1,2].

Time to maximum serum ganciclovir concentration (C_{max}) is approximately 2 hours. The C_{max} following administration of 900 mg of valganciclovir to adult patients with normal renal function is 5.6 mcg/mL and the serum concentration at 12 hours after the dose is approximately 1 mcg/mL. In vitro CMV resistance is defined as an IC_{50} greater than and equal to 1.5 mcg/mL. Ganciclovir has a volume of distribution of approximately 0.7 L/kg. Binding of ganciclovir to plasma proteins is about 1% to 2% [1-3]. Liver transplant recipients attained similar exposures to ganciclovir following the administration of 900 mg of valganciclovir and 5 mg/kg IV ganciclovir [4].

Valganciclovir is eliminated as ganciclovir in the urine via glomerular filtration and active tubular secretion. The renal clearance of ganciclovir is approximately 3 mL/min/kg [1-3].

Ganciclovir clearance is correlated with creatinine clearance. The elimination half-life of ganciclovir is about 4 hours in patients with a creatinine clearance of 75 mL/min and approximately 24 hours in patients with a creatinine clearance between 10 and 20 mL/min [1, 3, 5].

THERAPEUTIC USE

Valganciclovir is approved for the prevention of cytomegalovirus (CMV) disease in solid organ transplant recipients who are at risk.

ADVERSE DRUG REACTIONS

Valganciclovir is a prodrug of Ganciclovir, which is rapidly converted to ganciclovir after oral administration. The adverse effects associated with ganciclovir use can therefore be expected to occur with valganciclovir. All of the adverse effects observed in valganciclovir studies have been previously observed with ganciclovir [1, 2].

Valganciclovir Adverse Drug Reactions

Area of Effect	Adverse Effects
Gastrointestinal	Diarrhea, nausea, vomiting, abdominal pain, oral candidiasis
Hematologic	Neutropenia, anemia, thrombocytopenia
Body	Fever, headache, fatigue
CNS	Insomnia, paresthesia, peripheral, neuropathy, dizziness
Eye	Retinal detachment
Other	Sinusitis

In animal studies and *in vitro,* ganciclovir has been shown to be carcinogenic, teratogenic, mutagenic and has caused aspermatogenesis. Ganciclovir should be considered a potential teratogen and carcinogen in humans. Women of childbearing potential should be advised that ganciclovir causes birth defects in animals and should not be used during pregnancy. Due to the potential for serious adverse events in nursing infants, mothers should be instructed not to breast feed if they are receiving valganciclovir. Women and men of childbearing potential should be advised to use effective contraception (men–barrier contraception) during treatment with valganciclovir [1].

Valganciclovir should be used in caution in patients with renal failure and the dose should be adjusted based on the estimated creatinine clearance [5].

DRUG INTERACTIONS

Valganciclovir is a prodrug of ganciclovir, which is rapidly converted to ganciclovir after oral administration. The adverse effects associated with ganciclovir use can therefore be expected to occur with valganciclovir.

Probenecid and other medications secreted by renal organic anion transport system are likely to reduce ganciclovir clearance, causing ganciclovir accumulation, increasing the risk of ganciclovir toxicity.

Co-administration with other myelosuppressive agents (mycophenolic acids, azathioprine) increases the risk of toxicity.

Seizures have been reported in patients taking ganciclovir and imipenem-cilastatin concomitantly. This combination should be avoided [1].

DOSE AND ADMINISTRATION

The valganciclovir dose depends on patient's renal function and whether or not the patient is receiving valganciclovir for CMV prophylaxis, pre-emptive treatment or disease treatment. Refer to the tables of valganciclovir dosing with impaired renal function and CMV prophylaxis and treatment protocols for renal, liver and lung recipients on the following pages. Valganciclovir is administered with food.

Ganciclovir IV Dose for ADULT Patients with Impaired Renal Function [6]

Creatinine Clearance (mL/min)	Ganciclovir IV Dosage (mg/kg) TREATMENT and PRE-EMPTIVE Dosage	Ganciclovir IV Dosage (mg/kg) PROPHYLAXIS Dosage
Greater and equal to 70	5 mg/kg/dose q 12h	5 mg/kg/dose q 24h
50 to 69	5 mg/kg/dose q 24h OR 2.5 mg/kg/dose q 12h	2.5 mg/kg/dose q 24h
25 to 49	2.5 mg/kg/dose q 24h	1.25 mg/kg/dose q 24h
10 to 24	1.25 mg/kg/dose q 24h	0.625 mg/kg/dose q 24h
Less than 10	1.25 mg/kg/dose 3 times weekly post dialysis	0.625 mg/kg/dose 3 times weekly post dialysis

Valganciclovir Oral TABLET Dose for ADULT and Adolescent Patients Greater Than 16 Years of Age with Impaired Renal Function [1]

Creatinine Clearance (mL/min)	Valganciclovir TABLETS PO TREATMENT and PRE-EMPTIVE Dosage	Valganciclovir TABLETS PO PROPHYLACTIC Dosage
Greater and equal to 60	900 mg PO twice a day	900 mg PO daily
40 to 59	450 mg PO twice a day	450 mg PO daily
25 to 39	450 mg PO daily	450 mg PO every 2 days
10 to 24	450 mg PO every 2 days	450 mg PO twice weekly

Valganciclovir Oral SOLUTION Dose for ADULT and Adolescent Patients Greater Than 16 Years of Age with Impaired Renal Function [1,16]

Creatinine Clearance (mL/min)	Valganciclovir SOLUTION PO TREATMENT and PRE-EMPTIVE Dosage	Valganciclovir SOLUTION PO PROPHYLACTIC Dosage
Greater and equal to 60	900 mg PO twice a day	900 mg PO daily
40 to 59	450 mg PO twice a day	450 mg PO daily
25 to 39	450 mg PO daily	225 mg PO daily
10 to 24	225 mg PO daily	125 mg PO daily
Less than 10	200 mg three times a week post dialysis	100 mg PO three times a week post dialysis

***** Valganciclovir (Valcyte®) oral solution is commercially available – use hazardous drug precautions *****

Valganciclovir Oral Dose for Pediatric Transplant Recipients Aged Four Months to 16 Years [7, 16]

Body surface area (BSA)-based dosing:

Dose (mg) = 7 x BSA x CrCl, to a maximum dose of valganciclovir of 900mg once daily for CMV prophylaxis (Maximum: 900mg BID for CMV treatment)

$$\text{BSA } (m^2) = \frac{\sqrt{\text{height (cm) x weight (kg)}}}{3600}$$

CrCl estimate = GFR estimate = calculated as per new modified Schwartz equation

$$\text{New Modified Schwartz equation*} = \frac{0.413 \text{ x height (cm) x } 88.4}{\text{SCr mmol/L}}$$

*If calculated CrCl exceeds 100 mL/min/1.73 m^2, use a maximum of 100 mL/min/1.73 m^2 in dosage calculation.

Alternative weight-based dosing: 15-17 mg/kg/dose (maximum 900 mg/dose) once daily for CMV prophylaxis (Maximum: 900 mg BID for CMV treatment)

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Adult Solid Organ Transplant CMV Prophylaxis Duration *(Nov 2024)*

using Valganciclovir 900mg PO daily* or Ganciclovir 5mg/kg/IV q24h* (adjusted for CrCl)

Organ and Type of Immunosuppression			High Risk (D+/R-)	Intermediate Risk (R+)	Low Risk (D-/R-)
Kidney	Post Transplant	ATG Induction	6 months**	3 months	No+
		Basiliximab Induction	6 months**	No	No
	Rejection^	ATG therapy	3 months	3 months	Check CMV IgG~ Status+
		Steroids therapy	No	No	No
Heart	Post Transplant	ATG Induction	6 months**	3 months	No+
		Basiliximab Induction	6 months**	No+	No+
	Rejection^	ATG therapy	3 months	3 months	Check CMV IgG~ Status
		Steroids therapy	1 month	No	No
Liver	Post Transplant	ATG Induction	No	No	No
		Basiliximab Induction	No	No	No
	Rejection^	ATG therapy	3 months	3 months	Check CMV IgG~ Status
		Steroids therapy	No	No	No
Lung	Post Transplant	ATG Induction	1 year**	6 months**	No
		Basiliximab Induction	1 year**	6 months**	No
	Rejection^	ATG therapy	6 weeks	6 weeks	Check CMV IgG~ Status
		Steroids therapy	1 month	1 month	No

CMV Prophylaxis Monitoring
DURING CMV Prophylaxis
• Routine viral load monitoring not recommended • If holding valganciclovir in early period of prophylaxis due to neutropenia or other reasons, monitor CMV DNA viral load weekly
AFTER CMV Prophylaxis
• All organs except Kidney: CMV DNA viral load weekly for 8 to 12 weeks after prophylaxis completed. • Kidney: resume routine monitoring.
RESUME Routine (PRE-EMPTIVE) Monitoring
• CMV DNA viral loads per routine bloodwork for up to 1 year after end of prophylaxis therapy

* Adjust dose for impaired renal function – Refer to BCT medication guidelines

** If leukopenia is thought to be due to valganciclovir and patient has completed 4 to 6 months of prophylaxis, stop valganciclovir and start weekly CMV DNA viral loads and CBC with diff. If patient is neutropenic (ANC<0.5) or has declining WBC counts on therapeutic valganciclovir doses, may need to start filgrastim 300 mcg subcutaneously daily for 3 doses to increase the count and continue with valganciclovir for treatment. **Do not reduce** valganciclovir or ganciclovir for leukopenia. See BCT Filgrastim Neutropenia guideline http://www.transplant.bc.ca/Documents/Health%20Professionals/Clinical%20guidelines/BCT-Post-Transplant-Neutropenia-Filgrastim-GCSF-Protocol-FINALOct2017.pdf

~ Prior to ATG therapy for rejection, determine if CMV IgG status has changed (ie seroconverted). If patient is still IgG negative; then no prophylaxis needed after ATG for rejection. If patient is IgG positive, then provide prophylaxis as per R+

+ HSV prophylaxis with valacyclovir for 3 months (for kidney R-/D- who received ATG, and heart pts not taking valganciclovir)

^ If post-transplant and post-rejection prophylaxis overlap, ensure durations have been met for both

Pediatric Patients:

- All samples should be tested at BC Children's lab since the CMV assay at Children's differs from the adult assay at St. Paul's/VGH labs
- BC Children's lab reports CMV viral load as copies/mL
- Pediatric CMV guidelines from BCCH can be found here: https://shop.healthcarebc.ca/phsa/BCWH_2/Pharmacy,%20Therapeutics%20and%20Nutrition/C-05-07-62969.pdf

Table of Contents

Adult Solid Organ Transplant CMV Treatment *(Nov 2024)*

Valganciclovir 900mg PO BID* or Ganciclovir 5mg/kg/IV q12h* (adjusted for CrCl)

	Pre-emptive Treatment (asymptomatic)			Disease Treatment (symptomatic)
CMV Viral Load (IU/mL)	**High Risk (D+/R- mismatch; D-/R-; delayed reporting of CMV viral load** (e.g. Regional/remote communities))**		**Low risk (R+; timely access to CMV viral load results)**	
	Other	**Liver transplant within 100 days post- transplant**		
Below 200	• No treatment	• **CMV viremia at any level - START treatment** • Treat until 2 consecutive negative test (CMV <35 IU/mL) 1 week apart • All episodes of viremia within the first 100 days should be treated	• No treatment	**Regardless of CMV viral load – START treatment if symptomatic**
200 to 5000	• **For FIRST CMV viremic episode ONLY - START treatment** • For subsequent CMV viremia, repeat viral load in 1 week. If no significant change, continue routine monitoring • Re-evaluate immunosuppression and renal dosing • Check CMV IgG seroconversion for R- patients^		• No treatment • Re-evaluate immunosuppression and renal dosing • Can repeat CMV DNA viral load in 1 week if concerned may be above 5000	
Above 5000	• **START treatment**		• **START treatment**	

Treatment Duration	
Pre-emptive Treatment	**Disease Treatment**
Treat for at least 3 weeks with end point criteria: • CMV DNA viral load < 200 IU/mL for 2 consecutive readings (1 week apart) or • CMV viral load < 35 IU/mL x 1 For D+/R- Liver Transplants during the first 100 days: Treat until 2 consecutive negative tests (CMV < 35 IU/mL) resulted 1 week apart If practitioners are concerned about persistent low-level viremia (patient asymptomatic), or if considering resistance testing, suggest consulting transplant ID	Same as for pre-emptive, **PLUS resolution of symptoms**

CMV Treatment Monitoring
DURING CMV Treatment
• CMV DNA viral load weekly • If CMV DNA viral load is rising or stagnant by or at 3rd week of therapy, suggest consultation with Transplant ID
AFTER CMV Treatment
• CMV DNA viral load weekly for 8 to 12 weeks after treatment completed
RESUME Routine Monitoring
• CMV DNA viral loads per routine bloodwork for up to 1 year after end of treatment

* Adjust dose for impaired renal function - Refer to BCT medication guidelines

** Recommend using Hospital based labs for faster CMV DNA viral load results (e.g. regional/remote areas)

^ Check for CMV IgG seroconversion after FIRST CMV episode. If the patient has become CMV IgG seropositive, follow the CMV Recipient Positive pathway guidelines for subsequent episodes. [NOTE: If patient received IVIG; wait 3 month after IVIG infusion to avoid false positive result of CMG IgG test]

AVAILABILITY

Valganciclovir hydrochloride is available as a 450 mg tablets and as a powder for oral solution, 50 mg/mL when reconstituted. Reconstituted solution is stable for 49 days when stored under refrigeration.

Valganciclovir is a potential teratogen and carcinogen; care must be taken to avoid contact with the skin or eyes. If contact occurs, skin should be washed thoroughly with soap and water [(1)].

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Management Guidelines:

List of Management Guidelines	
Guideline 1	Dental Procedure Prophylaxis
Guideline 2	Herpes Simplex Virus Prophylaxis
Guideline 3	Immunizations
Guideline 4	Pneumocystis jirovecii Prophylaxis (PJP)
Guideline 5	Post-transplant diarrhea
Guideline 6	Post-transplant neutropenia

Dental Procedure Prophylactic Antibiotics

The American Heart Association Guidelines for the Prevention of Infective Endocarditis:
Recommend antibiotic prophylaxis before dental procedures ONLY for patients who have a history of previous infective endocarditis, or who have had cardiac valve replacement, or surgically constructed pulmonary shunts, or conduits. *(*American Heart Association, scientific statement 2021*)* American Dental Association – Antibiotics Prophylaxis Prior to Dental Procedures

Prophylactic antibiotic coverage for dental procedures is recommended ONLY for the following transplant recipients:

- Prosthetic cardiac valve, including transcatheter-implanted prostheses and homografts
- Prosthetic material used for cardiac valve repair, such as annuloplasty rings and chords
- Previous history of infective endocarditis
- Congenital heart disease (CHD)
  - Unrepaired cyanotic CHD
  - 6 months following repair of CHD with any prosthetic material or device
  - Repaired CHD with residual defects
- Cardiac transplant recipients who develop cardiac valvulopathy

Recommended Antibiotic Regimens for a Dental Procedure

Situation	Antibiotic	Regimen: Single dose 30 to 60 min prior to procedure^	
		Adults	**Children**
Oral	Amoxicillin	2 grams	50 mg/kg
Unable to Take Oral Medication	Ampicillin OR Cefazolin or Ceftriaxone	2 grams IV or IM 1 gram IV or IM	50 mg/kg IV or IM 50 mg/kg IV or IM
True Allergy to Penicillin Allergic to Penicillin or Ampicillin – Oral	Cephalexin*# OR Doxycycline OR Azithromycin or Clarithromycin+	2 grams 100 mg 500 mg	50 mg/kg <45 kg, 2.2 mg/kg; >45 kg 100mg 15 mg/kg
Allergic to Penicillin or Ampicillin and Unable to Ta Oral Medication	Cefazolin or Ceftriaxone#	1 gm IV or IM	50 mg/kg IM or IV

***** Or other first or second generation oral cephalosporin in equivalent adult or pediatric dosage
# Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema or urticaria with penicillin or ampicillin
^ If the patient forgets to take the dose prior to the dental procedure, the dosage may be administered as soon as possible, up to 2 hours after the procedure.
+ Caution clarithromycin drug interaction with CNIs – consider alternative

Herpes Simplex Virus (HSV) Prophylaxis

The current incidence of HSV related infections is much lower than those reported in the pre-CMV prophylaxis era in the 1990s.[1] HSV infections may occur any time post-transplant given the ongoing need for immunosuppression. However, data from the 1980s in renal *transplant recipients suggested that the first month post-transplant was the high risk period* for severe disease. Prophylaxis has only been studied in this time frame.[2]

HSV serology and antibody titers are not routinely recommended. For this protocol, we are assuming all adult recipients are HSV sero-positive.

For CMV D-/R- patients induced with ATG and are not receiving valganciclovir prophylaxis for CMV, valacyclovir prophylaxis should be considered immediately post-transplant.

- Valacyclovir 500mg PO BID x 3 months.

Valacyclovir is a BC Pharmacare benefit drug and therefore is not covered on the BC Transplant Formulary.

References:

1. Netchiporouk E, Tchervenkov J, Paraskevas S, Sasseville D, Billick R. Evaluation of herpes simplex virus infection morbidity and mortality in pancreas and kidney-pancreas transplant recipients. Transplant Proc 2013;45,3343-7.

2. Wilck MB, Zuckerman RA and the AST Infectious Diseases Community of Practice. Herpes simplex virus in solid organ transplantation. Am J Transplant 2013;13:121-7.

Immunization

Refer to most current BCCDC recommended Immunization of Special Populations Program as per Candidate For or Recipient of Solid Organ or Islet Cell Transplant

General Principles for Immunization of the Immunocompromised Patients

Maximize benefit while minimizing harm.

- There is potential for serious illness and death in the under-immunization of immunocompromised people and every effort should be made to ensure adequate protection through immunization.

Make no assumptions about susceptibility or protection.

- A history of childhood infection or previous vaccination may be irrelevant.

Vaccinate at the time when maximum immune response can be anticipated.

- Vaccines may be less effective when administered during the period of altered immunocompetence. Individuals who are fully immunized may remain at risk for vaccine-preventable diseases.
- Vaccinate early when immunologic decline is predictable.
- Delay vaccination if the immunodeficiency is transient (if this can be done safely).
- Primary health care provider may decide to stop or reduce immunosuppressive therapy to permit better vaccine response (if this is appropriate).

Consider the vaccination environment broadly.

- Vaccinate family and care givers when individuals need protection (i.e., against influenza).

Avoid live vaccines (not studied in transplant patients) unless:

- Data are available to support their use and
- The risk of natural infection is greater than the risk of vaccination.

Administer routine boosters as indicated.

- The degree and duration of vaccine-induced immunity are often reduced in immune compromised individuals.

Consider the use of passive immunizing agents.

These include:

- Immune globulin (Ig)
- Intravenous immune globulin (IVIg)
- The several "pathogen-specific" Ig preparation that are available (i.e., varicella zoster Ig, tetanus Ig).

Ideally, a solid organ transplant recipient should receive all vaccines before transplantation occurs. However, some patients may not have been fully vaccinated prior to transplantation.

Please refer to the latest Pre-Transplant Vaccination Provincial Guidelines.

There is a potential for serious illness and death in both the under immunization and over immunization of solid organ transplant recipients. Immunization of those with significant immunodeficiency should be performed only in consultation with experts. Following transplantation, previous immunizations should be assessed and vaccinations offered to complete the schedule; in addition, some vaccines require additional booster doses per latest guidelines. Immunization should begin or resume at least six to twelve months after transplantation.

Pneumocystis jirovecii Prophylaxis (PJP/PCP)

Adult Patients:

Patients are prescribed prophylactic trimethoprim-sulfamethoxazole (Cotrimoxazole, Septra) for Pneumocystis Pneumonia while receiving high dose immunosuppression.

- Cotrimoxazole single strength (Septra) 1 tablet PO daily or Cotrimoxazole double strength (Septra DS) 1 tablet PO on Mondays, Wednesdays and Fridays.
- Cotrimoxazole (or alternate PJP/PCP therapy) should be administered for at least one year post transplant. For patients tolerating cotrimoxazole, consider lifelong therapy. All lung transplant patients will require lifelong therapy.
- Re-introduce cotrimoxazole (or alternate PJP prophylaxis) anytime patients are receiving increased immunosuppression or undergoing therapy for rejection.
- If patients are allergic to cotrimoxazole, consult the primary transplant centre for alternative prophylaxis.
- Alternatives include:
    - Dapsone 100 mg PO once daily. Lower dose is preferred in kidney transplant recipients: either 50 mg PO daily, or 100 mg three times weekly.
    - If patient is allergic to dapsone, alternative is: pentamidine 300 mg inhalation administered through aerosolized nebulizer every 4 weeks for 1 year post transplant. Re-evaluate possible restarting of cotrimoxazole.

Pediatric Patients (consult BCCH Transplant Program for advice on PJP therapy)

Patients are prescribed prophylactic trimethoprim-sulfamethoxazole (Cotrimoxazole, Septra®) for Pneumocystis Pneumonia while receiving high dose immunosuppression.

Administer 5 mg/kg/day trimethoprim component ONCE daily or divided bid on 3 consecutive days per week OR on Monday, Wednesday and Friday. Maximum 80 mg of trimethoprim per dose.

Cotrimoxazole should be administered for 6 months in pediatric patients.

Re-introduce cotrimoxazole (or alternate PJP prophylaxis) anytime patients are receiving increased immunosuppression or undergoing therapy for rejection.

If patients are allergic to cotrimoxazole:

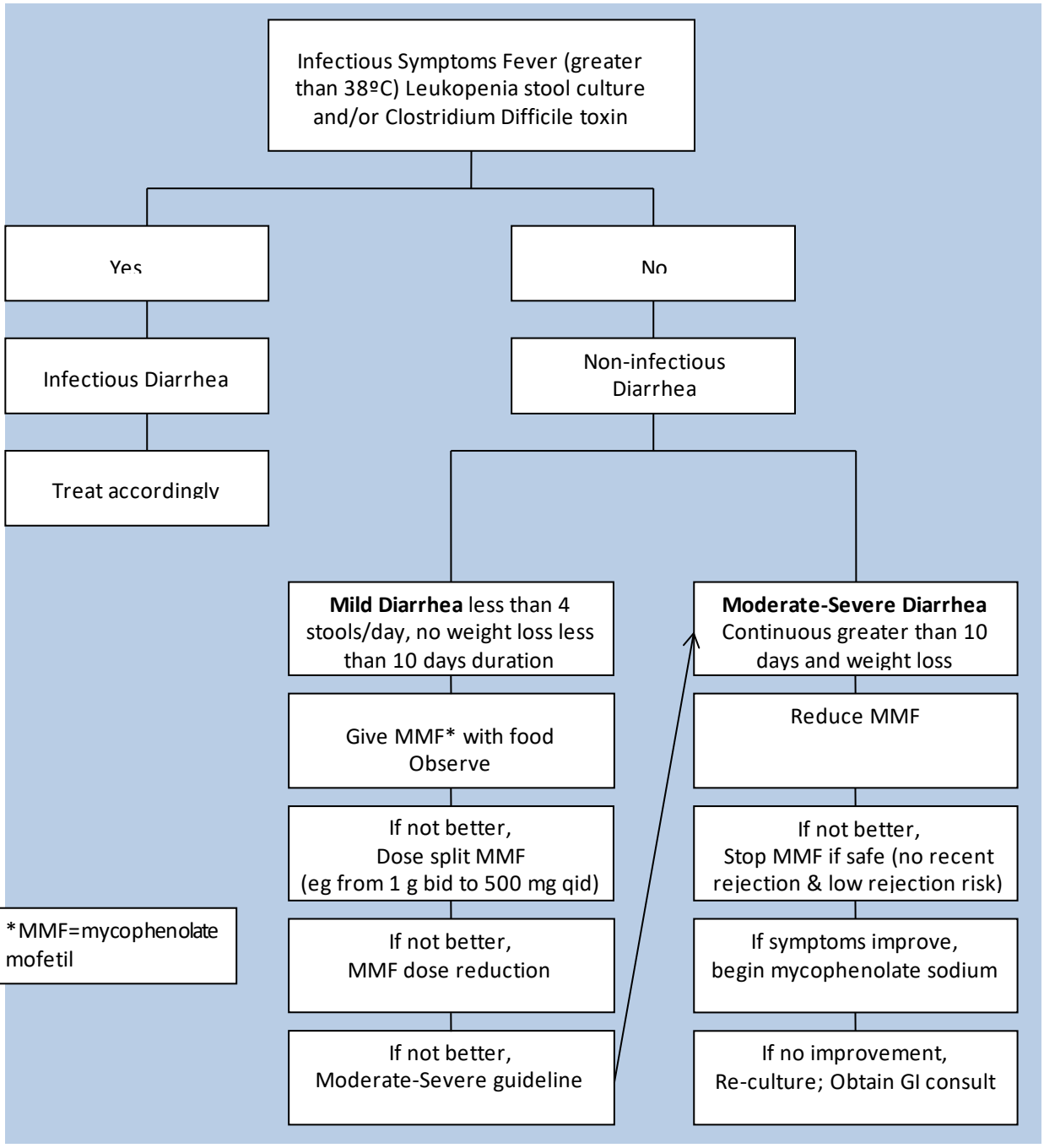
- dapsone 2 mg/kg/day PO three times a week. Maximum: 100 mg per dose.

If patient is allergic to dapsone:

- Pentamidine pediatric dose: age less than 5 years: 8 mg/kg/dose via nebulizer every 4 weeks. Maximum: 150 mg per dose.
- Age greater than 5 years: 300 mg via nebulizer every 4 weeks.

POST-TRANSPLANT DIARRHEA MANAGEMENT

Diarrhea is a frequent problem in post-transplant patients. One must make a distinction between medication induced and infectious diarrhea.



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Appendices

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Appendix A

Important Drug Interactions of Cyclosporine (CSA), Tacrolimus (TAC) and Sirolimus

(Initially prepared by Nilu Partovi, Clinical Pharmacy Specialist, Vancouver General Hospital, November 2008)

The table outlines major drug interactions only, and is not all-inclusive. The majority of interactions are the result of effects on the cytochrome P450 3A4 enzyme. Medications included below should be avoided when an appropriate alternative exists. If no alternatives are available, please advise the transplant clinic so that appropriate blood work can be arranged or advised. For a complete list of drug interactions, refer to tertiary references.

A) Drugs that **DECREASE** CSA/TAC/ Sirolimus levels			
Drug	**Possible Mechanism / Onset and severity**	**Adverse Effects**	**Management**
Anticonvulsants: ▪ phenytoin ▪ carbamazepine ▪ phenobarbital, primidone	Enzyme induction ↑ CSA/TAC/sirolimus metabolism • delayed / major • delayed/ moderate • delayed / major	↓ effectiveness of CSA/TAC/sirolimus which may lead to rejection	↑ CSA/TAC/sirolimus dose by 30% and monitor levels following addition, dose change or discontinuation. Consider alternative agent if available.
Antimicrobial: ▪ rifampin ▪ caspofungin **(tacrolimus ONLY)**	Induction of hepatic enzymes • delayed / major Mechanism is unknown • delayed/ moderate	Same as above	↑ CSA/TAC/sirolimus and monitor levels following addition, dose change or discontinuation. Monitor tacrolimus level closely when caspofungin is initiated or dose changes and when caspofungin discontinued.

Important Drug Interactions of Cyclosporine (CSA), Tacrolimus (TAC) and Sirolimus cont

B) Drugs that **INCREASE** CSA/TAC/ Sirolimus levels			
Drug	**Possible Mechanism / Onset and severity**	**Adverse Effects**	**Management**
Antimicrobial: ▪ erythromycin, clarithromycin (Biaxin®) ▪ azole antifungals (fluconazole, ketoconazole, itraconazole, posaconazole, voriconazole) ▪ nirmatrelvir-ritonavir (PAXLOVID)	↓ CSA/TAC/sirolimus metabolism, ↑ rate of absorption, ↓volume of distribution • delayed / major ↓CSA/TAC/sirolimus metabolism • delayed/ moderate ↓CSA/TAC/sirolimus metabolism • rapid / major	↑ CSA/TAC/sirolimus levels, ↑ risk of toxicity	May need to pre-emptively adjust CSA/TAC/Sirolimus dose, refer to tertiary drug interaction reference for detailed management. Consider alternative agent if available. Monitor CSA/TAC/sirolimus levels following addition, dose change or discontinuation. Monitor serum creatinine PAXLOVID: avoid use or contact transplant centre. Consider using alternative agent if available
Antidepressants: ▪ fluoxetine, fluvoxamine	↓ CSA/TAC/sirolimus metabolism • delayed/ moderate	↑ CSA/TAC/sirolimus levels, ↑ risk of toxicity	Consider another antidepressant and/or monitor CSA/TAC/sirolimus levels closely
Cardiovascular: ▪ diltiazem, verapamil ▪ amiodarone	May inhibit hepatic metabolism of CSA/TAC/sirolimus •delayed (rapid if IV amiodarone) / Major	↑CSA/TAC/sirolimus levels, ↑ risk of toxicity	Monitor CSA/TAC/sirolimus levels following addition, dose change or discontinuation.

Pharmacodynamic Interactions of Cyclosporine (CSA), Tacrolimus (TAC) and Sirolimus

Drug	Proposed Mechanism and Possible effects	Management
Aminoglycosides, Amphotericin B, NSAIDS, C0X-2 inhibitors **(CSA and tacrolimus ONLY)**	Additive nephrotoxicity	These drugs should be avoided in transplant recipients due to increased nephrotoxicity. The only exception is when the benefit clearly outweighs the potential risks and only used for short-term treatment. Renal function should be monitored closely while these drugs are used with cyclosporine or tacrolimus.
HMG-CoA Reductase Inhibitors: Example: lovastatin, simvastatin, atorvastatin	CSA/TAC/sirolimus may ↓ metabolism of these agents →accumulation of statin and toxicity Myalgia, myopathy, rhabdomyolysis	Start with low dose of these agents and monitor very closely for toxicity
Digoxin	↓ volume of distribution of digoxin by 50-70%, ↑ digoxin half-life by 30-40%, and increased digoxin levels digoxin toxicity such as vomiting, cardiac arrhythmia's	Initiate low dose and follow up with serum digoxin levels Closely monitor for symptoms of digoxin toxicity
nifedipine phenytoin **(cyclosporine ONLY)**	Additive incidence of gingival hyperplasia with CSA (not tacrolimus) Incidence increases from 8% (CSA alone) to 51% (combination)	Avoid long term use if possible. Good dental/oral hygiene with regular dentist visits

Appendix B

Filgrastim (G-CSF) Prescription/Worksheet (Optional)

1. Provider/Clinic to complete and fax to a BC Transplant contracted Pharmacy to dispense

2. Ensure patient is registered with BC Transplant and have BCT ID for coverage

Organ group: ☐ Heart ☐ Kidney ☐ Liver ☐ Lung ☐ Pancreas/Islet Requesting clinic: _____

Assessment:

(dd-mmm-yy)	Date:	Date:	Date:	Date:	Date
WBC: (10^9/L)					
Neutrophil: (10^9/L)					

Indication(s) for filgrastim:
☐ Neutrophil < 0.5
☐ Febrile neutropenia
☐ Other:

_____

☐ If transplant medication adjustments cannot be made, please indicate reason:

_____

Prescription: ☐ 1st course – recommend 300 mcg dose for first course
☐ 2nd course

*If neutrophils not responding after 2nd course in a 12 month period, please consult BCT and hematology

☐ filgrastim 300 mcg SC daily X 3 days

☐ filgrastim 480 mcg SC daily X 3days

Pharmacy:
☐ BCCH ☐ SPH
☐ RJH ☐ VGH

☐ Abb ☐ PG
☐ Kam ☐ Nan
☐ Kel ☐ Trl
☐ Lan ☐ Sur
☐ Pen

Prescriber signature Print Name College ID Date

Appendix C

Letermovir Authorization Request Form

v. April 2024

1. Transplant ID must be consulted and usage approved. Provider/clinic to then complete form and prescription, and fax to BC Transplant Pharmacy Manager Fax: 604-877-2111 (please call 604-833-6297 for urgent cases)

2. BC Transplant Pharmacy Manager to indicate authorization and fax form back to provider/clinic

3. Provider/clinic to fax form to relevant BC transplant pharmacy

BCT ID:

Name:

PHN:

A. **Organ group:** ☐ Heart ☐ Kidney ☐ Liver ☐ Lung ☐ Pancreas/Islet Requesting clinic:_____

B. ☐ Transplant Infectious Disease has been consulted & usage approved: Yes - Dr. _____

C. Indication(s) for letermovir prophylaxis:

- ☐ CMV resistance to ganciclovir or valganciclovir
- ☐ Allergy to ganciclovir or valganciclovir
- ☐ Significant neutropenia (neutrophils persistently <0.5) despite filgrastim/G-CSF support and unable to reduce immunosuppression
- ☐ Other: (with Transplant ID approval) _____

NOTE: If CMV VL > 450 IU/mL, discontinue letermovir and treat viremia using alternate CMV antivirals. Additional HSV/VZV therapy may be necessary as letermovir lacks herpes virus activity.

Prescription: Letermovir (Prevymis®) - available in 28 day blister pack

- **Ensure BCT has authorized prior to dispensing**
- **Dispense maximum 4 week supply at a time; maximum 24 week total course authorization***

☐ first course ☐ subsequent course

☐ letermovir 480 mg PO daily for
☐ 4 weeks ☐ 12 weeks ☐ 24 weeks (max) ☐ _____ weeks*

If patient is on cyclosporine:
☐ letermovir 240 mg PO daily for
☐ 4 weeks ☐ 12 weeks ☐ 24 weeks (max) ☐ _____ weeks*

Pharmacy (fax):
☐ BCCH (604-875-3663)
☐ RJH (250-519-1823)
☐ SPH (604-806-8675)
☐ VGH (604-875-4475)

*If a patient requires extended durations greater than 6 months or additional courses, a separate application needs to be submitted.

Prescriber signature Print Name College ID Date

Please fax completed form to BC Transplant office for authorization: Fax: 604-877-2111 Attn: Pharmacy Manager
BCT Authorization: ☐ Yes ☐ No Date _____ Notes: _____ Signature: _____

Appendix D

Maribavir Authorization Request Form *v.April 2025*

1. Transplant ID must be consulted and usage approved. Provider/clinic to then complete form and prescription, and fax to BC Transplant Pharmacy Manager Fax: 604-877-2111 (please call 604-833-6297 for urgent cases)

2. BC Transplant Pharmacy Manager to indicate authorization and fax form back to provider/clinic

3. Provider/clinic to fax form to relevant BC transplant pharmacy

BCT ID:

Name:

PHN:

A. Organ group: ☐ Heart ☐ Kidney ☐ Liver ☐ Lung ☐ Pancreas/Islet Requesting clinic: _____

B. ☐ Transplant Infectious Disease has been consulted and usage approved: Yes – Dr. _____

C. Indication(s) for maribavir treatment – Adult patient with CMV infection:

☐ 1. Refractory with suspected resistance to valganciclovir, ganciclovir, foscarnet, or cidofovir – must meet all criteria below:
- ☐ CMV viral load has plateaued or increased after at least 21 days of treatment, AND
- ☐ CMV viral load above 1000 IU/mL requiring treatment, AND
- ☐ Resistance testing ordered

OR

☐ 2. Genotypic resistance mutation to valganciclovir/ganciclovir – specify: _____, AND
- ☐ CMV viral load above 1000 IU/mL requiring treatment

OR

☐ Renewal due to persistent viremia if CMV viral load above 200 IU/mL. Only 1 renewal per treatment course.
Date of treatment initiation: _____ CMV viral load level & date: _____

OR

☐ Other: _____

NOTE: Discontinue maribavir if no change or an increase in CMV viral load after at least 2 weeks of maribavir treatment, and/or confirmed CMV genetic mutation associated with resistance to maribavir

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Prescription: Maribavir (LIVTENCITY®) • **Ensure BCT has authorized prior to dispensing**
☐ Treatment initiation: maribavir 400 mg PO twice daily for 8 weeks
☐ Renewal: maribavir 400 mg PO twice daily for 4 weeks (only 1 renewal per treatment course)

Pharmacy (fax):

☐ SPH (604-806-8675)

☐ VGH (604-875-4475)

Prescriber signature Print Name College ID Date

Please fax completed form to BC Transplant office for authorization: Fax: 604-877-2111 Attn: Pharmacy Manager
BCT Authorization: ☐ Yes ☐ No Date _____ Notes: _____ Signature: _____

Appendix E

Leflunomide Level Testing Form

- **Routine drug level monitoring is not recommended based on current available evidence**. However, therapeutic drug monitoring may be of benefit in difficult situations when patients demonstrate a lack of therapeutic response or exhibit signs of drug toxicity.

    - A clear relationship between drug concentration and efficacy or toxicity is lacking for leflunomide, and its therapeutic range is not well established in the literature. In addition, steady state concentrations are achieved after 14-20 weeks of therapy[2] due to the drug's very long half-life. In contrast, efficacy and toxicity endpoints, such as renal function and BKV clearance, can be readily assessed in a timely manner.
    - Based on limited data, a therapeutic range for leflunomide's active metabolite (teriflunomide/A77 1726) is suggested to be trough levels of 40-100 mcg/mL
    - A mean trough level of 81.1 ± 14mcg/mL has been associated with a higher incidence of hemolysis. If drug level is indicated, suggest to check an initial level at least 2 weeks after starting therapy and then 1 month later to assess for stability and trend.

- If drug level for leflunomide is indicated (active metabolite A771 1726), send trough (pre-dose) sample to:

  Hospitals-In-Common Laboratories, 57 Gervais Drive, North York, Ontario, M3C 1Z2, Phone: 416-422-3000 ext. 300 or 1-888-285-7817 (toll-free number)
  (See sample requisition below)

  Application form needs to be completed and consent form needs to be signed (by patient) to request an Out-of-Province laboratory testing funding:
  Out-of-Province & Out-of-Country Laboratory or Genetic Test Funding Request (phsa.ca)
  Once approved, testing and shipping of sample to In-Common Laboratories can be coordinated with the hospital laboratory site closest to the patient.

References:

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3. https://iclabs.ca/contact-us/
4. https://iclabs.ca/test/988/
5. http://www.phsa.ca/plms/forms-test-information/out-of-province-out-of-country-test-request-forms

Hospital Name: _____
Dept. of Pathology and Laboratory Medicine
Address: _____
_____
Phone: _____
Fax: _____

Leflunomide Level Instructions

Collection Date _____

Time _____

Collected by _____

Container: **RED TOP 1-3.5 mL**
Test Code: **DISPO** – Leflunomide level

Special Instructions for Laboratory Staff

- Allow blood to clot for approx. 30 min
- Centrifuge at 1200g for 10 min
- Transfer serum to 12 x 75 aliquot tube (minimum volume required is 1 mL)
- Freeze at **-20°C or colder**

Accessioned by: _____

Ship frozen sample on Dry Ice to:

Hospitals-In-Common Laboratories
57 Gervais Drive, North York,
Ontario, M3C 1Z2
Phone: 416-422-3000 ext. 300

SEND THIS REQUISITION WITH THE SAMPLE

For Hospitals-In-common Laboratories:
Please forward results to the phone/fax listed above: Attn:

_____

Appendix F

BCT Exceptional Drug Use Funding Request Form

Please complete fillable form and return to BC Transplant Pharmacy Manager

Date of Request:
Patient Initials: **BCTID:**
Transplant Program:

Requesting clinician: **Phone and email**:

Drug, dose, route, duration:
Indication:
Past therapeutic alternatives and response:
Other therapeutic alternatives:
Benefits compared to alternatives:

Evidence for use:

Off label use: ☐ No ☐ Yes (if yes please provide evidence of efficacy and potential risks:

Monitoring for efficacy:

Potential risks of therapy:

Potential risks of not receiving therapy:

Monitoring risks/side effects:

Projected costs (maximum potential costs):

Common Drug Review status: ☐ Under Review ☐ Reimbursement
☐ Restricted reimbursement ☐ No reimbursement
Pharmacare coverage: ☐ Under Review ☐ No ☐ Yes
Pharmacare Special Authority: ☐ No ☐ Yes, restricted to:

Evaluators: ☐ BCT Provincial Executive Director ☐ Chair TDTSC
☐ BCT Provincial Operations Director ☐ BCT Pharmacy Manager
☐ Transplant Specialist or Infectious Diseases Specialist

Date of Evaluation:

Approval: ☐ No (explanation why denied approval)
☐ Yes (parameters of approval)

Follow up: