

[TRANSPLANT] TIME

Providing care in the
community setting

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During 2007, 2,188 organ transplants were performed in Canada.¹ Short-term graft and patient survival (i.e. within the first year after transplantation) have long been the mainstays in the measurement of immunosuppressive drug efficacy in solid organ transplants. However, despite significant improvement in short-term results since the development of cyclosporine, this has not translated into better long-term outcomes. Consequently, the efforts of transplant specialists have now turned toward the development of strategies to maximize long-term allograft function while minimizing or managing chronic toxicities of the drugs that are required to sustain life.

The past decade in transplantation has seen the addition of one new class of oral immunosuppressant drugs (mTOR inhibitors) that can be used for maintenance immunosuppression, as well as new formulations for existing drugs (i.e., tacrolimus, cyclosporine, mycophenolic acid). In order to arm pharmacists with the tools needed for providing optimal pharmaceutical care to the growing number of solid organ transplant recipients, this article discusses basic concepts in immunosuppressive drug therapy and highlights important information about individual immunosuppressant drugs and their place in therapy. The role of the community pharmacist in patient care is also highlighted.

Immunosuppressive drug therapy: basic concepts

The foundation of antirejection drug therapy is obtaining a balance between efficacy (i.e., lack of graft rejection) and adverse effects, particularly infection resulting from over-immunosuppression. Atypical infections, such as cytomegalovirus (CMV), herpes simplex viruses, fungal infections and *Pneumocystis jirovecii* (formerly known as *Pneumocystis carinii* or PCP) are more common in immunocompromised populations, such as transplant recipients and patients with acquired immunodeficiency syndrome (AIDS). No single, reliable, commercially available blood test is yet on the market to determine the extent of immunosuppression. However, studies are underway to develop tests that measure immune cell function, which will hopefully permit better tailoring of immunosuppressive regimens to individual patient needs.² In the interim, transplant specialists will continue to use selective therapeutic drug monitoring in combination with surveillance of the clinical status of the patient to provide the best possible care.



Manipulation of immunosuppressive drugs and drug regimens should only be undertaken by knowledgeable and experienced clinicians. Patient adherence to medical advice is vital for enhancing patient and graft survival; noncompliance is a common cause of graft loss.³

In the immediate post-transplant period, “induction therapy” with rabbit-derived antithymocyte globulin (Thymoglobulin) or basiliximab (Simulect) may be used to rapidly suppress the immune system in patients who are at high risk for graft rejection, or to delay the initiation of potentially nephrotoxic maintenance oral immunosuppressive agents. These induction agents are only available as intravenous (IV) formulations. Thymoglobulin may also be used to treat episodes of corticosteroid-resistant rejection.

Long-term maintenance immunosuppression utilizes combinations of drugs with differing mechanisms of action to promote synergy, thereby allowing lower doses of each agent to be used and reducing the risk of side effects. Currently available oral agents include calcineurin inhibitors (CNIs), anti-metabolites, mTOR inhibitors and prednisone. Individual transplant centres tend to develop centre-specific and organ-specific drug protocols; therefore, pharmacists will see variations in prescribing practices.

With the continued development of anti-rejection drugs, it is now possible to tailor immunosuppressive drug regimens to specific patient characteristics (e.g., risk for diabetes) based on the side effect profiles of individual agents. As a result, transplant drugs are often used in combinations that

may not be approved in product monographs. Examples include steroid-free or steroid minimization protocols to reduce the long-term effects of corticosteroids, and CNI-minimizing or CNI-free protocols to ameliorate the long-term nephrotoxic effects of cyclosporine and tacrolimus.

Calcineurin inhibitors

Cyclosporine and tacrolimus are CNIs that interfere with the activation of calcineurin, but via separate pathways. The activation of calcineurin is required to stimulate interleukin-2 (IL-2), which ultimately results in T-cell activation. Because of their similarity in action, these medications should not be prescribed concurrently. A 24-hour washout period is recommended when switching between these two agents; how-

table 1

Common adverse effects of cyclosporine³⁰

EFFECT	MANIFESTATION	MANAGEMENT STRATEGIES
Nephrotoxicity	<ul style="list-style-type: none"> • ↑ Scr, BUN • ↓ GFR • oliguria • acute tubular necrosis • hypertension • hyperkalemia • edema • metabolic acidosis 	<ul style="list-style-type: none"> • associated with ↑ blood levels; therapeutic monitoring is necessary; C₂ level monitoring may reduce risk; may be reversible upon discontinuation • may cause DGF in renal transplantation; consider alternate agents or use of induction therapies • avoid other nephrotoxins • may progress to chronic renal failure over years; management is patient-specific • sodium bicarbonate tablets may help with persistent hyperkalemia due to renal tubular acidosis • avoid drug interactions that may ↑ blood levels
Neurological	<ul style="list-style-type: none"> • tremors • flushing • palmar/plantar paresthesias • visual changes • headache • confusion • somnolence • seizures 	<ul style="list-style-type: none"> • tremor usually subsides over time • headache may require discontinuation of cyclosporine • rule out other causes for seizure; phenytoin or carbamazepine ↓ cyclosporine levels; gabapentin has no effect • persistent change in neurologic status may necessitate discontinuation
Dermatological	<ul style="list-style-type: none"> • gingival hyperplasia • bleeding gums • hypertrichosis of face, arms, shoulders, back • acne • coarsening of facial features in children 	<ul style="list-style-type: none"> • regular dental checkups recommended; brush and floss regularly; may require surgical intervention or change of agent • azithromycin has been used to treat gingival hyperplasia³¹ • may bleach or wax unwanted hair
Endocrine/metabolic	<ul style="list-style-type: none"> • ↑ cholesterol • ↑ triglycerides • hyperuricemia/gout 	<ul style="list-style-type: none"> • lipid-lowering agents may be required, but use statins with caution due to risk of adverse statin effects; fluvastatin may be preferred due to lower risk of adverse effects³² • may require treatment of gout; avoid NSAIDs if possible due to additive nephrotoxicity
Hepatic	<ul style="list-style-type: none"> • ↑ bilirubin, • cholestasis • ↑ ALT, AST 	<ul style="list-style-type: none"> • monitor liver function tests
Immunologic	<ul style="list-style-type: none"> • ↑ risk of infection • ↑ risk for malignancy, especially skin cancer 	<ul style="list-style-type: none"> • patient education regarding signs/symptoms of infection • use sunblock to prevent skin cancer • report unintentional weight loss, night sweats, unusual skin lesions to physician • avoid live vaccines

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; C₂ level monitoring = monitoring post-dose level 2 hours after cyclosporine microemulsion ingestion; DGF = delayed graft function; GFR = glomerular filtration rate; NSAIDs = nonsteroidal anti-inflammatory drugs; Scr = serum creatinine

IT IS NOW POSSIBLE TO TAILOR IMMUNOSUPPRESSIVE DRUG REGIMENS TO SPECIFIC PATIENT CHARACTERISTICS

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ever, it is common practice at transplant centres to discontinue one medication and begin the other with the next subsequent dose to ensure adequate immunosuppression during the transition period.

CYCLOSPORINE

The development of cyclosporine in the early 1980s led to significant improvements in graft and patient survival from the previous era. Due to its complex and variable pharmacokinetics, particularly its bile-dependent absorption leading to wide fluctuations in blood levels, and its narrow therapeutic window, the original formulation of cyclosporine (Sandimmune) was reformulated in the mid 1990s. The newer formulation (Neoral) is a microemulsion, which does not depend on bile for absorption and is more soluble, leading to greater consistency in absorption and, consequently, blood levels.

Cyclosporine is available in IV, capsule and liquid formulations. Oral dosing generally begins at 10–15 mg/kg/day, divided q12h, and is titrated to target blood concentration. Historically, therapeutic drug level monitoring was done using trough blood levels (C_0). More recent research has demonstrated that, based on area-under-the-curve pharmacokinetic models, the two-hour post-dose level after cyclosporine microemulsion best represents the patient's total exposure to cyclosporine, and attaining therapeutic target levels may reduce adverse effects while providing better prevention of graft rejection than trough level monitoring.⁴ Many transplant centres in Canada have now turned to this type of monitoring, which is referred to as " C_2 level monitoring."

Several generic formulations of cyclosporine microemulsion are now on the market. Although deemed interchangeable by many provincial formularies, it is in the patient's best interest from a safety perspective to be maintained on only one brand. Interchanging brands may cause significant fluctuations in blood levels of this narrow therapeutic index drug, which could lead to side effects or rejection if levels are not monitored with each switch in brand.⁵ In addition, C_2 level monitoring has only been validated with the original cyclosporine microemulsion (Neoral) formulation.⁵

TACROLIMUS

Tacrolimus (also known as FK-506, the name used during pre-marketing trials) has generally replaced cyclosporine in most transplant centres,⁶ since meta-analyses have demonstrated reductions in patient mortality, graft loss, acute rejection and steroid-resistant rejection with tacrolimus-based immunosuppressive regimens versus cyclosporine-based regimens.^{7,8} In addition, tacrolimus has a greater potential to reduce acute rejection in high-risk renal transplant recipients,⁷ which may significantly prolong graft life.

Tacrolimus, also a narrow therapeutic index drug, is approximately 100 times more potent than cyclosporine. Initial oral dosing begins in the range of 0.1–0.3 mg/kg/day (depending on the type of transplant), divided q12h. The dosage is titrated to specific target levels by trough therapeutic drug level monitoring. With both cyclosporine and tacrolimus, target therapeutic blood levels will vary based on type of organ transplanted, concomitant therapies and patient-specific characteristics; they will also change over time (i.e., higher in the immediate post-transplant period and then decreasing over time). As well, target blood levels can be expected to vary slightly among transplant centres.

In 2008, a once-a-day extended-release formulation of tacrolimus (Advagraf) reached the Canadian market. If used in renal transplantation in the immediate post-transplant period, antibody induction therapy (with rabbit-derived antithymocyte globulin or basiliximab) is also recommended; this is due to the prolonged half-life of the extended-release tacrolimus formulation, which requires a longer period of time to reach therapeutic blood levels.⁹ Stable transplant recipients may be converted from immediate-release tacrolimus to the extended-release formulation at the same daily dose (i.e., Prograf 2 mg q12h can be converted to Advagraf 4 mg daily taken in the morning), with subsequent monitoring of trough levels. With its once-a-day dosing regimen, the extended-release formulation may help improve medication adherence in some patients. It is important for all members of the healthcare team and the patient to be aware of which formulation

is being prescribed in order to prevent overdosing or underdosing, particularly while the initial switch between products is being undertaken, as these two products are not considered interchangeable.

Side effects

As a result of similarities in mechanism of action, cyclosporine and tacrolimus exhibit many common side effects, such as nephrotoxicity, neurotoxicity and gastrointestinal (GI) effects. Cyclosporine is more likely to cause cosmetic adverse effects, such as gingival hyperplasia, hypertrichosis and coarsening of facial features in children. It is also more likely to cause elevations in liver function tests, gout and hypercholesterolemia.^{10,11}

Tacrolimus is generally free of these side effects; however, the onset of diabetes occurs more frequently in patients prescribed tacrolimus-based regimens. This phenomenon, often referred to as post-transplant diabetes mellitus (PTDM) or new-onset diabetes after transplant (NODT), may be seen at any time in the post-transplant

APPOINTMENT



Glen Shepherd

The Honourable Jake Epp, P.C., Chairman of the Board of Health Partners International of Canada, is pleased to announce the appointment of Glen Shepherd as President and Chief Executive Officer effective Jan. 1, 2009. Mr. Shepherd joined HPIC as Senior Vice-President and Chief Operating Officer in early 2008. Prior to serving HPIC, he served in several leadership positions with The Salvation Army in France and in Canada, including Chief Secretary (COO) from 2003–2008. HPIC is a Canadian medical aid agency dedicated to improving access to health care and medicine in the developing world. For more information, visit www.hpicanada.ca.



table 2

Common adverse effects of tacrolimus ³⁰		
EFFECT	MANIFESTATION	MANAGEMENT STRATEGIES
Nephrotoxicity	<ul style="list-style-type: none"> • ↓ GFR • ↑ SCr • delayed renal graft function • hypertension • hyperkalemia 	<ul style="list-style-type: none"> • previous cyclosporine use may enhance nephrotoxic effects, therefore monitor these patients more closely • avoid drug interactions that increase tacrolimus blood levels • avoid other nephrotoxins
Endocrine/metabolic	<ul style="list-style-type: none"> • diabetes mellitus • hypomagnesemia 	<ul style="list-style-type: none"> • treat new onset diabetes after transplant in the same manner as type 2 diabetes • oral magnesium supplements may interact with other anti-rejection agents; may also cause diarrhea; use with caution
Neurological	<ul style="list-style-type: none"> • tremor • headaches • insomnia/nightmares • hyperesthesias • confusion • dysarthrias • seizures 	<ul style="list-style-type: none"> • tremor may diminish over time • headache may be reversible with dose reduction • if required for treatment of seizures, phenytoin or carbamazepine ↓ tacrolimus levels; gabapentin has no effect
Gastrointestinal	<ul style="list-style-type: none"> • diarrhea • nausea/vomiting • abdominal pain 	<ul style="list-style-type: none"> • tacrolimus has macrolide structure similar to erythromycin • GI effects are often transient; may take tacrolimus with food; report severe diarrhea to transplant team
Immunological	<ul style="list-style-type: none"> • ↑ risk of infection • ↑ risk for malignancy, especially skin cancer 	<ul style="list-style-type: none"> • patient education regarding signs/symptoms of infection • use sunblock to prevent skin cancer • report unintentional weight loss, night sweats, unusual skin lesions to physician • avoid live vaccines
Cardiovascular	<ul style="list-style-type: none"> • rare case reports of cardiomyopathy 	<ul style="list-style-type: none"> • try another drug if possible

GFR = glomerular filtration rate; SCr = serum creatinine

period. It may be transient, subsiding as the steroid and tacrolimus doses are reduced, or permanent.¹² In addition to anti-rejection drug use, a history of hepatitis C seems to increase the risk for developing NODT.¹³ NODT is treated and monitored in the same manner as type 2 diabetes.^{13,14}

Tables 1 and 2 list the common side effects of cyclosporine and tacrolimus, along with management strategies. Differences in these side effect profiles can be used to personalize drug therapy.

DRUG INTERACTIONS

Tacrolimus and cyclosporine also have many drug interactions in common (Table 3), as they both undergo extensive metabolism by the CYP3A4 enzyme. These drug interactions can be classified into three basic types: enzyme induction leading to

decreased blood levels and possible graft rejection; enzyme inhibition resulting in elevated blood levels and an increased risk for adverse effects; or additive nephrotoxicity. Unintentional drug interactions with immunosuppressants are a common cause of morbidity in transplant recipients. This includes interactions with herbal medications and OTC products,¹⁵ for which there is very little information. It may be medically necessary for transplant recipients to be prescribed an interacting drug; however, the appropriate monitoring must be undertaken and should be done in conjunction with or by the patient’s transplant centre.

Antimetabolites

MYCOPHENOLIC ACID DERIVATIVES

Mycophenolic acid (MPA) derivatives include mycophenolate mofetil (also known

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as MMF, CellCept) and mycophenolate sodium (Myfortic). MMF is a prodrug ester that is rapidly absorbed in the stomach and presystemically metabolized to its active form, MPA (which has poor oral bioavailability). MPA is further metabolized to an inactive metabolite (mycophenolic acid glucuronide; MPAG), which then undergoes enterohepatic recirculation resulting in a secondary MPA peak six to 12 hours following ingestion of the initial dose.

MMF, which was introduced to the Canadian market in 1995, has generally replaced azathioprine, because of its greater efficacy.¹⁶⁻¹⁸ It is usually initiated immediately following transplantation, with target doses of 2 g/day or 3 g/day (depending on the type of transplant), divided q12h. Therapeutic drug monitoring of MPA levels is possible, but not undertaken on a routine basis. Therefore, dose adjustments are usually made on the basis of drug tolerability.

Adverse effects

The most common patient complaints from MMF are nausea, vomiting, heartburn and diarrhea, which may necessitate dose reductions. Several other strategies are commonly employed to manage GI side effects. Taking the medication with food (if unable to tolerate it on an empty stomach, as recommended in the product monograph) will reduce the Cmax by up to 40%, but does not reduce the extent of absorption.¹⁹ Other strategies include dose “splitting” (dividing the total daily dose into 3 or 4 smaller doses and administering with each meal rather than



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table 3

Common drug interactions with cyclosporine and tacrolimus^{10,11}

EFFECT	INTERACTING DRUG
Increased tacrolimus/ cyclosporine serum level (enzyme inhibition)	ketoconazole fluconazole (dose-related) itraconazole posaconazole voriconazole erythromycin clarithromycin (azithromycin has minimal effect) corticosteroids oral contraceptives calcium channel blockers (diltiazem, verapamil, nifedipine, nifedipine; nifedipine often used to treat hypertension) propafenone cimetidine ritonavir metoclopramide sirolimus (cyclosporine only) digoxin (cyclosporine only; also ↑ digoxin level)
Decreased tacrolimus/ cyclosporine serum level (enzyme induction)	phenytoin carbamazepine phenobarbital primidone isoniazid rifampin St. John's wort
Additive nephrotoxicity	aminoglycosides NSAIDs amphotericin B co-trimoxazole acyclovir ganciclovir/valganciclovir fluoroquinolones

(cont'd)

q12h); adding a proton pump inhibitor (PPI) or increasing the PPI dose; or using calcium-based antacids for mild GI distress. Starting MMF at lower than target doses in the early post-transplant period and titrating upwards may also help reduce the incidence of GI adverse effects. It is vital to graft survival to develop strategies for improving patient tolerance of MPA, as recent studies in renal transplant recipients have demonstrated a correlation between the length of time MMF doses remain subtherapeutic and incidence of acute rejection in the first post-transplant year.^{20,21} Another recent trial showed that diarrhea in renal transplant recipients is not always a direct result of MMF; other potential causes (e.g., other medications, bacterial or viral infections) should be ruled out in a stepwise manner prior to dose reduction.²²

In an attempt to improve patient tolerance of MPA, an enteric-coated formulation of mycophenolate sodium (Myfortic) was introduced in 2005. It is designed to dissolve and be absorbed in the neutral pH of the duodenum (not in the acidic pH of the stomach, like MMF) and thus potentially avoid gastric side effects resulting from direct toxic expo-

table 3 cont'd

EFFECT	INTERACTING DRUG
Other	immunizations (↓ vaccine efficacy; avoid live vaccines) statins (↑ risk of statin side effects) grapefruit/grapefruit juice (↑ immunosuppressant blood levels) food (↓ tacrolimus absorption) antacids (may ↓ tacrolimus absorption) sildenafil (↑ sildenafil blood level when administered with tacrolimus; ↑ risk of adverse effects) OTC drugs (minimal data, avoid when possible)
Note: Not a complete list. Please consult additional resources. NSAIDs = nonsteroidal anti-inflammatory drugs	

sure. Converting from MMF to enteric-coated mycophenolate sodium may not be effective in resolving GI complaints in all patients,^{23,24} as even the IV formulation of MMF has been associated with GI adverse effects.²⁵ However, because of the known increased risk of renal allograft rejection associated

with MMF dose reduction, conversion between products may be considered in an attempt to provide a full therapeutic dose of MPA. Oral MMF and enteric-coated mycophenolate sodium products are not pharmacokinetically interchangeable (see pharmacokinetic differences in Table 4 online). Conversion from one to another should be managed by experienced transplant professionals. Enteric-coated mycophenolate sodium must be taken on an empty stomach, one hour before or two hours after food,²⁶ because its pharmacokinetic

profile when taken with food other than a high fat meal (which can significantly delay absorption) has not been thoroughly studied. A 720 mg q12h dose of Myfortic and 1000 mg q12h of CellCept deliver equimolar doses of MPA.²⁶ Myfortic is only available as enteric-coated capsules (180 mg and 360 mg), which should not be crushed or chewed. CellCept is commercially available in IV, capsule (250 mg), tablet (500 mg) and suspension formulations, allowing for greater flexibility in dosing routes, including administration via nasogastric tube. CellCept capsules should not be opened or crushed, nor should the tablet be crushed.

Table 5 outlines common adverse effects associated with MPA, while Table 6 (available online) lists drug interactions.

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Table 6 (available online) lists drug interactions.

table 5

Side effects of mycophenolate products^{19,26,30}

EFFECT	MANIFESTATION	MANAGEMENT STRATEGIES
Gastrointestinal	<ul style="list-style-type: none"> nausea/vomiting diarrhea heartburn gastritis/esophagitis pancreatitis intestinal perforation (rare) GI bleed (rare) 	<ul style="list-style-type: none"> avoid using in patients with active or pre-existing GI disorders take with food (CellCept only) dose reduction (caution) dose splitting addition of PPI or increase PPI dose calcium-containing antacids for mild dyspepsia rule out other causes
Hematologic	<ul style="list-style-type: none"> leukopenia neutropenia anemia 	<ul style="list-style-type: none"> do not administer with azathioprine; combine other drugs with similar side effects cautiously and only when necessary leukopenia most common from days 31–180 of therapy; monitor CBC weekly for first month, twice monthly for second and third months, then monthly for first year ↓ dose or discontinue therapy if absolute neutrophil count < 1.3 x 10³/μL
Immunologic	<ul style="list-style-type: none"> ↑ risk of infection ↑ risk of malignancy 	<ul style="list-style-type: none"> atypical infections; CMV infection more common with 3 g/day dose (compared to 2 g/day dose in pivotal MMF trials) patient education regarding signs/symptoms of infection use sunblock to prevent skin cancer report unintentional weight loss, night sweats, unusual skin lesions to physician avoid live vaccines
Reproductive	<ul style="list-style-type: none"> teratogenic in animal studies 	<ul style="list-style-type: none"> consider cytotoxic; do not come in contact with contents of capsule; if contact occurs, wash area thoroughly with soap and water women should use reliable contraception during treatment and for 6 weeks following discontinuation may be excreted in breastmilk
CBC = complete blood count; CMV = cytomegalovirus; GI = gastrointestinal; PPI = proton pump inhibitor		

mTOR inhibitors

A new distinct class of immunosuppressant drugs called the mammalian target of rapamycin (mTOR) inhibitors was launched in 2001. Through complex mechanisms, mTOR inhibitors ultimately suppress cytokine-driven T-cell proliferation from the G1 to the S phase of the cell cycle.

SIROLIMUS

Sirolimus (Rapamune) is the first of this group to enter the market. Everolimus, which has a shorter half-life than sirolimus, is still in the clinical trials phase. Despite the similarity in nomenclature to tacrolimus, these drugs have different mechanisms of action and may be rationally combined in immunosuppressive regimens, although sirolimus is only approved for use in renal transplantation and only in combination with cyclosporine and corticosteroids.²⁷

Side effects

Sirolimus has a unique side effect profile compared to other anti-rejection drugs. It lacks the nephrotoxic, neurotoxic and diabetogenic effects of CNIs. It is particularly useful for patients who are intolerant of other immunosuppressive drugs. A list of common side effects and their management is found in Table 7 (available online).

Sirolimus has a long terminal half-life (approximately 62 hr), enabling once-daily administration. To attain therapeutic levels

more quickly, a loading dose may be prescribed; individual transplant centres generally have their own specific protocols. Trough blood levels can be monitored, but levels should be drawn no sooner than five days after initiation of therapy or a change in dose, due to its prolonged half-life.²⁸


Sirolimus is metabolized by CYP3A4 and can be expected to undergo many of the same drug interactions as cyclosporine and tacrolimus, as outlined in Table 3. Sirolimus can also reduce the clearance and increase the blood concentrations of cyclosporine when taken concurrently; the manufacturer recommends administration of sirolimus four hours after cyclosporine.²⁷ Sirolimus is available in both liquid (1 mg/mL oral solution) and tablet formulations (1 mg).

The manufacturer warns of the potential for excess mortality, graft loss and increased risk of hepatic artery thrombosis in de novo liver transplant recipients prescribed sirolimus in combination with tacrolimus or cyclosporine, as well as a risk for bronchial anastomotic dehiscence

in lung allograft recipients.²⁷ In 2006, Health Canada issued a warning concerning the increased risk for rejection in patients who were receiving a combination of sirolimus (immediately post-renal transplant), MMF and corticosteroids, with interleukin-2 receptor antibody induction, in an investigational study.²⁹ Still, sirolimus holds a valuable place in providing long-term maintenance immunosuppression. Its role in organ transplantation will evolve as more experience is gained by clinicians.

The community pharmacist's role

During their hospital stay, transplant recipients receive extensive education regarding care of their transplanted organ, including signs and symptoms of infection, signs of rejection, how to take their medications properly in order to gain maximum benefit with minimal toxicity, and the importance of never running out of their medication. Upon leaving the transplant centre and

returning to their home communities, most patients will obtain their life-sustaining anti-rejection medications from their local pharmacy. They are encouraged to dialogue with their community pharmacist about their medication regimen. Community pharmacists will interact with the transplant patient more often than staff at the transplant centre; therefore, they are in ideal positions to support their patients' medication-taking. They can do this by monitoring for drug interactions with prescription, OTC and herbal medications; ensuring the same brand of cyclosporine is always dispensed; ensuring the correct formulation of tacrolimus is being prescribed and dispensed; and liaising with the transplant team or transplant pharmacist, or referring the patient back to the transplant centre when necessary, in order to provide optimal pharmaceutical care. 

References and Tables 4, 6 and 7 are available at www.pharmacygateway.ca (Go to Publication Archives, *Pharmacy Practice*, February/March 2009, Transplant Time).

table 4

Pharmacokinetic comparison of mycophenolate products ^{19,26}		
	MYCOPHENOLATE SODIUM (MYFORTIC)	MYCOPHENOLATE MOFETIL (CELLCEPT)
T _{max} (fasting)	1.5–8 hr	0.5–2 hr
C _{max} (fasting)	26.1 µg/mL	24.5 µg/mL
T _{max} (with food)	5–20 hr	0.5–3 hr
C _{max} (with food)	decreased by 33%	decreased by 40%
Area under the curve	66.5 µg*hr/mL	63.7 µg*hr/mL
Half-life	~ 11 hr	~ 11 hr
Equimolar dose	720 mg BID	1000 mg BID
Formulation	sodium salt	prodrug ester
Site of dissolution and absorption	small intestine (delayed release), relies on gastric emptying	stomach (immediate release) independent of gastric emptying

table 6

Drug interactions with mycophenolate products ^{19,26,30}	
DRUG	EFFECT
azathioprine	additive toxicity; do not use concomitantly
acyclovir ganciclovir valganciclovir valacyclovir	additive toxicity due to competition for tubular excretion
probenecid	↑ MPAG level due to competition for tubular excretion, leading to ↑ MPA levels
Mg- and Al-containing products (also possibly iron, zinc, multivitamins with minerals), sevelamer and other calcium-free phosphate binders	↓ absorption of mycophenolate; if necessary to use these products, space as far apart as possible; calcium-containing products do not appear to interact
cyclosporine	↓ MPA levels due to interference with enterohepatic recirculation of MPAG; since tacrolimus is devoid of this effect some clinicians feel the optimal dose of MMF when co-administered with tacrolimus is 750 mg BID (rather than 1000 mg BID)
cholestyramine	40% ↓ in MPA AUC due to interruption in enterohepatic recirculation of MPAG. Can be used to manage mycophenolate overdose
food	↓ rate of absorption, particularly with mycophenolate sodium (Myfortic). Administration of Myfortic with food not recommended until further pharmacokinetic data available

AUC = area under the curve; MMF = mycophenolate mofetil; MPA = mycophenolic acid; MPAG = mycophenolic acid glucuronide

table 7

Common adverse effects of sirolimus²⁷

EFFECT	MANIFESTATION	MANAGEMENT STRATEGIES
Hematologic	<ul style="list-style-type: none"> • anemia • leukopenia • thrombocytopenia 	<ul style="list-style-type: none"> • may require dose reduction or discontinuation • erythropoietin has been used to treat anemia
Endocrine/metabolic	<ul style="list-style-type: none"> • ↑↑↑ cholesterol • ↑ triglycerides 	<ul style="list-style-type: none"> • lipid-lowering agents may be required, but use with caution due to risk of statin and fibrate adverse effects. Fluvastatin may be preferred³²
Cardiovascular	<ul style="list-style-type: none"> • hypertension • edema • tachycardia 	<ul style="list-style-type: none"> • manage as for the general population • tachycardia may require a change in drug
Immunologic	<ul style="list-style-type: none"> • ↑ risk of infection • ↑ risk for malignancy (however, recent evidence demonstrates antitumor properties³³) 	<ul style="list-style-type: none"> • patient education regarding signs/symptoms of infection • use sunblock to prevent skin cancer • report unintentional weight loss, night sweats, unusual skin lesions to physician • avoid live vaccines
Reproductive	<ul style="list-style-type: none"> • embryo and fetotoxic in rats; insufficient data in humans 	<ul style="list-style-type: none"> • discontinue 12 weeks prior to conception • excretion into breast milk unknown
Other	<ul style="list-style-type: none"> • lymphocele • wound complications/ impaired healing • oral ulceration • interstitial lung disease • diarrhea • arthralgia • proteinuria 	<ul style="list-style-type: none"> • specialized management strategies required

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