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CHAPTER 97

LONG-TERM TOXICITY OF IMMUNOSUPPRESSIVE THERAPY

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CHAPTER OUTLINE

The continued success of liver transplantation over the past quarter century can be attributed to a number of factors: better understanding of disease pathophysiology, enhanced intraoperative management, and improved posttransplantation care, to name a few. Atop this list, however, is the introduction of new immunosuppressive agents, all of which have contributed to improved graft and patient survival. Like any medication, these agents are not without side effects. This chapter focuses on the long-term toxicities of frequently used immunosuppressive medications.

MALIGNANCY

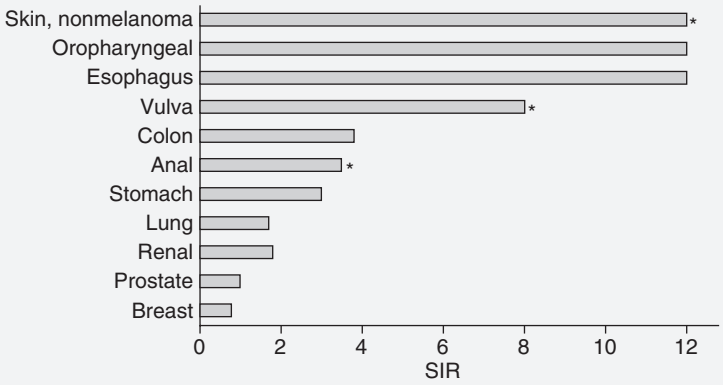
The goal of immunosuppressive therapy is to dampen the immune response at the time of transplantation. Unfortunately, these agents are not specifically targeted against the immune response to the transplanted organ. As a result, other protective functions of the human immune system are jeopardized. Among them is the body's ability to neutralize malignantly transformed cells, particularly those driven by viral infection. As such, one of the long-recognized side effects of immunosuppression is an increased risk for selected malignancies. The most common malignancies among transplant recipients are nonmelanomatous skin cancers, which may affect nearly a quarter of liver transplant recipients. Other more life-threatening cancers, however, are present at elevated rates in this patient population and generally involve the gastrointestinal (GI) tract, and in particular GI malignancies with the human papillomavirus (Table 97-1).[1] In a recent analysis of all solid organ transplant recipients using the U.S. Organ Procurement and Transplantation Network (OPTN)/United Network for Organ Sharing (UNOS) database, the overall incidence of posttransplantation malignancy in liver transplant recipients was 4.46%, with GI cancers (as a whole) being the most common type.[2]

Regardless of malignancy type, standard preventative practices (e.g., smoking cessation, sun protection, breast self-examinations) and routine cancer screening examinations (e.g., chest x-ray, colonoscopy, dermatological evaluation) should be highly encouraged after transplantation and incorporated into the posttransplantation management pathway for all recipients.

Posttransplantation Lymphoproliferative Disorder

More specific to the transplant population is the collection of lymphoid malignancies known as *posttransplantation lymphoproliferative disorder* (PTLD). This was the single most common type of cancer reported among liver transplant recipients in the recent review by Sampaio et al.[2] PTLD differs from lymphomas seen in immunocompetent patients in that it may present outside of nodal tissue, tends to arise (and regress) rapidly, and is

TABLE 97-1 **Standard Incidence Ratio for Malignancies in Liver Transplant Recipients**



From Chandok N, Watt KD. Burden of de novo malignancy in the liver transplant recipient. Liver Transpl. *2012;18(11):1281.*
SIR, Standard incidence ratio.

frequently driven by Epstein-Barr virus (EBV). Indeed, the greatest risk for PTLD is seen in EBV-seronegative patients who receive an EBV-seropositive organ. Thus PTLD may reasonably be considered an infectious disease risk with oncological sequelae rather than a case of direct oncological transformation. Accordingly, PTLD responds to reduction or withdrawal of immunosuppression in approximately 50% of affected individuals, making prompt and aggressive reduction of immunosuppression the first therapeutic maneuver upon diagnosis. In a long-term follow-up study of liver transplant patients at the Mayo Clinic in Rochester, Minnesota, the overall incidence of PTLD was 3.1% with EBV-negative disease predominating later after transplantation (Fig. 97-1).[3]

PTLD may occur anytime after transplant and usually presents with the typical viral prodrome of malaise, fever, and weight loss. Laboratory findings typically include an elevated L-lactate dehydrogenase level and EBV viremia. Graft involvement and central nervous system invasion, as well as multiple site involvement, are poor prognostic factors. Diagnosis requires biopsy-proven disease of the affected organ or lymph node. Oncological evaluation is required. An elevated EBV level on polymerase chain reaction, although not diagnostic, may be suggestive of PTLD and can be used to gauge its course. Treatment consists primarily of immunosuppression withdrawal, allowing the patient to mount a response against EBV and PTLD. In addition, antiviral directed therapy (e.g., ganciclovir) is started. When withdrawal is insufficient, adjuvant therapies, including irradiation and chemotherapy, may be considered, typically CHOP (cyclophosphamide, hydroxydaunomycin [doxorubicin], Oncovin [vincristine], and prednisone)-based regimens.

Rituximab, an anti-CD20 antibody, may lead to remission in certain cases of PTLD. Early-onset PTLD is frequently B cell in origin and CD20 positive, making Rituximab a viable option and an often-used adjuvant to standard chemotherapeutic agents. Late-onset PTLD is usually non-Hodgkin's lymphoma and is not viral related.

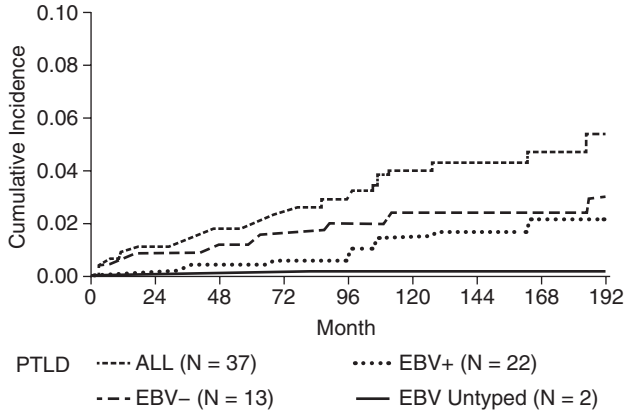


FIGURE 97-1 ■ **Incidence of Epstein-Barr virus (EBV)-positive and EBV-negative posttransplantation lymphoproliferative disorder (PTLD) in liver transplant recipients.** (From Kremers WK, Devarbhavi HC, Wiesner RH,et al. Post-transplant lymphoproliferative disorders following liver transplantation: incidence, risk factors and survival. *Am J Transplant.* 2006;6[5 Pt 1]:1019.)

INFECTIONS

Another complication of immunosuppressive therapy is the development of posttransplantation infections. The vast majority of infections occur within the first 6 months after transplantation, when the intensity of immunosuppression is at its highest. However, infections may happen at any time and generally occur in a predictable pattern after transplant (Table 97-2).[4] Common and life-threatening opportunistic infections are addressed in detail in Chapter 78. Long term, the risk for infection persists and is still directly related to a patient's level of immunosuppression. Thus patients undergoing treatment for rejection remain at a high risk for infection, even after therapy has ceased. Although serious bacterial and fungal infections predominate early after transplantation, viral conditions prevail over the long term. These include reactivation of latent

TABLE 97-2 **Common Infections in Solid Organ Transplant Recipients**

Less Than 1 Month After Transplantation	1-6 Months After Transplantation	More Than 6 Months After Transplantation
Infection with antimicrobial-resistant species: MRSA VRE *Candia* species (non-albicans) Aspiration Catheter infection Wound infection Anastomotic leaks and ischemia *Clostridium difficile* colitis Donor-derived infection (uncommon): HSV, LCMV, rhabdovirus (rabies), West Nile virus, HIV, *Trypanosoma cruzi* Recipient-derived infection (colonization): *Aspergillus, Pseudomonas*	With PCP and antiviral (CMV, HBV) prophylaxis: BK polyomavirus infection, nephropathy *C. difficile* colitis HCV infection Adenovirus infection, influenza *Cryptococcus neoformans* infection *Mycobacterium tuberculosis* infection Anastomotic complications Without prophylaxis: Pneumocystis Infection with herpesviruses (HSV, VZV, CMV, EBV) HBV infection Infection with *Listeria, Nocardia, Toxoplasma, Strongyloides, Leishmania, T. cruzi*	Community-acquired pneumonia, urinary tract infection Infection with *Aspergillus*, atypical Molds, *Mucor* species Infection with *Nocardia, Rhodococcus* species Late viral infections: CMV infection (colitis and retinitis) Hepatitis (HBV, HCV) HSV encephalitis Community-acquired (SARS, West Nile virus infections) JC polyomavirus infection (PML) Skin cancer, lymphoma (PTLD)

From Fishman JA. Infection in solid-organ transplant recipients. N Engl J Med. *2007;357(25):2606.*

CMV, Cytomegalovirus; *EBV*, Epstein-Barr virus; *HBV*, hepatitis B virus; *HCV*, hepatitis C virus; *HIV*, human immunodeficiency virus; *HSV*, herpes simplex virus; *LCMV*, lymphocytic choriomeningitis virus; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *PCP*, *Pneumocystis carinii* pneumonia; *PML*, progressive multifocal leukoencephalopathy; *PTLD*, posttransplantation lymphoproliferative disorder; *SARS*, severe acute respiratory syndrome; *VRE*, vancomycin-resistant enterococcus; *VZV*, varicella zoster virus.

herpes viruses, including cytomegalovirus (CMV), EBV, herpes simplex, or herpes zoster. The relationship of these reactivations leads many to reinstitute viral-specific prophylaxis when treating for rejection (e.g., ganciclovir).

Hepatitis C recurrence is ubiquitous in infected individuals, although the phenotype of recurrence varies considerably from an asymptomatic carrier state to rapid hepatic deterioration. The primary approach for all these conditions includes reduction of immunosuppression in addition to targeted antiviral therapy against hepatitis C. Nearly 100 antiviral agents have been developed against hepatitis C, which are in various experimental phases. The two recently approved agents, boceprevir and telaprevir, are both protease inhibitors that, when used in combination with pegylated interferon and ribavirin, have been shown to improve cure rates with a shorter duration of therapy.

Although the immunocompromised state is the principal reason behind posttransplantation infections, attentiveness to other perioperative factors may help to mitigate the risks. This includes minimizing immunosuppression in recipients who are ill or deconditioned, who have overcome a recent infection, or who are hospitalized at the time of transplant. Specific issues common to patients recovering from hepatic failure include hypogammaglobulinemia and leukocytopenia and should be recognized as clues to limit the immunosuppressive load. Maneuvers to thwart any potential infection after transplantation include (1) treating any donor-related infections, (2) taking precautions against health care–associated bacterial infections (i.e., surgical site, catheter-associated, and urinary tract infections; ventilator-assisted pneumonias), and (3) providing prophylaxis against potential opportunistic infections via the routine use of antimicrobials such as trimethoprim-sulfamethoxazole, amphotericin, and ganciclovir.

CORTICOSTEROIDS

Pioneering studies found that corticosteroids (CSs) could prolong skin graft survival in rabbits.[5] Fifty years ago Starzl et al[6] showed that CS, along with azathioprine (AZA), extended patient and graft survival after kidney transplantation. Today CSs remain a cornerstone of immunosuppressive therapy, both as an induction agent at the time of transplant and as a pulse agent in the treatment of posttransplantation rejection episodes. The long-term consequences of CS use are numerous and well known (Table 97-3). Here we focus on some of the more common complications of CS use in liver transplantation.

Endocrine

A well-known complication of long-term CS use is diabetes, which occurs in up to 40% of adult liver transplant recipients.[7] CS-induced diabetes results in impaired glucose metabolism through increased insulin resistance. The mechanisms resulting in hyperglycemia include (1) a reduction in insulin production, (2) an increase in gluconeogenesis, (3) a decrease in peripheral glucose utilization, and (4) reduced glycogen synthesis. These effects are thought to be dose dependent, because reduced doses of CS have been shown to decrease insulin resistance.[8] In addition, CSs enhance appetite, particularly for sweetened foods. As will be described later, calcineurin inhibitors (CNIs) contribute significantly to the development of posttransplantation diabetes mellitus (PTDM). Even

TABLE 97-3 **Side Effects of Long-Term Corticosteroid Use**

System	Long-Term Side Effects
Cardiovascular	Sodium and fluid retention, hypertension, atherosclerosis
Gastroenterological	Gastritis, peptic ulcer, gastrointestinal bleeding, pancreatitis
Dermatological	Acne, increased bruising, impaired wound healing
Endocrine	Diabetes mellitus/glucose intolerance, cushingoid facies, hyperlipidemia, growth retardation, menstrual irregularities, hirsutism, weight gain—increased appetite, adrenal gland hormone suppression
Infectious	Increased risk for infections, including fungal
Musculoskeletal	Osteoporosis, vertebral and femoral fractures, osteonecrosis of femoral head; myopathy, muscle weakness
Ophthalmic	Cataracts, increased intraocular pressure, glaucoma, exophthalmos
Psychiatric	Psychosis, mood swings, depression, aggressive behavior, insomnia

though many programs have employed steroid avoidance or low-maintenance-dose CS protocols, PTDM remains a considerable problem. Thus one can extrapolate that PTDM is primarily due to the CNI.

The prevalence of dyslipidemia has been documented in up to 45% of liver transplant recipients.[9] The mechanism or mechanisms leading to dyslipidemia are not clear but may be due to steroid-induced insulin resistance, which leads to increased levels of very-low-density lipoprotein (VLDL), triglycerides, and low-density lipoprotein (LDL). Lipogenesis may also be pronounced with CS use.

Cardiovascular

The endocrine complications just described (diabetes and dyslipidemia) increase the risk for cardiovascular events after transplantation. Another risk factor contributing to cardiac disease is hypertension. The mechanisms involved in causing an increase in blood pressure include (1) sodium and water retention in the distal nephron, (2) upregulation of receptors present on vascular smooth muscle, and (3) contributions involving pathways in the central nervous system, adipose tissue, and liver.[10]

Liver transplant recipients not previously diagnosed with hypertension may develop elevated blood pressure after transplantation. While no one medication can tackle all the mechanisms listed earlier, use of a calcium channel blocker and a diuretic (if merited) may prove effective as first-line therapy.

Musculoskeletal

The musculoskeletal complications of prolonged CS use are devastating. CS use is the leading cause of secondary (drug-induced) osteoporosis. Bone metabolism is affected through several pathways, mainly by (1) suppressing osteoblast proliferation and activity, (2) stimulating osteoclasts to induce bone resorption, (3) decreasing calcium absorption in the GI tract, and (4) increasing urinary calcium excretion.[11] Bone loss due to CS use is greater in trabecular bone compared to cortical bone; thus the risk for fractures is greatest in the vertebral bodies, ribs, and femoral heads.

In liver transplant candidates the risk for osteoporosis and fractures is already elevated due to the effects of chronic disease, medications, and immobilization. Other common risk factors seen in liver transplant recipients include advanced age, increased body weight, and female sex, specifically postmenopausal women.

The incidence of fractures in transplant recipients is highest within the first 6 to 12 months after transplantation, with documented rates ranging from 24% to 65%.[12] Fractures may even occur with doses as low as 2.5 mg of prednisone daily.[13] Fortunately, the risk for bone loss is dose dependent, and the likelihood of fracture rapidly decreases after CSs are discontinued. Measures to prevent and manage osteoporosis will be discussed elsewhere in this textbook. At our center all posttransplantation patients are placed on supplemental calcium and vitamin D.

Because of the numerous side effects of CSs, attempts have been made to reduce or remove CSs from standard posttransplantation immunosuppressive regimens. At our center, steroids are eliminated within 2 weeks after transplantation in the majority of our recipients, except for those with autoimmune etiologies (autoimmune hepatitis, primary sclerosing cholangitis, primary biliary cirrhosis), where complete elimination may result in an early flare of the underlying disease. Eliminating CSs completely from our armamentarium is unlikely. Although linked to many long-term effects, CSs are effective agents that have resulted in the success of transplantation.

CALCINEURIN INHIBITORS

Until the ideal immunosuppressive agent or regimen is found, most transplant centers' immunosuppressive regimens will include a CNI. Cyclosporine (CyA) and tacrolimus (Tac) are the medications against which all new immunosuppressive agents are compared. The superiority seen with these agents with respect to graft and patient survival and acute graft rejection has been overwhelming since their approval for organ transplantation. Nonetheless, CNIs are imperfect and have well-known long-term side effects.

Neurotoxicity

Principally considered an immediate side effect of CNIs, neurotoxicity may become apparent months or years after initiation.[14] In addition, one must be cognizant of this side effect when converting patients onto CNI immunosuppression or when anticipating a rise in CNI levels in the face of drug interactions. Thus this potentially harmful consequence merits attention here.

The frequency of CNI-induced neurotoxicity has been reported to range from 7% to 32%[15,16] and is generally more common and severe with Tac than with CyA.[17] The

mildest forms of neurotoxicity are headaches, migraines, or a fine tremor. Not typically responsive to acetaminophen, headaches and migraines are generally responsive to sumatriptan (Imitrex). These events are usually dose related and reversible with reduction of the CNI. For symptoms that persist, conversion off Tac to CyA or another agent may be necessary.

On the opposite end of the spectrum, severe side effects include cognitive changes (psychosis, hallucinations), posturing (opisthotonus), seizure activity, and coma. The most severe consequence of CNI neurotoxicity is posterior reversible encephalopathy syndrome (PRES), a condition consisting of severe neurological deficits with magnetic resonance imaging findings of cortical and subcortical cytotoxic edema. Whether CNI trough levels are elevated or not, the CNI should be discontinued immediately. Furthermore, for the more severe neurological complications, there is no correlation with CNI levels, suggesting an idiosyncratic response.[18] Serum magnesium monitoring and supplementation are recommended. Potentially fatal in the most extreme circumstances, CNI-induced neurotoxicity is generally reversible, but functional recovery may require months.

Renal Dysfunction

CNI-associated nephrotoxicity was described early, with the use of CyA in bone marrow transplantation.[19] Not surprisingly, the administered doses of CyA were many times greater (15 mg/kg) than what is recommended today. Further studies in animal and human biopsy tissue confirmed the various pathological changes in the nephron caused by CyA.[20,21] Striking was the vasculopathy of the afferent arterioles, resulting in intimal fibrosis, eventual glomerular collapse, and the nephropathy seen today (Fig. 97-2).[20] For practical purposes, Tac and CyA are equally nephrotoxic.

The development and severity of chronic kidney disease after solid organ transplantation was uncovered in two landmark papers. First, Gonwa et al[22] demonstrated a 40% decline in renal function (by measured glomerular filtration rate) at 3 months in liver transplant recipients without renal dysfunction. Next, Ojo et al[23] found the cumulative incidence of chronic renal failure in liver transplant recipients to be nearly 20% at 5 years. Since then a major focus in the field of transplantation has been to identify and address the causes of perioperative renal dysfunction. Topping this list is the nephrotoxic effects of CNI, which has been the principal stimulus for the development of new immunosuppressive agents.

Metabolic Syndrome

Other recognized long-term side effects associated with CNIs are posttransplantation hyperlipidemia, diabetes, and hypertension, all of which are elements of the metabolic syndrome. Of course, there are other factors that predispose transplant recipients to these risks, including race, age, unrecognized preexisting disease, body mass index, and CS use, to name a few. These consequences ultimately contribute to the increasing cardiovascular morbidity and mortality seen long-term. Thus early screening and interventions may aid in reducing these risks.

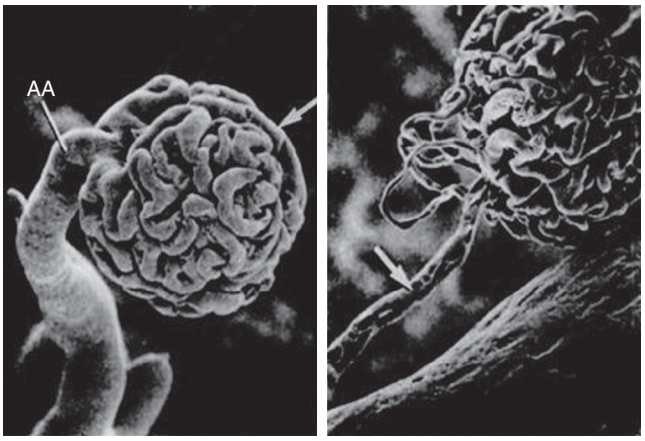


FIGURE 97-2 ■ Glomerulus of a control rat compared to one after 14 days of cyclosporine treatment. *Left,* Gomerular tuft (*arrow*). *Right,* Afferent arteriole shows narrowing (*arrow*). *AA,* Afferent arteriole. (From English J, Evan A, Houghton DC, Bennett WM. Cyclosporine-induced acute renal dysfunction in the rat. Evidence of arteriolar vasoconstriction with preservation of tubular function. *Transplantation.* 1987;44[1]:138-140.)

The prevalence of hyperlipidemia after transplantation is upwards of 50% in multiple studies.[24-26] CNIs have been associated with this side effect, as have CSs. Postulated mechanisms for CNI-related hyperlipidemia include (1) binding to the LDL receptor (increasing serum LDL), (2) decreased activity of lipoprotein lipase (increasing serum VLDL and LDL), and (3) inhibition of bile acid synthesis leading to increases in cholesterol.[27]

PTDM is seen in upwards of 40% of liver transplant recipients. CNIs cause PTDM by inhibiting insulin secretion by pancreatic β-islet cells. Tac is significantly more diabetogenic than CyA. In a meta-analysis comparing the effects of Tac and CyA in renal transplantation, Tac-treated patients had a significantly increased risk for new-onset PTDM compared to CyA-treated patients (relative risk, 1.85 at 1 year), and further increased risk with increasing Tac trough concentrations.[28] Also, African Americans are at increased risk relative to whites. The combination of CNI and CS further exacerbates the predilection to glucose intolerance.

The prevalence of posttransplantation hypertension is also high in patients taking CNI. In one early study of liver transplant recipients taking either CyA or Tac, elevated blood pressure (>140/90 mm Hg) was seen in up to 75% of patients during the first few months after liver transplant.[29] The modern incidence is likely lower because reduced doses of the CNI are used and CS use has been minimized. Nonetheless, treating hypertension after liver transplantation is the norm. Mechanisms causing CNI-induced hypertension include sodium retention, decreased production of vasodilating substances (nitric oxide and prostacyclin), and renal vasoconstriction.[30]

Other undesirable outcomes associated with CyA include acne, hirsutism, and gingival hyperplasia. These unfavorable aesthetic results may lead to a patient's request to change CyA to Tac, which has a lesser risk for these consequences. Table 97-4 outlines some of the more common side effects of CNI.

TABLE 97-4 **Side Effects of Calcineurin Inhibitor (Tacrolimus, Cyclosporine) Use**

	Tacrolimus	Cyclosporine
Neurological	Tremor, headache, seizure, coma, PRES	Tremor, headache
Cardiovascular	Hypertension	Hypertension
Gastroenterological	Nausea, diarrhea	
Renal	Renal dysfunction	Renal dysfunction
Infectious	Increased risk for infections	Increased risk for infections
Hematological	Hemolytic uremic syndrome	Hemolytic uremic syndrome
Endocrine	Hyperglycemia, hyperlipidemia	Hyperglycemia, hyperlipidemia, hirsutism, gingival hyperplasia
Oncological	Increased risk for malignancies, PTLD	Increased risk for malignancies, PTLD
Metabolic	Hyperkalemia, hypomagnesemia	Hyperkalemia, hyperuricemia

PRES, Posterior reversible encephalopathy syndrome; *PTLD*, posttransplantation lymphoproliferative disorder.

MAMMALIAN TARGET OF RAPAMYCIN INHIBITORS

Sirolimus (SRL), discovered in the mid-1960s, was approved by the Food and Drug Administration in 1999 for kidney transplantation only. Because of its demonstrated lack of direct nephrotoxic and neurotoxic properties, off-label use in liver transplantation followed, with suggested benefits for recipients with hepatocellular carcinoma and hepatitis C.[31,32] More recently, everolimus (EVR) has been introduced and recently approved by the Food and Drug Administration for use in kidney transplantation. Trials in liver transplantation are under way. Despite their known benefits, the mammalian target of rapamycin (mTOR) inhibitors have their own set of long-term consequences.

Dyslipidemia

In a review of randomized controlled trials on the subject, increases in cholesterol and triglyceride levels were shown to be associated with mTOR inhibitor use.[33] Roughly twice as many recipients on mTOR inhibitors were treated with lipid-lowering agents. The cause for the dyslipidemia may be increased plasma levels of apolipoprotein B-100, resulting in elevated VLDL and LDL levels.[34] Interestingly, whether this translates into increased atherosclerotic disease is not supported, because SRL has been shown to reduce atherosclerosis in an animal model.[35] In a recent study by McKenna et al,[36] liver transplant recipients on de novo SRL had similar incidences of cardiovascular events (e.g., myocardial infarction, stroke) after transplant as the control patients (never on SRL) despite statistically higher total cholesterol and triglyceride levels and a significantly higher Framingham risk score in the SRL cohort. Thus, despite causing dyslipidemias, SRL may have cardioprotective properties stemming from immune modulation of various pathways causing atherosclerosis.

Proteinuria

Although mTOR inhibitors do not cause any renal tubular dysfunction, they are associated with a higher incidence of proteinuria, generally a marker of chronic renal disease. This has been documented in kidney transplantation not only for de novo use, but also for early and late conversions after transplantation. The long-term implications of proteinuria in de novo use are unknown; however, among kidney transplant patients converted to SRL, Gutierrez et al[37] found that patients with baseline proteinuria greater than 0.8 mg/dL along with a greater degree of renal insufficiency were at higher risk for further proteinuria and progressive renal dysfunction. Although not mentioned as a potential complication in the early trials for SRL, proteinuria was clearly documented when EVR was approved for kidney transplantation. The mechanism by which SRL causes or accentuates proteinuria is not yet defined. However, angiotensin-converting enzyme inhibitors and statins have been shown to reduce proteinuria in patients with renal dysfunction, with one study suggesting that these therapies are effective in limiting mTOR inhibitor–induced proteinuria.[38]

Patients being considered for SRL conversion should be assessed for preexisting proteinuria with a 24-hour urine collection. If the proteinuria is less than 300 mg/day, the renal dysfunction can be reversed through conversion of CNI to SRL. In those patients with established proteinuria of more than 300 mg/day, a conversion to SRL may exacerbate the existing proteinuria and accelerate renal dysfunction. Therefore these patients should be maintained on low levels of CNI. Late conversion (more than 2 years after transplantation) to SRL usually does not improve renal function but instead may exacerbate renal dysfunction.

Wound Complications

Patients taking mTOR inhibitors have a known increased risk for developing wound complications. The same antiproliferative mechanism that is thought to produce their beneficial oncological effects (e.g., against hepatocellular carcinoma) may also account for their poor wound-healing properties (by limiting fibroblast proliferation). Examples of wound complications include tracheal dehiscence in lung transplant recipients and an increased occurrence of lymphoceles in kidney transplant recipients.[39,40]

The literature assessing wound complications in liver transplant is not plentiful. Early experiences with SRL in liver transplantation confirmed that wound infections and dehiscences were more frequent.[41,42] However, initial trials with SRL used higher doses and trough levels than is generally used today. In one randomized controlled trial looking

at the efficacy of EVR, there was a trend for more incisional hernias in the EVR arm (46% versus 27%, $P = .16$).[43] In the recent PROTECT study on EVR in liver transplantation, no increase in wound-healing problems was noted.[44]

At the Baylor Simmons Transplant Institute we have vast experience using SRL in our liver transplant patients, with both de novo and conversion therapy. The rate of wound complications, including the development of incisional hernias, is anecdotally high (and currently being reviewed). For the transplant patient on de novo SRL, incisions are monitored carefully. An incision-line wound vacuum-assisted closure can assist with wound healing. For long-term recipients who have developed an incisional hernia and are taking SRL, precaution is taken before herniorrhaphy by converting the patient off SRL and onto a CNI for 2 weeks before repair, with reinstitution of SRL (and discontinuation of the CNI) at least 4 weeks after repair or until the wound heals completely. This conversion can be carried out with minimal concern for rejection. (Of note, conversion back to SRL requires the readdition of the secondary agent [e.g., mycophenolate or AZA] because SRL monotherapy is not practiced at our center.)

Oral Ulcers

Oral ulcers are a common side effect of mTOR inhibitors, affecting up to 40% of patients taking these medications.[45,46] They can also occur late after long-term use. Often mistaken for oral herpes simplex virus infections, these ulcers can be painful and are one of the most common reasons for discontinuation. Current management involves a topical steroid combined with a dental paste (e.g., Kenalog in Orabase) applied directly to the ulcer. Secondarily, the dose of the mTOR inhibitor can be reduced.

Another troublesome consequence seen with the use of mTOR inhibitors is bone marrow suppression (namely leukopenia and anemia), which may be ameliorated via dose reduction and treatment (i.e., filgrastim [Neupogen] injection, iron supplementation, and transfusion). SRL is also associated with an atypical noninfectious pneumonitis, which is rarely seen today, in approximately 1% of patients. This side effect was more frequently observed with higher doses of SRL during its initial experience. Once recognized, it can be treated by SRL discontinuation.

AZATHIOPRINE

Categorized as an antimetabolite, AZA is a purine analogue that inhibits purine nucleotide (and thus DNA) synthesis. It inhibits the proliferation of fast-growing cells, such as B and T cells. AZA was first introduced to transplantation nearly 60 years ago and along with glucocorticoids, was the standard regimen in liver and kidney transplantation until the introduction of CyA in 1978. It would be used as a secondary agent thereafter until its replacement by another antimetabolite, mycophenolate mofetil (MMF).

Long-term toxicities associated with AZA use include hematological deficiencies, GI disturbances, and hypersensitivity reactions, including skin rashes. As with most immunosuppressive agents, AZA has been associated with the development of malignancies, namely, an increased risk for skin cancer. AZA has been shown to enhance the development of ultraviolet-induced carcinogenesis.[47]

AZA still remains a viable alternative in immunosuppressive therapy and in doses as low as 50 mg daily. Recent comparisons of AZA to MMF have resulted in favorable evaluations of the former. A systematic review of randomized controlled trials comparing both agents in kidney transplantation showed a lesser occurrence of GI-adverse events (diarrhea, emesis, and abdominal pain), leukopenia and anemia, and CMV infections in the AZA groups, with similar rates of malignancies for AZA and MMF.[48] In another review comparing both agents in liver transplantation, Germani et al[49] found no significant benefit of MMF over AZA as an antirejection agent (when used with CyA). Interestingly, in this study the rate of hepatitis C virus recurrence and its severity were more frequently reported with AZA, a finding already noted by Wiesner et al[50] in an international, multicenter comparative study of AZA and MMF.

An unavoidable corollary meriting discussion is the cost of using AZA or MMF, which indisputably would favor AZA. A analysis of cost-effectiveness would need to be undertaken to prove the point, but intuitively AZA is the more affordable option.

MYCOPHENOLATE MOFETIL

MMF is another purine synthesis inhibitor that essentially replaced AZA as the complementary immunosuppressive agent to the CNI in the early 1990s. CNI-induced toxicities were curtailed by adding MMF, and steroids were withdrawn earlier after liver transplantation. The most common side effects associated with MMF are GI in nature and include nausea, vomiting, diarrhea, abdominal cramps, and anorexia, which lead to MMF reduction or withdrawal in up to 50% of cases.[51] The active form of MMF, mycophenolic acid (MPA), was developed as enteric-coated mycophenolate sodium in an attempt to improve GI tolerability. Since its release, studies have confirmed therapeutic equivalence when compared to MMF.[52] More importantly, a benefit in GI-related symptoms has been overwhelmingly shown.[53,54]

Another side effect of MMF is myelosuppression, usually in the form of leukopenia and less commonly, anemia. These effects are reversible, however, and appear to be dose related. Whether GI or hematological, an adverse event from MMF may be addressed by dose splitting (i.e., changing the dose from 1000 mg twice daily to 500 mg four times daily), dose reduction, or discontinuation. Because MMF and enteric-coated mycophenolate sodium are usually prescribed in conjunction with other agents, they have not been strongly implicated with an increased incidence of infection. However, in patients using MPA for psoriasis there were multiple reported cases of herpes zoster reactivation.[55,56] This has also been documented among kidney transplant recipients receiving MPA.[57] In a study from Spain, among 33 adult liver transplant patients on MMF monotherapy, the most common adverse effect was a herpes simplex infection.[58] Thus there may be a link between MMF use and varicella infection. In general, MMF is a safe and effective agent in the prevention of organ transplant rejection. Unlike other agents, long-term toxicities are not cumulative.

INDUCTION AGENTS

Some transplant programs use antibody therapies against targets on B and T cells in the immediate perioperative period to thwart the rejection response in the recipient. These agents are covered in depth in Chapter 96. Both acute toxicities and long-term complications of induction agents have become recognized, leading to a reduction in their use at our center. However, they are still used for atypical or steroid-resistant rejections.

Antithymocyte globulin (ATG) or rabbit ATG (Thymoglobulin) is not routinely used as an induction agent in liver transplantation but is still used in the treatment of steroid-resistant rejection. Over the short term, ATG administration is associated with side effects, including flulike symptoms termed *cytokine release syndrome*, characterized in severe cases by tachycardia, dyspnea, chest pain, pulmonary edema, and fever. Premedication with acetaminophen, an antihistamine, and steroids usually ameliorates the symptoms. The syndrome is most prevalent during the first dose and abates with repeated doses. Serum sickness, manifesting as an urticarial rash and arthralgias, occurs in some patients, particularly if they have prior exposure to ATG. This typically emerges after several doses have been given. Pancytopenia is also commonly seen. Only a few reports have been published regarding long-term follow-up of patients receiving ATG as an induction agent in liver transplantation. These studies have not suggested an increased risk for infectious complications or malignancy after transplantation.[59,60]

Interleukin-2 receptor inhibitors, basiliximab and daclizumab, are inert agents, causing neither infusion-related phenomena nor untoward long-term side effects such as nephrotoxicity. Early studies in liver transplantation focused on their ability to provide effective early immunosuppression in recipients with renal dysfunction, allowing for delayed introduction of a CNI. In addition, daclizumab was shown to be effective in reducing acute rejection episodes while avoiding steroid therapy.[61,62] However, basiliximab showed no significant improvement over a conventional immunosuppressive regimen.[63] In a meta-analysis of randomized trials on these interleukin--2 blockers, no evidence of increased infections or malignancies was noted at 1-year after transplantation.[64] Finally, in a multicenter trial by Klintmalm et al[65] the addition of daclizumab to the immunosuppressive regimen of hepatitis C patients did not show a clear benefit over standard treatment. As a result, we no longer use any induction agents or steroids on our patients with viral hepatitis.

Alemtuzumab, a recombinant anti-CD52 monoclonal antibody, generates a profound depletion of circulating B- and T-cell lymphocytes, macrophages, and natural killer cells, the effects of which can last for weeks. As a result it has been used increasingly in recent years to prevent rejection in organ transplant recipients. Conversely, there are concerns about the risks for infection and malignancy due to its mechanism of action. In a review of 547 patients receiving various organ transplants (liver transplants, N = 54 [10%]) at the University of Pittsburgh, alemtuzumab used in the treatment of rejection was shown to cause more opportunistic infections (namely CMV) than alemtuzumab used for induction therapy.[66] In a multicenter study on kidney transplantation, alemtuzumab was evaluated against patients receiving conventional therapy (i.e., rabbit ATG or basiliximab induction). The incidence of malignancy was higher in the alemtuzumab group (P = .03), and the rate of serious adverse infectious events with alemtuzumab was greater when compared to basiliximab (35% versus 22%, P = .02), but similar compared to ATG.[67] In liver transplantation there is scant literature on the long-term effects of this antibody. However, a recent retrospective study on non–hepatitis C recipients receiving alemtuzumab found a greater incidence of infections, specifically viral, when compared to those who did not receive induction.[68] The incidence of malignancy was not different between the groups.

SUMMARY

The holy grail of immunosuppressive therapy has yet to be discovered. Until that time, there must be an understanding of all the potential complications of the current immunosuppressive medications. With proper identification, management, and treatment of these side effects, improved outcomes for liver transplant recipients can be achieved.

Pearls & Pitfalls

- Knowledge and understanding of the long-term side effects of immunosuppression can lead to the early detection and treatment of potential complications.
- Identification and treatment of posttransplantation lymphoproliferative disorder require suspicion of diagnosis, prompt reduction of immunosuppressive medications, and early oncological evaluation.
- Skin cancer is the most common malignancy after liver transplantation. Precautions such as sunscreen, protective cover, and dermatological evaluation should be followed.
- Prolonged corticosteroid and calcineurin inhibitor use contribute to increased cardiovascular morbidity (e.g., hypertension, hyperlipidemia, and hyperglycemia) and mortality. Management of these issues should be incorporated into all patients' general maintenance plans early to mitigate their long-term effects.
- Despite their established nephrotoxicity and risk for renal failure, calcineurin inhibitors (tacrolimus and cyclosporine) remain the gold standard oral immunosuppressive agents.
- Mammalian target of rapamycin (mTOR) inhibitors should be considered early for conversion therapy in recipients with renal dysfunction. Dyslipidemia, proteinuria, and wound complications are their well-known side effects.
- Thymoglobulin and, to a lesser degree, alemtuzumab are associated with infusion-related symptoms collectively referred to as *cytokine release syndrome* (fever, chest pain, dyspnea, tachycardia) which require appropriate premedication and vigilance during administration, particularly in patients with limited cardiovascular reserve.

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