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REVIEW

Brief overview of immunosuppression and its side effects after liver transplantation

Anahita Rabiee[1] | **Gianna Girone**[2] | **Jessica P.E. Davis**[3]

[1]Section of Digestive Diseases, Yale School of Medicine, New Haven, Connecticut, USA

[2]Department of Pharmacy Services, Yale-New Haven Hospital, New Haven, Connecticut, USA

[3]Division of Gastroenterology and Hepatology, Washington DC VA Medical Center, Washington, District of Columbia, USA

Correspondence
Email: Anahita Rabiee, anahita.rabiee@yale.edu

HISTORY OF IMMUNOSUPPRESSION FOR LIVER TRANSPLANT

The first liver transplant was performed by Dr. Thomas E. Starzl in 1963, and the first patient to survive more than a year after the transplant received a combination of azathioprine, steroids, and antilymphocyte globulin. Infectious complications and rejections were common, and 1-year survival was <30%. Calcineurin inhibitors (CNIs), including cyclosporine and tacrolimus, were introduced in the 1980s and changed the landscape of liver transplant, with less rejection and a more favorable side effect profile, resulting in better overall outcomes.[1]

Management of immunosuppression (IS) is a balancing act between achieving tolerance and minimizing side effects and should be tailored to each patient's risk of rejection and comorbidities. The goal of this review is to provide a summary of the most frequently used IS regimens, their mechanisms, and common side effects.

IS REGIMENS

Post-transplant IS can be looked at in 2 phases: induction and maintenance. The induction phase can further be subdivided into the acute perioperative management period (days 0–4) and the initial 3 months after transplant (Figure 1). The perioperative induction management varies based on transplant center practices. Some centers use IL-2 receptor antibodies (basiliximab) in the perioperative induction phase as part of a renal-sparing strategy to delay the initiation of CNI. Pulse dose corticosteroids are used in the perioperative induction phase and then tapered and typically weaned by 3 months post-transplant in the absence of rejection or a history of autoimmune hepatitis (Table 1).

The maintenance phase can be subdivided into 3–6, 6–12, and >12 months post-transplant. As time from transplant increases, the risk of acute rejection decreases, and less IS is required to prevent acute cellular rejection.[2] There are 3 main classes of medications that are most commonly used in this phase: (1) CNIs (such as tacrolimus and cyclosporine), (2) mammalian target of rapamycin inhibitors (mTORi) (such as sirolimus and everolimus), and (3) antimetabolites such as mycophenolic acid and azathioprine.

CNIs are the mainstay of maintenance phase, with tacrolimus being preferred over cyclosporine, as it is more effective in prevention of acute rejection and has superior patient and graft survival.[2,3] During the first year post-transplant, the use of combination therapy is common, most often mycophenolic acid and CNI, to target lower trough levels and minimize renal toxicity caused by CNI. Generally, after 6–12 months, the majority of patients will transition to monotherapy (either CNI or less commonly mTORi). Tacrolimus trough level is followed closely to adjust the dose (with a higher trough goal in the first 3 months which is then

Abbreviations: AKI, acute kidney injury; AZA, azathioprine; CKD, chronic kidney disease; CNIs, calcineurin inhibitors; CSA, cyclosporine; FDA, Food and Drug Administration; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; MPA, mycophenolic acid; mTORi, mammalian target of rapamycin inhibitors; PRES, posterior reversible encephalopathy syndrome; TAC, tacrolimus.

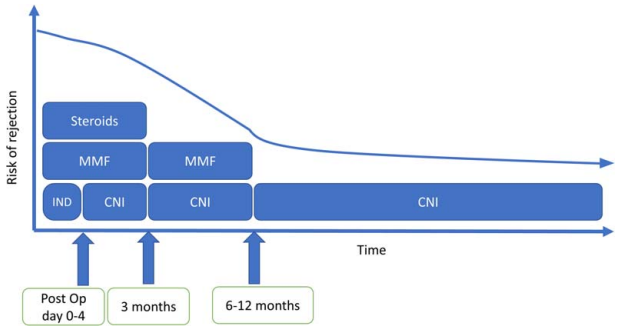

FIGURE 1 A sample renal-sparing medication regimen after liver transplant.

decreased over the remainder of the year). In the absence of autoimmune hepatitis or a history of rejection, tacrolimus can be adjusted to achieve a trough level no >5 ng/mL after 12 months post-transplant.[2] After 5 years, if there is good graft function (normal liver chemistries), trough levels just above the lower limit of detection are acceptable.[2]

Non-CNI monotherapy with mTORi can be considered in patients at low immunological risk and may be of interest in patients with a history of malignancy or those experiencing significant CNI-related side effects. Although used at many centers, sirolimus is not Food and Drug Administration (FDA) approved for liver transplant. Everolimus, which is a synthetic derivative of sirolimus, is FDA approved. In general, mTORi should be avoided in the first 30 days after transplant because of the increased risk for hepatic artery thrombosis and impaired wound healing. It has been proposed that in patients with HCC (within Milan criteria), mTORi-based regimens can achieve higher recurrence-free and overall survival, and can also reduce the risk of nonmelanoma skin cancer recurrence, renal cell cancer, and neuroendocrine tumors[2]; however, more data are needed to confirm this hypothesis.

COMMON ISSUES WITH IS

Drug-drug interactions

Both CNI and mTORi are metabolized by CYP-450 3A4 and therefore have interactions with many drugs. It is important to consider these interactions and adjust dosage accordingly, as completely avoiding drug-drug interaction is usually not possible. Common classes of drugs that inhibit CYP-450 3A4 include azoles, macrolides, protease inhibitors, and calcium-channel blockers (especially non-dihydropyridine) (Table 2). Of note, the recently approved antiviral Paxlovid for the treatment of COVID-19 contains protease inhibitor ritonavir, which is a potent CYP-450 3A4 inhibitor that leads to very high CNI levels and requires close monitoring.[4]

TABLE 1 Most common immunosuppression medications, mechanism of action, and timing of use after liver transplant

Mechanism of action	Class	Drug name	Induction	Maintenance	Timing	Limitations
T-cell activation inhibitor	Corticosteroids	Prednisone	✓		By 3 mo after liver transplant most patients should be tapered off. Patients with history of autoimmune liver disease may require long-term steroids.	Minimize long-term use due to numerous side effects
	CNI	Tacrolimus (TAC)		✓ (Mono or combination therapy)	All patients who are eligible for minimization of immunosuppression are potential candidates for CNI monotherapy after 3 mo	Nephrotoxicity
		Cyclosporine (CSA)				
T-cell proliferation inhibitor	Antimetabolites	Mycophenolic acid (MPA)		✓ (Combination therapy)	Usually considered as an adjuvant to CNI as renal sparing (reduced dose or delayed initiation of CNI)	Increased risk of acute rejection with monotherapy Gastrointestinal toxicity/cytopenia
		Azathioprine (AZA)				
	mTOR inhibitor (mTORi)	Sirolimus (SRL)		✓ (Mono or combination therapy)	Early institution of EVR at 1 mo combination TAC (targeting lower trough) results in a significantly better renal function than is achieved with standard dosing of TAC. Generally after >3 mo non-CNI monotherapy with mTORi may be considered in patients at low immunological risk.	Higher risk of rejection and hepatic artery thrombosis, negative effect on wound healing
		Everolimus (EVR)				

Abbreviations: AZA, azathioprine; CNI, calcineurin inhibitor; MPA, mycophenolic acid; mTORi, mammalian target of rapamycin inhibitors.

TABLE 2 Most common side effects of immunosuppression medications used after liver transplant

	Increase levels of IS					Decrease levels of IS			Other interactions	
	Azoles	Calcium channel blockers	Macrolide antibiotics	Protease inhibitors	*Allopurinol (AZA only)*	St. John's Wort	Antiseizure medications	Cholestyramine iron prep	Statins	NSAID
	Fluconazole Voriconazole	*Diltiazem verapamil*	*Clarithromycin Erythromycin*	*Paxlovid, ritonavir*			*Phenobarbital Phenytoin*		*Atorvastatin*	
CNI	TAC ↑ CSA ↑	TAC ↑ CSA ↑	TAC ↑ CSA ↑	TAC ↑ CSA ↑		TAC ↓ CSA ↓	TAC ↓ CSA ↓		Rhabdomyolysis [a]	Kidney injury [b]
mTORi	SRL ↑ EVR ↑	SRL ↑ EVR ↑	SRL ↑ EVR ↑	SRL ↑ EVR ↑		SRL ↓ EVR ↓	SRL ↓ EVR ↓			
AZA, MPA					AZA ↑			AZA ↓ MPA ↓		

Abbreviations: AKI, acute kidney injury; AZA, azathioprine; CKD, chronic kidney disease; CNI, calcineurin inhibitor; CSA, cyclosporine; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; MPA, mycophenolic acid; mTORi, mammalian target of rapamycin inhibitors; PRES, posterior reversible encephalopathy syndrome; TAC, tacrolimus.

Kidney injury

One of the major side effects of CNI is kidney injury. CNI can cause both acute and chronic nephrotoxicity (lasting >3 mo). Although acute nephrotoxicity is reversible and is caused by afferent arterial vasoconstriction, chronic nephrotoxicity, which is caused by interstitial fibrosis, is irreversible and can even lead to End Stage Renal Disease. The cumulative incidence of chronic stage 3 kidney disease ranges from 36% to 57% with CNI.[5] The risk of kidney injury can be reduced with a lower dose and/or delayed initiation of CNI after transplant (use of renal-sparing regimens).

Metabolic syndrome

Metabolic syndrome is a major concern post-transplant and is becoming more relevant as more patients with NASH cirrhosis undergo liver transplant. Corticosteroids, CNI, and mTORi are associated with the development of metabolic syndrome (Table 3). Metabolic syndrome has been reported in >50% of patients 6 months after liver transplant and is associated with an increased risk of cardiovascular events.[6,7] Metabolic syndrome includes new-onset diabetes (30%–40%), hypertension (60%–70%), dyslipidemia (50%–70%), and obesity.[8] First-line treatment for hypertension includes calcium-channel blockers. In the treatment of dyslipidemia, and as statins interact with cyclosporine, switching to tacrolimus should be considered. Treatment of diabetes is based on endocrine guidelines, but the modification of IS regimen can also be considered.[9]

Bone marrow suppression

Antiproliferative agents, including mycophenolate, azathioprine, and mTORi, can cause bone marrow suppression and cytopenia. Initial treatment involves dose reduction of culprit medications (commonly IS and/or valganciclovir) and evaluation for cytomegalovirus. In post-transplant patients with severe neutropenia (absolute neutrophil count <500), a granulocyte colony-stimulating factor may be required to improve neutrophil counts and reduce infection risk.

Gastrointestinal symptoms

Antiproliferative agents can cause nausea, vomiting, and diarrhea. Initial management includes dose reduction where possible. Switching to mycophenolate sodium may improve symptoms as it is enteric coated.

TABLE 3 Most common drug-drug interactions with immunosuppression medications used after liver transplant

Category	Side effects	Culprit Agents	Approach
Nephrotoxicity	AKI CKD	CNI	Use of renal sparing regimen at time of transplant Addition of a antimetabolites. to allow a lower trough target
Cardiovascular and metabolic syndrome	Diabetes	CNI ITAC > CSA), steroids	Treat based on endocrine diabetes management guidelines
	Hypertension	CNI ICSA>TACj, steroids	Treatment with nifedipine or earvedilol
	Hyperlipidemia	mTORi> CSA> TAC, steroids	mTORi dose-red jction or switching to alternative medication Use caution in using statins with CSA Pravastatin may be preferred in CSA
Bone marrow suppression	Leukopenia Neutropenia Anemia Thrombocytopenia	Antiproliferative (MPA, AZA), mTORi	Switch to a different agent or dose reduction G-CSF/G M-C5F to treat neutropenia
Gastrointestinal symptoms	Nausea and vomiting, Diarrhea	Antiproliferative (MPA. AZA)	Need to rule out other causes, can consider switching to Myfortic (enteric coated)
Neurotoxicity	Tremors, headache, seizure, delirium, mood changes, PRE5	CNI	Addition of Magnesium Switching to Envaraus for tremors [peak related) Can consider switching to cyclosporine from tacrolimus for PRES

Abbreviations: AKI: Acute Kidney Injury; CKD: Chronic Kidney Disease; CNI: Calcineurin Inhibitor; TAC: Tacrolimus; CSA: Cyclosporine; MMF: Mycophenolic acid; AZA: Azathioprine; PRES: posterior reversible encephalopathy syndrome; mTORi: Mammalian Target of Rapamycin Inhibitors; G-C5F: Granulocyte colony-stimulating factor; GM-C5F: Granulacyte-macrophage colony-stimulating factor.

Neurotoxicity

CNI can cause tremors, seizures, headaches, mood changes, altered mental status, and posterior reversible encephalopathy syndrome. Major neurotoxicities such as posterior reversible encephalopathy syndrome should be managed by conversion to a different IS (either within the same class or a different class).[10] Less severe forms of neurotoxicity can be managed symptomatically. Hypomagnesemia caused by CNIs is a risk factor for worsening neurotoxicity, so magnesium supplements can be helpful.[10] The use of long-acting tacrolimus (Envarsus XR) may reduce tremors, which are peak-related[11]; however, it should be noted that Envarsus XR is not FDA approved for liver transplant (Table 4).

TABLE 4 Pharmacokinetics of commonly used immunosuppression medications after liver transplant

Drug class	Common Oral Formulations	Absorption	Metabolism	Requires trough monitoring	Half-life	Excretion
CNI	TAC • Prograf (immediate release) • Envarsus (extended release)	Poor bioavailability: 15%-20% High intrapatient and interpatient variability	Metabolized by CYP3A4 *TAC is additionally metabolized by CYP3A5	Yes	Prograf: 12 h Envarsus: 30–36 h	Primary clearance is biliary, and found in feces <2% through renal clearance
	CSA				8 h	
mTORi	Sirolimus Everolimus				Sirolimus: 60 h Everolimus: 30 h	
MPA	Mycophenolate Mofetil (MMF) Mycophenolate sodium (Enteric coated)	90% bioavailability	Glucuronidation to 7-O-glucuronide (MPAG)	No	18 h	Primary clearance is renal (>90%)

Abbreviations: CNI, calcineurin inhibitor; CSA, cyclosporine; MPA, mycophenolic acid; mTORi, mammalian target of rapamycin inhibitors; TAC, tacrolimus.

CONCLUSIONS

Innovation in IS over the past 80 years has led to a dramatic reduction in post-liver transplant mortality. This improved survival has shifted the focus of IS management away from rejection to minimization of IS-related morbidity and mortality. Modern IS management includes an individualized approach with the goal of exposing the patient to the minimum amount of IS required to maintain a healthy graft.

CONFLICTS OF INTEREST

The authors have no conflicts to report.

ORCID

Anahita Rabiee https://orcid.org/0000–0002–5190–6959
Gianna Girone https://orcid.org/0000–0002–8833–3592
Jessica P.E. Davis https://orcid.org/0000–0002–8918–7806

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