



Immunosuppressive pharmacotherapy in liver transplantation

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Abstract: The discovery of effective immunosuppressive medications, namely cyclosporine in the early 80's, was the seminal event that dramatically improved patient and graft survival after liver transplantation and solidified its status as the treatment of choice for end-stage liver disease (ESLD). Over the ensuing 30 years, the immunosuppressive armamentarium has expanded dramatically leading to a significant decrease in acute cellular rejection (ACR), and hence improvements in graft and patient survival. Unfortunately, long-term exposure to immunosuppressive medications and their cumulative adverse effects, including renal dysfunction, metabolic syndrome, and malignancy, contribute to morbidity and mortality in the long-term transplant recipients leading to late graft loss. Therefore, judicious use of immunosuppressive medications, with utmost attention to their unique adverse event profiles, pharmacokinetics, and pharmacodynamics are essential in designing individualized regimens best suited for each transplant recipient. In this article, major classes of immunosuppressive medications used for induction and maintenance therapy in liver transplantation are reviewed, including their pharmacology, pharmacokinetics, drug interactions and common adverse drug reactions. The evidence for their preferential use is presented where available.

Keywords: Immunosuppression; liver transplantation; rejection; drug interactions

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Introduction

The success of liver transplantation as the treatment of choice for end-stage liver disease (ESLD) has paralleled the discovery of effective immunosuppressive (IMS) medications. The first surgically successful liver transplant was performed by Dr. Starzl in 1967 but the patient survived just over 1 year. Throughout the 1970s, despite improvements in surgical techniques, liver transplantation remained firmly in the experimental realm with dismal patient survival of 15% at 1 year (1). In the early 80's, the development of Cyclosporine markedly improved liver transplant outcomes leading to its recognition as the definitive therapy for ESLD by the US National Institutes of Health (1,2). Over the ensuing

30 years, the immunosuppressive armamentarium has expanded dramatically leading to a significant decrease in acute cellular rejection (ACR) and improvements in graft and patient survival. Today however, the long-term complications of immunosuppression have replaced rejection as the major therapeutic challenge in transplantation (3). In fact, a significant proportion of late graft loss or patient death with functional graft is attributed to long-term exposure to immunosuppressive medications, such as renal dysfunction, metabolic syndrome and malignancies. As such, the art of transplantation is a balancing act of adequate immunosuppression to prevent allo-recognition and rejection while avoiding over-immunosuppression and its long-term consequences (4). Alloreactivity and risk of rejection are highest in the first 3

to 6 months after transplantation and decrease with time. Therefore, the highest intensity of immunosuppression is employed immediately after surgery and decreased over time, eventually settling on the lowest maintenance immunosuppression required to prevent graft rejection.

Immunosuppressive medications are classified as induction and maintenance agents. Induction therapy is a short course of potent immunosuppressive agents utilized in the immediate post-transplant period to reduce the initial robust immune response of T lymphocytes against the transplanted liver. Induction therapy is often initiated intra-operatively or immediately post-operatively and generally is concluded within the first 7–10 days of transplantation. Induction agents most commonly used include polyclonal antibody preparation, Antithymocyte Globulin (ATG), and interleukin 2 (IL-2) receptor antagonist, Basiliximab. Maintenance immunosuppression regimens can include a combination of agents from different therapeutic classes including calcineurin inhibitors (CNI), antiproliferative agents, mammalian target of rapamycin (mTOR) inhibitors, and corticosteroids. They may be initiated at the same time as induction therapy or started after transplantation and continued long term to provide continuous prophylaxis against rejection. In this article, pharmacology and therapeutics of major classes of immunosuppressive medications utilized in liver transplantation are reviewed. The evidence for their preferential use is presented where available.

Calcineurin inhibitors: cyclosporine (CSA) and tacrolimus (Tac)

The discovery of CNI, cyclosporine, was a major breakthrough in modern transplantation, leading to significant improvements in patient and graft survival. As such, CNIs are the backbone of most immunosuppressive protocols.

Cyclosporine is a lipophilic undecapeptide and tacrolimus is a macrolide antibiotic both extracted from fungi with similar immunosuppressive properties. Their mechanism of action is mediated through inhibiting the production of IL-2 and other cytokines required for T-cell activation and proliferation (5,6). They both bind to cytosolic proteins, cyclophilin in the case of CSA and FK-binding proteins for tacrolimus. The CNI—cyclophilin complex will then inhibit the phosphatase activity of calcineurin, thus preventing the activation of nuclear factors involved in the gene transcription for IL-2 and other cytokines (5,7). Pharmacokinetic parameters and dosing information for

cyclosporine and tacrolimus are presented in *Table 1*. Due to their narrow therapeutic index, and inter- and intra-patient variability in exposure, therapeutic drug monitoring (TDM) is recommended for both agents. Tacrolimus trough levels (C_0) and cyclosporine trough (C_0) and 2 hour post levels (C_2) should be monitored regularly. In the cyclosporine case, C_2 levels better correlate with systemic exposure (8); however, C_0 monitoring is more common due to convenience. Target serum concentration levels depend on individual patient factors such as time since transplantation, other immunosuppressive medications onboard, history of rejection, co-morbidities and the underlying etiology of liver disease. However, in general, levels at the higher end of the therapeutic range are targeted immediately post transplantation and then reduced over time, if tolerated.

Tacrolimus is associated with superior patient and graft survival and has replaced CSA as the first line immunosuppressive therapy. In a landmark open label, randomized trial (9), 606 patients were randomly assigned to either CSA or Tac. Tacrolimus was superior with regards to patient and graft survival and prevention of severe rejection episodes at one and 3 years follow ups (10). Multiple subsequent studies were performed and a meta-analysis of 16 randomized controlled trials (RCTs) confirmed the superiority of Tacrolimus over cyclosporine (11,12). These findings have made tacrolimus first line therapy in most liver transplant centers.

Tacrolimus and cyclosporine have similar adverse event profiles including nephrotoxicity, neurotoxicity, post-transplant metabolic syndrome, and electrolyte abnormalities. CNI induced nephrotoxicity is the ‘Achilles heel’ of transplantation. Up to 20% of LT recipients develop chronic kidney disease (CKD) within 5 years after transplant, and once patients progress to end-stage renal disease (ESRD), their mortality is up to four folds higher than those without renal dysfunction (13). To mitigate CNI associated nephropathy, minimization or withdrawal of cyclosporine and tacrolimus have been attempted albeit with variable success (14). Hypertension, hyperlipidemia and dysmorphic side effects such as hirsutism and gingival hypertrophy develop more frequently with cyclosporine; whereas, post-transplant diabetes, tremors, and alopecia occur more commonly with tacrolimus (15) (*Table 1*).

Recognizing drug-drug interactions are paramount in managing patients receiving CNIs as pharmacokinetic and pharmacodynamic interactions are common with these agents. Cyclosporine and tacrolimus are metabolized by Cytochrome P-450 3A4 (CYP 3A4) and medications that inhibit or induce CYP 3A4 isoenzymes can increase or decrease CNI exposure

Table 1 Maintenance immunosuppression pharmacokinetics and therapeutics

Agent	Immune target	ADME	Dosage	Adverse events
Cyclosporine	T-lymphocytes	A: improved with microemulsion versus oil based formulation; 90% protein bound; M: Hepatic; E: Bile; T _{1/2} : 8–12 hours	5 mg/kg PO Q12H; IV dosage 30% to 50% of PO dosage	Nephrotoxicity; hypertension; hyperlipidemia; hyperuricemia; hirsutism; acne; gingival hyperplasia
Tacrolimus	T-lymphocytes	A: incomplete, variable, lower with food; 99% protein bound; M: hepatic; E: bile; T _{1/2} : 10–14 hours	0.03–0.05 mg/kg PO Q12H; IV dosage 25% of PO dosage	Nephrotoxicity; neurotoxicity; glucose intolerance; alopecia; diarrhea
Azathioprine	T- and B-lymphocytes	A: well absorbed; 30% protein bound; M: hepatic; E: urine, primarily as metabolites; T _{1/2} : variable, ~2 hours	1–2.5 mg/kg PO daily	Leukopenia, thrombocytopenia; gastrointestinal disturbances, pancreatitis; hepatotoxicity
Mycophenolate	T- and B-lymphocytes	A: rapidly absorbed and converted to MPA with 90% bioavailability; MPA is 98% protein bound; M: hepatic to MPA glucuronide which is excreted renally; T _{1/2} : 11–18 hours	500–1,500 mg Q12H; usual dosage 1,000 mg Q12H; IV to PO 1:1	Leukopenia; thrombocytopenia; gastrointestinal disturbances; diarrhea; CMV reactivation
Sirolimus	T- and B-lymphocytes	A: rapid; 92% protein bound; M: hepatic and intestinal wall (P-gp); E: feces 91%; T _{1/2} : 62 hours	Start with 1–2 mg PO daily and up-titrate to target levels	Anemia; thrombocytopenia; mouth ulcers hypercholesterolemia; impaired wound healing; lymphocele; pneumonitis

A, absorption; CSA, cyclosporine; CMV, cytomegalovirus; E, elimination; M, metabolism; MPA, mycophenolic acid; P-gp, P-glycoprotein; T_{1/2}, half-life.

(Table 2). Additionally, pharmacodynamic interactions include co-administration of medications with overlapping toxicities, such as nephrotoxicity in the case of aminoglycosides and intravenous contrast dye.

Antimetabolites: azathioprine (AZA) and mycophenolate mofetil (MMF)

Antimetabolites are commonly added to CNIs and short-term steroids as part of the standard maintenance immunosuppressive (IMS) protocols. AZA is a prodrug of 6-mercaptopurine which inhibits purine biosynthesis, therefore, inhibiting DNA and RNA synthesis necessary for B and T lymphocyte proliferation (16). It is typically dosed at 1.5 to 2.0 mg/kg/day (17). AZA is associated with significant myelotoxicity especially at higher dosages (18). Other side effects include nausea, vomiting, pancreatitis, and hepatotoxicity (18) (Table 1).

Since 2000, mycophenolate has replaced AZA as the preferred antimetabolite agent in most transplant centers due to its superior immunosuppressive efficacy and less marrow toxicity (19). MMF is a pro-drug that is converted to mycophenolic acid (MPA). MPA inhibits inosine monophosphate dehydrogenase (IMPDH), the

rate limiting enzyme responsible for *de novo* synthesis of guanosine nucleotides, leading to inhibition of both T- and B-lymphocytes proliferation (15).

Mycophenolate’s pharmacokinetics are less variable than that of the CNIs, hence TDM is not required and in fact the drug is usually administered as a fixed dosage regimen of 1,500 to 2,000 mg per day in two divided doses. MMF is rapidly hydrolyzed and converted to MPA in the liver (20). MPA is highly protein bound (97.5%) and only the free fraction is pharmacologically active. MPA is metabolised in the liver to an inactive metabolite, 7-O-MPA-glucuronide (MPAG), which is excreted in urine and bile. Once excreted in bile, MPAG can be converted back to MPA which is then reabsorbed. This enterohepatic recirculation (EHRC) produces a second pharmacokinetic peak at 6 to 12 hours after the dosage and increases the total exposure of mycophenolate by as much as 30%. Hence medications that interfere with the EHRC, such as CSA and oral antibiotics, will decrease the systemic exposure to MMF (20).

Since mycophenolate is devoid of neurotoxicity and nephrotoxicity, it is often used as a CNI-sparing-agent. The main side effect associated with mycophenolate is bone marrow suppression and gastrointestinal complaints such as diarrhea, nausea, vomiting, and abdominal pain.

Table 2 Drug-drug interactions with maintenance immunosuppressive agents

Agent	Metabolism	Enzyme inhibition	Interactions	
			Increase IMS levels	Decrease IMS levels
Cyclosporine	CYP3A4 (major), P-glycoprotein	CYP2C9 (weak); CYP3A4 (weak); transporter proteins	Ketoconazole; fluconazole; itraconazole; voriconazole; posaconazole; erythromycin; clarithromycin; diltiazem; verapamil; amiodarone; cimetidine; danazol; fluvoxamine; protease inhibitors (HIV & HCV); grapefruit juice	Rifampin; Rifabutin; phenytoin; phenobarbital; carbamazepine; St. John's wort; Isoniazid
Tacrolimus	CYP3A4 (major), P-glycoprotein	CYP3A4 (weak) Transporter proteins	As above, CSA—separate administration by 4 hours	As above
Sirolimus	CYP3A4 (major), P-glycoprotein	CYP3A4 (weak)	Allopurinol; methotrexate; febuxostat	N/A
Azathioprine	Glutathione S-transferase reduction (6-MP-active); hypoxanthine guanine phosphoribosyltransferase (6-TGNs-active); xanthine oxidase (6-thiouric acid-inactive); TPMT (6-methylmercaptapurine-inactive)	N/A	Renal dysfunction	Magnesium- or aluminum-containing products (decreased absorption); antacids; cholestyramine; CSA (↓ EHRC); antibiotics (↓ EHRC); probenecid
Mycophenolate	Hydrolyzed in the liver to mycophenolic acid (active); MPA is glucuronidated to MPAG (inactive)	N/A		

↓, Decreased. CYP 3A4, cytochrome P-450 3A4; EHRC, enterohepatic recirculation; IMS, immunosuppressant; 6-MP, 6-mercaptopurine; MPA, mycophenolic acid; MPAG, mycophenolic acid glucuronide; 6-TGNs, 6-thioguanine-nucleotides; TPMT, thiopurine methyltransferase.

In liver transplantation, the benefit of mycophenolate over AZA is not fully elucidated or extensively studied. Two RCTs compared MMF versus AZA in combination with CSA and steroids (21-23). In these trials, patient and graft survival were similar in both groups albeit short follow up duration. One trial demonstrated lower biopsy proven ACR with MMF (23), while the larger registration trial failed to show a difference in recurrent rejection rates (22). Switching to MMF monotherapy as a renal sparing strategy has also been shown to be effective in liver transplant patients who are more than 5 years post-transplant (24).

mTOR inhibitors: sirolimus

Sirolimus (SRL) is a macrolide antibiotic which is structurally similar to tacrolimus and binds to the same target (FK-binding protein), but it has a different mechanism of action (25). It acts later in the lymphocyte activation/proliferation cycle, blocking the transduction signal from the IL-2 receptor, and thus inhibiting T- and B-cell proliferation. Its advantage

over the CNIs is its relative lack of nephrotoxicity and neurotoxicity, in addition to antineoplastic properties against certain types of cancers. However, sirolimus's side effect profile is extensive limiting its use in clinical practice. It is estimated that up to 30% of patients will discontinue sirolimus due to adverse drug reactions (26). Oromucosal ulcers, dyslipidemia, anemia, proteinuria, interstitial lung disease, peripheral edema, and delayed wound healing are amongst commonly reported side effects with sirolimus. In 2002, the Food and Drug Administration (FDA) issued a black box warning regarding the risk of hepatic artery thrombosis (HAT) with *de novo* sirolimus-based immunosuppression; hence, sirolimus should not be initiated within the first month after transplantation. The role of sirolimus in liver transplantation is one of a second line agent/alternative therapy in the cases of CNI induced nephrotoxicity, neurotoxicity or HCC recurrence prevention.

The benefit of sirolimus in renal dysfunction remains controversial. While small observational studies failed to demonstrate an improvement in renal function with

sirolimus based therapy (27-29), others reported renal-sparing effects with conversion to sirolimus (30). A meta-analysis of 11 observational studies and controlled trials found a small (3.4 mL/min), nonsignificant increase in glomerular filtration rate after 1 year of sirolimus use (26). However, when focusing only on controlled trials in this meta-analysis, sirolimus use in patients with eGFR >50 mL/min at baseline was associated with a significant improvement in renal function. A retrospective study showed that early conversion (within 3 months after transplant) to sirolimus was associated with improved renal function, while late conversion was of little benefit (31). In another large prospective randomized trial, late conversion to SRL failed to demonstrate improved GFR at 12 months post conversion (32). Spare the Nephron Trial was a large prospective multicenter trial that looked at early conversion (within 4 to 12 weeks) to SRL/MMF as compared to maintenance with CNI/MMF. MMF/SRL was associated with a significantly greater renal function improvement from baseline at the expense of higher incidence of biopsy proven acute rejection (BPAR) and treatment discontinuation due to side effects (33). It appears that timing for sirolimus conversion matters for renal-sparing strategy as CNI induced nephropathy will become irreversible at some point. Therefore, conversion to a SRL based immunosuppression as a renal sparing strategy, should take place early (within 3 months) after transplantation prior to significant chronic CNI induced nephrotoxicity is established. It must be stressed that this strategy might lead to higher rates of BPAR and treatment discontinuation due to adverse events. Because mTOR inhibitors possess antiangiogenic, antiproliferative, and proimmunogenic properties, they have been proposed as the ideal choice for immunosuppression after LT in patients with a history of hepatocellular carcinoma (HCC). Although, many small retrospective or non-randomized pilot trials demonstrated a benefit with SRL based immunosuppression in this setting (34-38), the single large randomized multicenter trial did not confirm their findings (39). The SiLVER trial failed to demonstrate an improvement in recurrence-free survival (RFS) beyond 5 years with SRL based therapy, although RFS and overall survival were improved at 3 to 5 years (39). However, due to methodological flaws, caution must be exercised when interpreting the results of the SiLVER trial.

Corticosteroids

From the early days, corticosteroids have been the cornerstone of immunosuppression in modern transplantation. They

are extensively used as induction and maintenance immunosuppression (IMS), and are considered first line agents for the treatment of ACR. Although their mechanism of action is poorly understood, corticosteroids exert their broad and dose dependent immunosuppressive effects by blocking cytokine activation such as interleukin 1, 2, and 6 and non-specifically inhibiting T-cell activation (15). A typical prednisone dosage for maintenance immunosuppression is 0.3 mg/kg/day tapered over 3 to 6 months after transplantation. Despite their undisputed efficacy, many transplant programs attempt to eliminate, minimize or avoid corticosteroid use due to their extensive short- and long-term adverse event profiles. Hypertension, hyperglycaemia, hypercholesterolemia, metabolic bone disease and obesity are well known side effects of corticosteroids. A recent Cochrane systematic review found no statistically significant difference between glucocorticosteroid-containing immunosuppression versus glucocorticosteroid avoidance or withdrawal in terms of mortality, graft loss or infection rates (40). Glucocorticosteroid avoidance or withdrawal was associated with reduced diabetes mellitus and hypertension, but increased rates of acute rejection, and renal impairment (40). As such, the majority of transplant centers continue to use corticosteroids despite the availability of newer immunosuppressants. In fact, a recent survey of North American liver transplant centers demonstrated that up to 80% of all centers use short term steroids as part of their early maintenance immunosuppressive regimens (4).

Induction agents

In the setting of liver transplantation, induction therapy is most commonly utilized to facilitate CNI minimization or steroid avoidance. Induction therapy is achieved by administering a short course of antibody therapy immediately after transplantation, employing either depleting or receptor modulating agents.

Interleukin-2 receptor Antagonists (IL-2RA)

Basiliximab, and daclizumab which is no longer marketed, are humanized monoclonal antibodies that block the IL-2 receptor on activated T-lymphocytes, therefore preventing T-cell proliferation (17). Basiliximab is administered as two intravenous infusions of 20 mg, first given during the anhepatic phase or immediately after the operation and the second, four days after transplantation. It has an elimination half-life of approximately 4 days, but the receptor suppression effects of basiliximab can last up to 4 weeks (18).

Basiliximab infusion is well tolerated with few side effects.

IL-2RA induction is mainly utilized to reduce or delay the use of CNIs, particularly in patients with renal insufficiency. Earlier small non-randomized trials suggested IL-2RA induction with delayed introduction of CNIs, or immediate initiation of low-dose CNIs in patients with renal dysfunction resulted in improved renal function and lower rates of ACR (41,42). Multicenter randomised controlled trials in patients with normal renal function demonstrated no difference in the rates of ACR between the two groups with variable effects on renal function (43-45). ReSpECT study was the largest RCT which compared standard dose tacrolimus to low dose and delayed tacrolimus initiation with daclizumab induction looking at the primary endpoint of a change in renal function at 52 weeks (45). Patients in the daclizumab group had improved renal function while patient and graft survival were similar among all groups. The two smaller RCTs showed similar rates of ACR, but no long-term improvement in renal function with daclizumab induction (43,44). Although there was a distinct improvement in GFR in the first week with the allowance of delayed, low dose tacrolimus dosing. These studies demonstrate that IL-2RA induction to facilitate delayed use of CNIs does not increase the risk of rejection and may improve renal function.

Antithymocyte globulins

Antithymocyte globulins (ATG, thymoglobulin) are potent polyclonal depleting antibodies used for induction of immunosuppression and the treatment of steroid refractory ACR. ATGs are prepared by immunizing animals (horses or rabbits) against human T-cells or thymocytes (18). The resulting preparations have antibodies to multiple epitopes on T lymphocytes, resulting in nonspecific T cell depletion. Rabbit ATG is used preferentially and more commonly over the equine preparations as it is less immunogenic and more potent. Administration of ATG is often accompanied by an extensive release of cytokines due to cell destruction. This cytokine release syndrome manifests as fever, chills, tachycardia, gastrointestinal disturbances, bronchospasm, and fluctuations of blood pressure, and can be ameliorated by slow infusion rates and premedication with corticosteroids, antihistamines and acetaminophen (46).

The usual dosage for rabbit ATG ranges from 1 to 2 mg/kg/day administered intravenously for 3 to 10 days depending on the therapeutic indication. The pharmacologic effects of ATG are profound and last longer than the presence of antibodies themselves. Reconstitution

of the immune system can take several months, possibly up to a year, and full recovery is questionable, especially in the elderly population (47). Due to profound and long-lasting immunosuppression imparted by depleting antibodies, their use is associated with increased risk of infectious complications, and malignancies, in particular posttransplant lymphoproliferative disease (PTLD) (17).

Many studies have examined ATG induction to facilitate steroid avoidance (48-50) or as a CNI-sparing strategy (51,52). A large retrospective study of 500 consecutive LT recipients who received ATG induction, steroid elimination after one dose of methylprednisolone, in addition to MMF and delayed Tacrolimus/Sirolimus reported 1-year patient and graft survival of 92.8% and 89.6% and ACR rate of 22.8% (50). A recent Cochrane meta-analysis failed to demonstrate any benefit with antibody induction due to small number of randomized trials with methodological flaws and limited numbers of participants (53).

According to the 2015 Scientific Registry of Transplant Recipients (SRTR) report, up to 15% of adult liver transplant centers use thymoglobulin for induction immunosuppression (54) even though the use of ATG in liver transplantation is not an approved indication and remains "off-label".

Pragmatic RCTs are need to further delineate the role of ATG induction in liver transplantation.

Conclusions

Half a century of experience in liver transplantation has witnessed advancements in surgical techniques, organ procurement, and immunosuppressive pharmacotherapy leading to dramatic improvements in patient and graft survival. State of the art individualized immunosuppression remains the challenge for the next 50 years.

Evidence based knowledge of immunosuppressive pharmacotherapy in liver transplantation is essential in designing an appropriate medication regimen for each individual patient, taking into account their co-morbidities and the intricacies of each immunosuppressive medication.

CNIs, tacrolimus in particular, remain the backbone of immunosuppression in most protocols. Long-term complications of CNI exposure, such as nephrotoxicity and metabolic syndrome have spurred RCTs to investigate CNI minimization or withdrawal with variable success. Mycophenolate has replaced AZA as the antiproliferative agent most commonly used in combination with tacrolimus. Sirolimus may offer another IMS option in patients with

HCC or CNI-induced nephropathy. Corticosteroids, despite their significant adverse drug reactions, remain a part of early maintenance IMS therapy. Increasingly, more centers utilize induction antibody agents to either minimize steroids or delay CNI initiation. However, the practice is not uniform and requires further research.

Current thinking is that significant immunosuppression is needed in the immediate post-transplant period. Beyond this period, the complications of excessive immunosuppression outweigh the ever-decreasing risk of organ rejection. With careful monitoring, low doses of immunosuppression are usually well tolerated and safe. Therefore, the art of transplantation is a balancing act of adequate immunosuppression to prevent rejection while avoiding over-immunosuppression and its long-term consequences.

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