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doi:10.3748/wjg.15.4225

World J Gastroenterol 2009 September 14; 15(34): 4225-4233
World Journal of Gastroenterology ISSN 1007-9327

EDITORIAL

Overview of immunosuppression in liver transplantation

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Received: July 1, 2009 Revised: July 30, 2009
Accepted: August 6, 2009
Published online: September 14, 2009

Abstract

Continued advances in surgical techniques and immunosuppressive therapy have allowed liver transplantation to become an extremely successful treatment option for patients with end-stage liver disease. Beginning with the revolutionary discovery of cyclosporine in the 1970s, immunosuppressive regimens have evolved greatly and current statistics confirm one-year graft survival rates in excess of 80%. Immunosuppressive regimens include calcineurin inhibitors, anti-metabolites, mTOR inhibitors, steroids and antibody-based therapies. These agents target different sites in the T cell activation cascade, usually by inhibiting T cell activation or *via* T cell depletion. They are used as induction therapy in the immediate peri- and post-operative period, as long-term maintenance medications to preserve graft function and as salvage therapy for acute rejection in liver transplant recipients. This review will focus on existing immunosuppressive agents for liver transplantation and consider newer medications on the horizon.

Key words: Immunosuppression; Liver transplantation; Induction therapy; Rejection

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Pillai AA, Levitsky J. Overview of immunosuppression in liver transplantation. *World J Gastroenterol* 2009; 15(34): 4225-4233 Available from: URL: http://www.wjgnet.com/1007-9327/15/4225.asp DOI: http://dx.doi.org/10.3748/wjg.15.4225

INTRODUCTION

Due to advances in immunosuppression and improvements in surgical techniques, liver transplantation has become an extremely successful treatment option for patients with end-stage liver disease, with one-year graft survival rates exceeding 80%[1]. Currently, there are eight patients worldwide who have survived more than three decades after liver transplantation[2].

Organ transplantation initially came to light with the first successful kidney transplantation in 1954 on monozygotic twins; however, immunosuppression was limited to total body irradiation which was largely fatal[3,4]. With the invention of 6-mercaptopurine (6-MP) and azathioprine (AZA) in the 1950s along with the introduction of corticosteroids as combination therapy by Starzl in the 1960s, there was noticeable improvement in kidney allograft survival, although one-year survival still did not exceed 50%[4]. Multiple interventions including splenectomy, thymectomy and thoracic duct drainage were employed with minimal success.

The first successful human liver transplant was performed by Thomas Starzl in Denver in 1967 on an 18-month-old child with unresectable hepatoblastoma[2]. The immunosuppressive regimen included anti-lymphocyte globulin (ALG), AZA and prednisolone and the child survived for more than a year.

However, the next significant breakthrough in immunosuppression did not occur until the discovery of cyclosporine (CYA) in 1972 from the soil fungus *Tolypocladium inflatum*. Borel *et al*[5] first described its remarkable immunosuppressive properties in 1976 and by the 1980s there was international affirmation of its effectiveness. CYA quickly became the standard of care for maintenance immunosuppression in solid organ transplant recipients. This paved the way for the current era of liver transplantation, which has since continued to evolve with the discovery of multiple novel immunosuppressive agents.

IMMUNOSUPPRESSION

Effective immunosuppression in transplantation relies on preventing the immune system from rejecting the allograft while preserving immunologic control of infection and

Table 1 Drugs that increase CNI and sirolimus levels

Drugs that increase CNI levels
Macrolides: clarithromycin, erythromycin, azithromycin
Antifungals: fluconazole, itraconazole, ketoconazole, voriconazole, clotrimazole
Calcium channel blockers: verapamil, diltiazem, nifedipine
Others: cisapride, metaclopramide, amiodarone, cimetidine, protease inhibitors
Drugs that decrease CNI and sirolimus levels
Antibiotics: rifabutin, rifampin
Anticonvulsants: carbamazepine, phenobarbital, phenytoin, fosphenytoin
Others: St. John's Wort

CNI: Calcineurin inhibitor.

Table 2 Common side effects of immunosuppressive agents

Drug	Adverse effects
Tacrolimus	Nephrotoxicity, neurotoxicity[1], diabetes[1], hyperkalemia, metabolic acidosis, hypertension, hyperlipidemia
Cyclosporine	Nephrotoxicity, neurotoxicity, diabetes, hyperlipidemia[1], hypertension[1], hyperkalemia, metabolic acidosis, gingival hyperplasia, hypertrichosis
MMF	Myelosuppression, gastrointestinal side effects, viral infections (CMV, HSV), spontaneous abortions in pregnant women
Sirolimus	Hyperlipidemia, myelosuppression, proteinuria, poor wound healing, pneumonitis, skin rash
Corticosteroids	Diabetes, hypertension, obesity, osteoporosis, avascular necrosis, growth retardation, Cushingoid features, psychosis, poor wound healing, adrenal suppression, cataracts

[1]More common in respective agent. MMF: Mycophenolate mofetil; CMV: Cytomegalovirus; HSV: Herpes simplex virus.

neoplasia. Although the mechanism is not completely understood, transplanted livers rarely reject compared to other organs, do not require an HLA-matched donor, and may offer a protective effect for other simultaneously transplanted organs[6,7]. Both micro- and macrochimerism models have been used to explain this phenomenon, as well as that of hepatic dissolution of donor specific antibodies. Ideally, the long-term objective is to achieve immune tolerance or the ability to alter the recipient's immune system in order to promote long-term graft function without immunosuppressive therapy, while maintaining immunity to infectious agents[8]. Unfortunately, except for a small minority of patients (approximately 20%) who have been successfully weaned off immunosuppressive medications, most experience immunologic rejection with the discontinuation of these drugs and have to be maintained on at least low doses of these medications[9-13].

Immunosuppressive regimens include calcineurin inhibitors, anti-metabolites, mTOR inhibitors, steroids and antibody-based therapies. These agents target different sites in the T cell activation cascade, usually by inhibiting T cell activation or proliferation or *via* T cell depletion. The selection of agents is based on an individual's medical history as well as on institution experience and preference. Most immunosuppressive regimens combine drugs with different sites of action of T cell response, allowing for dosage adjustments to minimize side effects and toxicities. Currently, the mainstay of maintenance immunosuppressive regimens are calcineurin inhibitors (CNIs), used in greater than 95% of transplant centers upon discharge, although there is a known increased risk of renal impairment[14,15], metabolic derangements, neurotoxicity and *de novo* malignancies[16] with the long-term use of these medications.

CALCINEURIN INHIBITORS

CYA and tacrolimus are the two CNIs approved for use in organ transplantation and are the principal immunosuppressives used for maintenance therapy. The routine use of these medications in liver transplant recipients has dramatically decreased the incidence of rejection and graft loss. The primary mode of action is inhibition of T cell activation. CYA binds to cyclophilin which results in inhibition of the calcium/calmodulin-dependent phosphatase, calcineurin. The binding to cyclophilin interferes with calcineurin's de-phosphorylation of nuclear factor of activated T cells (NFAT), preventing translocation of NFAT into the nucleus and up-regulation of pro-inflammatory cytokines. The end result is the inhibition of IL-2 gene transcription and T cell activation and proliferation[4,8]. Tacrolimus also inhibits calcineurin but binds specifically to FK506-binding protein (FKBP-12).

The immunosuppressive effects of the CNIs are related to total drug exposure which can be estimated by measuring blood 12-h troughs. The potency of tacrolimus is estimated to be 100 times greater on a molar level[8] when compared to CYA. Although several earlier studies showed tacrolimus to be superior to CYA in the prevention of cellular rejection[17-19], another more recent multi-center trial showed no significant differences between the two medications with regard to acute rejection episodes, death or graft loss[20]. Both CNIs are metabolized principally by the cytochrome P450 system and therefore have significant interactions with multiple medications requiring careful monitoring of drug levels (Table 1).

CNIs have a wide range of toxicities, many of which are dose-dependent (Table 2). Nephrotoxicity is a well-recognized side effect and it has been documented that nearly 20% of liver transplant recipients experience chronic renal failure within 5 years[15]. This can be best managed by either discontinuation or reduction of the medication. Neurotoxicity is another common problem; one which is more predominant with tacrolimus. The clinical presentation varies from headaches and tremors to agitation, confusion, hallucinations or overt psychosis. Hypertension, hyperlipidemia, hyperkalemia, metabolic acidosis and diabetes are also frequent side effects. Diabetes is more common with tacrolimus use, whereas hypertension and hyperlipidemia tend to be more prominent with CYA use. Gingival hyperplasia and hypertrichosis are specific side effects of CYA only.

Another important feature of CNIs is their interaction with transforming growth factor-β (TGF-β), a cytokine that augments fibrosis development and promotes tumor cell invasiveness[21]. TGF-β transcription is increased with CNI use, which is of concern given the possibility of hepatocellular carcinoma (HCC) recurrence or the emergence of post-transplant lymphoproliferative disorder (PTLD).

ANTIMETABOLITES

Both mycophenolate mofetil (MMF) and mycophenolate sodium (MPS) undergo immediate first-pass metabolism in the liver into the active compound mycophenolic acid (MPA), which was first discovered in 1893[22]. However, the immunosuppressive properties of MPA were not recognized until the 1990s. MPA inhibits inosine-5'-monophosphate dehydrogenase (IMPDH)[23], the rate-limiting enzyme in the *de novo* synthesis of guanosine nucleotides. Inhibition of the IMPDH pathway results in selective blockade of lymphocyte proliferation[24].

The major advantage in using the MPAs is their lack of renal toxicity. In patients with pre-existing renal disease, they have been used in conjunction with low-dose CNIs as part of a renal-sparing protocol with promising results[25,26]. Ideally, these medications should be initiated when renal dysfunction is first noted, although emerging data suggests the benefits of MPAs in reversing long-standing renal disease due to its association with decreased TGF-β levels[27-29]. MPAs are rarely used as monotherapy in transplant recipients given their higher rates of rejection compared to the CNIs[30,31], although more recent data demonstrate the safety of this approach when carried out carefully[32,33]. However, in patients previously on CNIs or mTOR inhibitors with evidence of acute rejection, MPAs are often added as supplemental immunosuppressive therapy.

The predominant side effects of MPAs are related to gastrointestinal disorders and bone marrow suppression (Table 2). Diarrhea is the most common dose-limiting adverse effect, although abdominal pain, nausea and vomiting can frequently occur[34]. Studies have also shown increased incidences of cytomegalovirus (CMV)[35-37], herpes simplex virus (HSV)[38,39], *Candida* infections, and, rarely, progressive multifocal leukoencephalopathy (PML)[40] with the use of MPAs. In pregnant patients, increased risks of spontaneous abortions during the first trimester and serious congenital malformations have also been reported (www.fda.gov). Routine monitoring of MPA levels is not generally employed in clinical practice.

Azathioprine is another antimetabolite which was predominantly used for the prevention of rejection in the 1960s but has since been largely replaced by the MPAs. It is selectively used in a few centers in combination with other immunosuppressive medications, primarily CNIs and steroids.

mTOR INHIBITORS

The two mTOR inhibitors approved for organ transplantation are sirolimus (SRL) and everolimus (EVL), although neither has been approved for use in liver transplantation to date. They bind intracellularly to FK506 binding protein (FKBP12) but unlike tacrolimus, they do not inhibit calcineurin activity. Rather, the complex is a highly specific inhibitor of mammalian target of rapamycin complex 1 (mTORC1)[41] which has a direct effect on the cell signaling pathway required for cell cycle progression. This subsequently inhibits IL-2 signaling to T cells, thus preventing T cell proliferation. Similar to the CNIs, sirolimus is metabolized by the cytochrome P450 system and requires therapeutic drug monitoring (Table 1).

The first reported study illustrating the effectiveness of sirolimus monotherapy for maintenance of immunosuppression in liver transplantation was in 1999 by Watson *et al*[42]. However, two subsequent large studies examining sirolimus *de novo* therapy with tacrolimus and corticosteroids were terminated early due to excess hepatic artery thrombosis (HAT). As a result, sirolimus carries a black box label warning which cautions against the possible development of early post-transplant HAT. Subsequent studies have since disputed this finding[43-45]; however, mTOR inhibitors are rarely used as *de novo* therapy.

Importantly, in patients with CNI-induced nephrotoxicity, conversion to sirolimus therapy has proved to be effective with ensuing improvements in renal function[46-48]. Again, sirolimus conversion should be initiated early since late conversion rarely improves chronic renal dysfunction[49]. In fact, several studies have shown that in patients with pre-existing renal disease, sirolimus can worsen nephrotoxicity and promote proteinuria[50-52].

Recent studies have also shown potential anti-tumor properties of sirolimus[53-56] which might be of importance in patients undergoing liver transplantation for HCC. Zimmerman *et al*[57] examined the role of sirolimus-based maintenance therapy in post-transplant recipients with a history of HCC and found that overall survival was increased in the sirolimus arm compared to the CNI arm. Clinical trials examining the anti-cancer effects of mTOR inhibitors in liver transplant recipients with HCC have been encouraging[44,58] and new trials are ongoing.

Metabolic side effects of mTOR inhibitors include proteinuria and increases in serum cholesterol and triglycerides (Table 2). Bone marrow suppression, interstitial pneumonitis, peripheral edema, dermatological effects (acne, mouth ulcers) and delayed wound healing are all well-documented. Inhibition of fibroblast growth factor by sirolimus impairs tissue repair and plays a role in delayed wound healing[59]. Interstitial pneumonitis is rarely life-threatening, is dose-dependent and resolves on withdrawal of the drug[60].

CORTICOSTEROIDS

Corticosteroids are well-known for their anti-inflammatory properties such as suppression of prostaglandin synthesis,

stabilization of lysosomal membranes and reduction of histamine and bradykinin release[30,31]. They also exhibit various immunomodulatory effects including effects on antigen presentation by dendritic cells and induction of a decrease in the number of circulating CD4+ T cells, IL-1 transcription and IL-1-dependent lymphocyte activation[4,8].

High-dose corticosteroids were used judiciously in the 1960s in post-transplant recipients, with resulting increased morbidity due to their well-known deleterious side effects. This led to several studies in the 1980s on renal transplant recipients which confirmed that graft and patient survivals, as well as rejection episodes, were similar in the high- and low-dose steroid groups as long as AZA was also used[61-63]. Currently, intravenous corticosteroids are predominantly used as first-line therapy for the treatment of acute cellular rejection. Regarding maintenance therapy, they are often successfully withdrawn within 3-6 mo post-transplantation in patients without evidence of rejection or liver disease attributed to autoimmune disorders[64]. The primary concern with corticosteroid use is exacerbation of hepatitis C virus (HCV) recurrence and liver fibrosis with high-dose pulsed therapy[65]; however, this has not been evident with low, gradually tapered doses[66,67].

Well-documented side effects of corticosteroids include diabetes, hypertension, central obesity, Cushingoid features, osteoporosis, avascular necrosis, psychosis, poor wound healing, adrenal suppression and cataracts (Table 2).

ANTIBODY-BASED THERAPIES

Polyclonal antibodies

Polyclonal antibodies, including anti-thymocyte (ATG) and anti-lymphocyte globulins (ALG), have been used since the early days of liver transplantation and are prepared by inoculating rabbits or horses with human lymphocytes or thymocytes[4]. Their mechanism of action is rapid lymphocyte depletion due to complement-mediated cell lysis and uptake by the reticulo-endothelial system (RES) of opsonized T cells[68]. In addition, they may also cause partial T cell activation and blockade of T cell proliferation[69]. Polyclonal antibodies were routinely used as induction therapy in liver transplantation along with corticosteroids and AZA before the discovery of CYA.

Lymphocyte depletion is believed to play a role in preparing the recipient's immune system to adapt and recognize the transplanted organ as self and prevent destruction of the allograft. Accordingly, studies have shown that ATG administration results in regulatory T cell (Treg) expansion *in vitro* and *in vivo*[70-72]. Tregs or suppressor T cells are responsible for preventing activation of the immune system and maintaining tolerance to self-antigens.

Currently, approximately 20% of transplant centers use these agents for induction purposes[73] and recent data support the administration of thymoglobulin induction to delay CNI use and avoid renal toxicity without increasing the risk of rejection or HCV recurrence[74-76]. A few studies have also successfully shown the benefit of using these medications as induction therapy to avoid post-transplant corticosteroid use[77,78] without an increased incidence of acute rejection. This is especially important in HCV recipients where high-dose pulsed corticosteroid therapy can significantly accelerate liver fibrosis. At present, anti-lymphocyte antibodies are used extensively to treat steroid-resistant acute rejection and are successful in 70%-96% of patients[79-81].

The main side effect of these medications, affecting 80% of patients, is a "first-dose reaction" and febrile episode which can often be ameliorated by pre-medication with antipyretics, antihistamines and intravenous steroids. This effect is likely due to pyrogen release from the massive destruction of lymphocytes[69,82]. Other adverse effects include thrombocytopenia, anemia, CMV infection, PTLD, pruritic skin rashes, serum sickness and anaphylaxis[83-85].

Monoclonal antibodies

Monoclonal antibodies include the anti-IL-2 receptor (CD25) antibodies, anti-CD52 antibody and muromonab-CD3 (OKT3). The two anti-IL-2 receptor antibodies approved for clinical use are basiliximab (Simulect), a chimeric protein, and daclizumab (Zenapax), a humanized protein. Both antibodies are specific for the α chain of the IL-2 receptor, CD25, which is only expressed on activated T cells[8]. These antibodies remain in the circulatory system for weeks after initiation of therapy and have been used successfully with low-dose CNIs in preventing acute rejection in the early post-transplant period[86-88]. They also have fewer side effects compared to the anti-lymphocyte globulins, rarely cause the typical first-dose infusion reactions and are associated with less risk of opportunistic infections and PTLD.

Muromonab-CD3 (OKT3) targets the CD3 molecule on T cells and causes depletion of lymphocytes by massive T cell lysis[89] and cytokine release[90]. This profound cytokine release can lead to pulmonary edema and acute respiratory distress and rarely, intra-graft thrombosis and aseptic meningitis[91,92]. As a result, antihistamines and intravenous steroids are routinely used as pre-medication to reduce this "cytokine release syndrome". Several days after OKT3 administration, T lymphocytes no longer express CD3 and are considered to be immunologically incompetent[93]. OKT3 is primarily used in liver transplantation for steroid-resistant acute rejection[94,95] and has a success rate of complete recovery in 50% of patients. OKT3 use should be limited in the HCV population as several studies have confirmed exacerbation of disease recurrence with this agent[96,97].

The humanized anti-CD52 antibody, alemtuzumab (Campath-1) targets lymphocytes, monocytes, macrophages, natural killer cells and thymocytes but spares plasma cells and memory lymphocytes[8,98]. It is unique in that it depletes lymphocytes from the circulation as well as peripheral lymph nodes. Several studies in renal transplant patients have shown its efficacy in preventing rejection when used in

combination with low-dose CNIs or sirolimus[99-101]. Tzakis *et al*[102] compared the use of alemtuzumab induction therapy combined with low-dose tacrolimus in liver transplant recipients receiving standard doses of tacrolimus and corticosteroids. Although patients who received alemtuzumab had less renal dysfunction and acute rejection in the first two months post-transplant, the overall incidence of rejection was not significantly different between the two groups. Similarly, Marcos *et al*[103] proposed that alemtuzumab, in conjunction with minimal CNI use, is a successful treatment strategy in liver transplant recipients, improving overall graft and patient survival, especially in HCV-infected subjects.

FUTURE DIRECTION OF IMMUNOSUPPRESSION

Costimulation blockade (Belatacept)

Belatacept is a soluble cytotoxic T-lymphocyte antigen-4 (CTLA-4) agent which binds CD80 and CD86 and inhibits T cell activation[4,8]. Belatacept competes with the CD28 receptor on T cells which normally binds CD80 and CD86 on the antigen presenting cell (APC) as a co-stimulatory signal required for T cell activation. Belatacept is administered intravenously once a month and does not carry the renal toxicity of CNIs. Clinical trials in liver transplant patients are currently ongoing with this agent.

Efalizumab

Efalizumab is a humanized leukocyte function-associated antigen-1 (LFA-1; CD11a) specific monoclonal antibody that inhibits T cell-APC stabilization and blocks lymphocyte adhesion to endothelial cells[104,105]. This agent was approved for the treatment of psoriasis in 2003 and has not yet been used in liver transplantation, although a few clinical trials have been carried out in renal transplant patients with mixed results[106]. Although the results regarding immunosuppression were promising, an increased risk for PTLD was shown when efalizumab was used in combination with high-dose CYA.

Other newer agents on the horizon undergoing phase Ⅱ/Ⅲ trials include Janus Kinase (JAK) 3 inhibitors, AEB071 (a protein kinase C (PKC) isoforms inhibitor), and Alefacept (a LFA3-IgG1 fusion receptor protein). JAKs are intermediaries between cytokine receptors and signal transducers and activators of transcription (STATs) which lead to immune cell activation[107,108]. JAK-3, a cytoplasmic tyrosine kinase, is primarily found on hematopoetic cells and its stimulation is specific for the IL-2 family of cytokines which makes it a very attractive target for immunosuppression. Clinical trials are underway in renal transplant patients using these agents. AEB071 (PKC inhibitor) is an oral agent that blocks early T cell activation and IL-2 production[109]. Three phase Ⅱ renal transplant trials using AEB were started, two of which had to be stopped due to increased episodes of acute rejection; the third trial is ongoing in Europe[110]. Alefacept, a LFA3-IgG1 fusion receptor protein initially approved for the treatment of psoriasis, interferes with T-cell activation and produces a dose-dependent reduction in T-effector memory cells[111]. A multi-center clinical trial in renal transplant recipients is currently underway.

CONCLUSION

The current era of immunosuppressive therapy continues to evolve with the discovery of novel agents, targeting different sites of the immune cascade. Important objectives when using these medications include decreasing the incidence of renal toxicity from CNIs while preserving graft function as well as optimizing immunosuppression without creating an environment for increased infections, aggressive recurrence of hepatitis C or triggering PTLD and other malignancies.

At our institution, high-dose intravenous corticosteroids are used in the immediate peri- and post-operative period and then tapered accordingly. In patients without renal dysfunction post-transplantation, CNIs are the mainstay of therapy with the long-term goal of low levels of immunosuppression and minimization of medication. In patients with renal insufficiency, we have had success with a combination of low-dose CNI therapy and MPAs or a switch to mTOR inhibitors to preserve graft function and prevent further renal deterioration. We typically avoid the switch to mTOR inhibitors within the first 3-6 mo post-transplantation given the risk of hepatic artery thrombosis, rejection, and wound healing. Patients are weaned off corticosteroids within 6 mo to 1 year, providing they do not have evidence of autoimmune disease or recurrent episodes of rejection.

As evidenced by prior studies, the recommended approach to the patient with HCV infection is gradual, cautious weaning of corticosteroids within the first 3-6 mo while continuing low levels of maintenance immunosuppression, typically with CNIs. While HCV recurrence is universal after liver transplantation, avoiding excessive and erratic changes in the immuno-suppressive regimen should prevent clinically aggressive disease.

The ultimate goal remains the ability to induce tolerance in transplant recipients. While this is not a current available practice, data from selected patients demonstrate that it may become a viable option with advances in future research and improved understanding of the genetic make-up and predisposition of this population. Until then, finding the balance between preserving graft function and optimizing immuno-suppression while minimizing toxicities remains a challenge.

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