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REVIEW

Evolving concepts in the selection of immunosuppression regimen for liver transplant recipients

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Abstract: The introduction of calcineurin inhibitor (CNI) based immunosuppression has revolutionized the field of liver transplantation by dramatically reducing the incidence of acute cellular rejection and prolonging patient and allograft survival. However, the introduction of CNIs has also come at the price of increased patient morbidity, particularly with regard to the well-known nephrotoxic effects of the medications. In an effort to minimize the adverse effects, immunosuppression regimen have evolved to include the use of various induction agents and purine synthesis inhibitors to limit the dose of CNI necessary to achieve low acute cellular rejection rates. Careful assessments of risks and benefits are needed as these newer agents have their own side effect profiles. In addition, the impact of newer immunosuppression regimen on hepatitis C (HCV) recurrence has not been completely elucidated. This review will provide an overview of the most common immunosuppression regimen used in liver transplantation and discuss their impact on acute cellular rejection, patient and allograft survival, and HCV recurrence.

Keywords: liver transplantation, immunosuppression, acute cellular rejection, patient and graft survival, hepatitis C recurrence

Introduction

A new era in liver transplantation began in the early 1980s heralded by the introduction of cyclosporine (CsA), a powerful immunosuppressant that in combination with corticosteroids was capable of reducing the incidence of acute rejection.[1] The ability to dramatically reduce the incidence of acute rejection among liver transplant recipients, and therefore reduce mortality, paved the way for a 1983 National Institutes of Health Consensus Meeting approving the use of liver transplantation as the treatment for end-stage liver disease.[2] Over the next decade, further developments in immunosuppressant agents were made, and in 1994 the FK506 Liver Study Group reported results from their multicenter randomized controlled trial demonstrating a lower incidence of steroid-resistant acute rejection with tacrolimus compared to CsA-based immunosuppression regimen.[3]

Despite these early advances, acute rejection among liver transplant recipients remains a major source of morbidity and mortality, as the immunosupppression regimen capable of inducing or promoting immunologic tolerance continues to elude the transplant community. This has resulted in a lack of standardization with regard to immunosuppression regimen across centers.[4] Current protocols have implemented many different strategies, including combinations of drugs with different modes of

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action to minimize side effects,[5] steroid minimization,[6,7] calcineurin inhibitor minimization or avoidance,[8–10] and the use of induction therapy in the perioperative period to delay the introduction of maintenance immunosuppression.[11] A report from the Scientific Registry of Transplant Recipients outlined the use of various immunosuppressive agents across centers. The report found that 18% of centers use induction antibody therapy, 97% use calcineurin inhibitor (CNI) therapy, 90% use corticosteroids, 48% use mycophenolate-temofetil (MMF), 4% use azathioprine (AZA), and 7% of centers use mTOR inhibitors.[12,13]

As outlined, currently no one standard immunosuppressive regimen exists in liver transplantation, yet the goal of therapy continues to be to reduce or eliminate acute cellular rejection while simultaneously limiting harmful side effects. There are various classes of immunosuppressive agents used in liver transplantation. Each is designed to disrupt the process along the complex path of acute cellular rejection, such as at the point of alloantigen recognition,[14–16] T-cell activation,[17] clonal expansion, and/or graft inflammation.[18] The following review will focus on and discuss the current use of immunosuppressive drugs in liver transplantation.

Immunosuppressive agents

Immunosuppressive agents are typically broadly classified as either induction agents or maintenance immunosuppression drugs (Table 1 and Figure 1). Induction therapy refers to those drugs given at the time of liver transplantation to profoundly quiet immune response during recovery from ischemia reperfusion injury and allows for delay of the introduction of maintenance agents. Induction drugs are classically steroids with or without the addition of biologic agents, such as potent monoclonal and polyclonal antibodies. Examples of induction agents include antithymocyte antibodies and anticytokine receptor antibodies. Recent data suggest that induction immunosuppression improves patient and graft survival among liver transplant recipients.[19] Maintenance immunosuppressive agents are those used on a daily basis to attenuate the patient's immune response post-transplant. These agents include CNIs, mTOR inhibitors, corticosteroids, and antimetabolites.

Induction agents

Antilymphocyte antibody therapy

Antilymphocyte antibody therapy is also referred to as lymphoid depletion therapy as these antibodies have

Table 1 Therapeutic advantages and disadvantages of various immunosuppression agents

Type of immunosuppression	Advantages	Disadvantages
Induction agents		
Antilymphocyte antibody	Reduce the amount of maintenance immunosuppression required	Hypotension, bronchospasm, fever, tachycardia
Anti-T-cell receptor antibodies (OKT3)	Superior to steroids and CsA at reversing acute cellular rejection	Fever, hypotension, aseptic meningitis, flash pulmonary edema; PTLD; acceleration of HCV
Polyclonal antibodies (ATGAM and thymoglobulin)	Treat steroid resistant rejection; no impact on HCV recurrence; may promote immunologic tolerance	Lymphopenia; variations in clinical efficiency of various preparations
Alemtuzumab	Reduce the amount of maintenance immunosuppression required	Associated with higher rates of vascular rejection; profound lymphopenia
Interleukin-2 receptor antibodies	Reduce the amount of maintenance immunosuppression required; No adverse impact on HCV recurrence	Monotherapy associated with increased rates of acute cellular rejection and steroid-resistant rejection
Maintenance agents		
Corticosteroids	Suppress antibody and complement binding	Hypertension, osteoporosis, diabetes, impaired wound healing
Calcineurin inhibitors (CsA and tacrolimus)	Allow for steroid minimization	Hypertension, nephrotoxicity, neurotoxicity, hirsuitism, diabetes, lipid abnormalities
m-TOR inhibitors (Sirolimus)	Less renal toxic effects	Dose-related hyperlipidemia and cytopenias; nephrotic syndrome; interstitial pneumonia; liver function test abnormalities; wound dehiscence; question of increased incidence of hepatic artery thrombosis
Purine synthesis inhibitors (MMF)	Not associated with neurotoxicity or nephrotoxicity, used as a calcineurin inhibitor sparing agent	Leukopenia and GI disturbances

Abbreviations: CsA, cyclosporine; HCV, hepatitis C; MMF, mycophenolatemofetil; PTLD, post-transplant lymphoproliferative disorder.

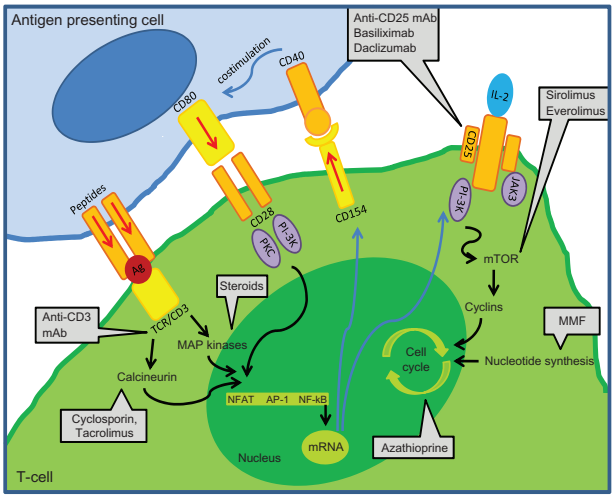

Figure 1 Mechanisms of action for various immunosuppression agents. Antigen presenting cells present antigen to T-cells, resulting in activation and costimulation of the T-cell. The activated T-cell then undergoes clonal expansion and differentiation to express a specific effector function.
Abbreviation: MMF, mycophenolatemofetil.

specificity for T- and B-cell antigens resulting in the elimination of these cell populations.[20] As a result, lymphoid depletion is often reserved for either induction therapy to reduce the amount of maintenance immunosuppression required or to treat steroid resistant rejection. These antibodies elicit cytokine release from lymphocytes. Clinically this is 1 manifested as hypotension, bronchospasm, fever, and tachycardia. These side effects can be eliminated or reduced by premedication with steroids and antihistamines prior to administration.[18]

Anti-T-cell receptor antibodies – muromonab-CD3 (OKT3)

OKT3 is a monoclonal antibody that has a defined specificity to the CD3 receptor on mature T-cells, and has no impact on immature thymocytes.[21] The administration of OKT3 results in a greater than 55% decline in circulating CD3+ T-cells.[22] The onset of action is within minutes, the drug persists for approximately 1 week, and the effects continue for weeks to months. There are severe side effects associated with the medication related to the release of proinflammatory cytokines, which include fever, hypotension, aseptic meningitis, and flash pulmonary edema. The potential for the development of these side effects is greatest with the first several doses of OKT3 administered. OKT3 administration has also been associated with higher rates of post-transplant lymphoproliferative disorder (PTLD).[23,24] The development of PTLD is even more common among patients transplanted for hepatitis C (HCV) cirrhosis.[25] Furthermore, there appears to be a rapid acceleration of HCV replication leading to earlier and more severe recurrent disease among patients undergoing liver transplantation for HCV cirrhosis.[26] Despite these negative effects, OKT3 has been shown in several randomized controlled trials to be useful in steroid-resistant rejections.[27,28]

Polyclonal antibodies – ATGAM (Pfizer, New York, NY) and thymoglobulin (Genzyme, Boston, MA)

Polyclonal antibodies are heterologous preparations made by immunizing animals with human T-cells and thymocytes. The purified gamma globulin fraction of the antisera is collected, which is also known as the antithymocyte globulin (ATG). Specifically ATG is directed against human thymocytes, which leads to depletion of peripheral lymphocytes and peripheral lymphopenia. Variations in the clinical efficiency of various ATG preparations have been well documented. It is believed that the polyclonal antibodies ability to recognize multiple cell surface molecules is responsible for this variation.[29,30] In general ATG has been primarily used as an induction agent, corticosteroid sparing agent, and as treatment for steroid resistant rejection.[31,32] Although there is concern for use of ATG in patients with HCV, there are no convincing data that they have a negative impact on HCV recurrence.[33,34] Some studies have suggested that a regimen which includes ATG may promote immunologic tolerance, as ATG therapy has been shown to result in an expansion in regulatory T-cells.[35–37]

Alemtuzumab – campath-1H (C-1H)

C-1H is a humanized recombinant anti-CD52 monoclonal antibody. CD52 is a cell surface glycoprotein expressed on 95% of peripheral lymphocytes, monocytes, macrophages, and natural killer cells.[38] Binding of CD52 by C-1H results in profound depletion of circulating lymphocytes in blood and lymph nodes, with the exception of plasma and memory cells.[39,40] C-1H was initially used as an induction agent to facilitate lower doses of maintenance immunosuppressant agents.[41] However, C-1H did not prevent the development or lower the incidence of acute cellular rejection,[42,43] and in fact, was associated with a higher rate of vascular rejection.[44] Therefore, C-1H is not widely used in liver transplantation today.

Interleukin-2 receptor antibodies – basiliximab (Simulect, Novartis, Basel, Switzerland) and daclizumab (Zenapax, Hoffman–La Roche, Basel, Switzerland)

Interleukin-2 receptor (IL-2) antibodies are chimeric IgG1 monoclonal antibodies that are less immunogenic than other monoclonal antibodies such as OKT3. These antibodies bind the IL-2 receptor on activated T-cells, leading to inhibition of T-cell proliferation.[45] Of note, the half-life of IL-2 receptor antibodies is decreased in liver transplant recipients secondary to higher volume of distribution in patients with ascites.[46] As a result, early trials reported acute cellular rejection rates as high as 35%, which was attributed to activated T-cells bypassing the IL-2 receptor blockade.[47–49] With proper dosing adjustments, more recent trials demonstrate no difference in incidence of acute cellular rejection.[50] There also appears to be no adverse impact on HCV recurrence and graft or patient survival, and in fact, there appears to be an improvement in renal function as IL-2 receptor antibody induction allows for lower doses of maintenance immunosuppression with calcineurin inhibitors (CNIs).[22,50–55] It is important to note, however, that IL-2 receptor antibodies should always be used in combination with CNIs, as monotherapy has been associated with increased rates of acute cellular rejection and in particular steroid-resistant rejection.[56]

Maintenance immunosuppression agents

Corticosteroids

Corticosteroids inhibit the production of T-cell cytokines, such as IL-2, IL-6, and interferon gamma, which are required to activate T-cells against alloantigen. In addition, corticosteroids also suppress antibody and complement binding and stimulate migration of T-cells from the intravascular compartment to lymphoid tissue. Prior to the introduction of CsA, corticosteroids were the main stay of immunosuppression.[57–59] Since the introduction of CNIs, there has been a trend toward steroid minimization in an effort to reduce the adverse effects associated with prolonged steroid use, such as hypertension, osteoporosis, diabetes, and impaired wound healing.[18] In fact more recent studies have shown that early tapering of steroids to CNI monotherapy does not adversely impact acute cellular rejection rates, graft, and/or patient survival, and does not increase the risk of graft fibrosis in the long term.[6,7] Furthermore, steroid avoidance has proven beneficial in patients transplanted for HCV cirrhosis. However, studies have shown that rapid steroid taper can result in acute cellular rejection requiring rescue therapy which may promote rapid recurrence of HCV.[60–62]

Calcineurin inhibitors – cyclosporin (Neoral, Novartis) and tacrolimus (Prograf, FK506, Astellas Pharmaceuticals, Deerfield, IL)

Both CsA and tacrolimus are CNIs that bind to their specific immunophilins, cyclophilin and FK binding proteins respectively. The drug-receptor complex then binds to and inhibits calcineurin, a phosphatase that regulates subcellular localization, and in turn activation, of transcription factors including nuclear factor of activated T-cells (NF-AT). Tacrolimus and Csa have similar side effect profiles. The most common side effects include hypertension, nephrotoxicity, neurotoxicity, hirsuitism, diabetes, and lipid abnormalities.[63] A recent meta-analysis reported similar rates of patient and graft survival independent of which CNI used,[64] although this remains a controversial topic within the liver transplant community.

The immunosuppressive activity of CsA was discovered in 1976,[65] and the drug was approved for use in liver transplantation in 1982.[66,67] Initial studies demonstrated a 37% improvement in graft and patient survival at 1-year compared to the then standard immunosuppression regimen of AZA and corticosteroids (70% vs 33%)[68] revolutionizing the field of liver transplantation. Further studies examining the mechanisms of action of the drug elucidated the ability of CsA to inhibit HCV replication in vitro.[69] In fact several studies were able to demonstrate in vivo that CsA inhibited HCV in a dose-dependent fashion, CsA-treated patients had lower HCV RNA levels, and that compared to tacrolimus-based immunosuppression Ishak fibrosis scores and fibrosis grades were significantly lower in CsA-treated patients compared to tacrolimus-treated patients.[70,71] However, current data do not support a beneficial effect of CsA over tacrolimus for the prevention of HCV recurrence after liver transplantation.[72–74] Interestingly, a recent study has demonstrated higher de novo cancer risk among liver transplant recipients under the age of 50 years treated with CsA- versus tacrolimus-based maintenance immunosuppression.[75]

Tacrolimus is known to be 100 times more potent than CsA.[76] Multiple studies have been performed comparing the efficacy of tacrolimus- and CsA-based immunosuppression regimen. Controversy remains as these studies often have

conflicting conclusions. Three prospective randomized controlled clinical trials reported decreased incidence of acute cellular rejection with the use of tacrolimus compared to CsA, but no difference in patient and/or graft survival.[3,77,78] Grady and colleagues found tacrolimus to be more beneficial with regard to graft loss and rejection but not patient death or retransplant.[73] Their work was later supported in several meta-analyses.[79,80] Renal dysfunction is a well-known complication of tacrolimus-based immunosuppression. Multiple studies have documented that tapering of tacrolimus dose and/or discontinuation of tacrolimus-based immunosuppression results in significant improvement in renal function.[81–83] In fact, one study demonstrated a 63% improvement in the glomerular filtration rate at 1-year after cessation of CNIs.[81]

mTOR inhibitor – sirolimus (Rapamycin, Wyeth-Ayerst, Madison, NJ) and everolimus (Afinitor, Novartis)

Sirolimus binds the mammalian target of rapamycin (mTOR), which blocks IL-2 induction of B- and T-cell proliferation by preventing the progression of the cell cycle from G1 to S phase.[84,85] The most common side effects associated with sirolimus include dose-related hyperlipidemia and cytopenias.[86,87] Less common side effects include the development of proteinuria leading to nephrotic syndrome,[88,89] interstitial pneumonia,[90] and in some patients, liver function test abnormalities.[91] An associated increased risk of wound dehiscence and hepatic artery thrombosis (HAT) with the use of sirolimus has also been reported, particularly in the first post-transplant month.[92–94] Subsequent larger series, however, have failed to demonstrate increased HAT.[95] Sirolimus may prevent hepatic fibrosis, and therefore, prevent or delay cirrhosis.[96] However, sirolimus does not significantly affect the timing or severity of HCV recurrence post-liver transplant.[97] Sirolimus has also been documented to have anticancer effects and its use has been associated with improved survival among patients transplanted with hepatocellular carcinomas.[98–100] Sirolimus is known to have a long half-life and narrow therapeutic window, and as a result, frequent drug monitoring is required. A newer agent everolimus has improved pharmacokinetic properties. Everolimus has a good safety profile and has been shown to be efficacious in preventing acute cellular rejection in a calcineurin inhibitor-free immunosuppressive regimen.[101]

Early reports found that acute cellular rejection was more common with monotherapy.[102] However, subsequent studies noted that with the addition of corticosteroids to sirolimus maintenance immunosuppression, lower rates of acute cellular rejection can be achieved along with excellent patient and graft survival.[103–107] Sirolimus is thought to have less renal toxic effects compared to CNI-based immunosuppression. However, controversy exists about the nephrotoxic sparing effects of sirolimus. Several single center studies demonstrated improved renal function when switching from CNI alone to low-dose CNI plus sirolimus or sirolimus monotherapy.[108,109] In fact, one of the studies documented a 71% improvement in renal function.[109] Contrary to these reports, several randomized controlled trials and a case controlled study have demonstrated no difference in renal function at 1-year when switching from CNI-based to a sirolimus-based immunosuppression regimen.[110–112] It appears as though the renal-sparing effects of sirolimus-based immunosuppression therapy are more likely to be achieved when treatment is initiated early in the post-transplant period prior to CNI toxicity developing.[113–116]

Purine synthesis inhibitors – mycophenolatemofetil (Cellcept, Roche) and enteric-coated mycophenolate sodium (Myfortic, Novartis)

Replacing the prototypical agent of this class, azathioprine, MMF blocks de novo purine nucleotide synthesis by inhibiting the production of guanasine nucleotides, such as guanasine monophosphate.[117,118] Cells lacking guanasine monophosphate cannot synthesize guanine triphosphate, and therefore cannot replicate unless they are able to maintain guanine triphosphate levels via the purine salvage pathway. T- and B-cells lack a key enzyme in the salvage pathway, and therefore cannot replicate in the presence of MMF.[119] MMF is hydrolyzed to its active form mycophenolic acid (MPA).[120,121] Interestingly, food decreases the bioavailability of MPA, and therefore, MMF should be administered at least 1 hour before or 2 hours after meals.[18] In addition, variations in serum albumin levels, as seen in liver transplant patients, can lead to fluctuations in MMF pharmacokinetics.[122] The most common side effects of MMF administration are leucopenia and GI disturbances.[123,124] MMF does not cause nephrotoxicity or neurotoxicity, and as a result, has been used as a CNI-sparing agent.[125–127]

Currently, there does not appear to be a role for MMF monotherapy in liver transplantation as there is an associated

unacceptably high incidence of acute cellular rejection, severe chronic rejection, and steroid-resistant rejection.[128,129] However, when added to a CNI/corticosteroid-based immunosuppression regimen, lower rates of acute cellular rejection can be achieved.[130] Furthermore, it has been observed to reverse steroid-resistant rejection when added to a CNI/corticosteroid-based immunosuppression regimen.[131,132] In fact, in one study, 81% of patients with cellular rejection had normalization of their liver function tests.[132] It has also been shown in a recent Scientific Registry for Transplant Recipients database analysis to be an important factor in improved outcomes among liver transplant recipients on tacrolimus-based immunosuppression regimen.[133] Current data suggest that MMF has no impact on HCV recurrence.[134]

Induction of immune tolerance

Current immunosuppressive strategies have resulted in improved allograft survival. However, long-term immunosuppression is associated with increased risk of infection, development of cancer, and even cardiovascular disease. In addition, current immunosuppressive strategies cannot reliably prevent chronic allograft injury. Overcoming the problems associated with long-term immunosuppressive strategies would require the development of a state of immune tolerance or a state in which there is graft acceptance in the absence of immune suppression. Many clinical protocols have been developed to facilitate immune tolerance, including the use of hematopoietic cells as tolerance inducing antigens,[135] establishment of mixed chimerism,[136] pretransplant total irradiation,[137] lymphocyte depletion,[138] and costimulation blockade.[139] Unfortunately, while these protocols have been successful in small animal models, the findings have not translated to similar results in humans. Recently, Scandling et al published a case series describing the ability to eliminate the need for immunosuppression after combined bone marrow and kidney transplants from a human leukocyte antigen matched donor, providing insight into a potential mechanism for inducing tolerance in liver transplant recipients.[140]

Conclusion

Advances in immunosuppression have revolutionized the field of liver transplantation over the last 30 years. Immunologic tolerance has yet to be achieved, and as such, the success of liver transplantation in the immediate future will continue to depend on the discovery and implementation of newer immunosuppressant agents. This will require continued rigor within the field with regard to the use of randomized controlled trials. Finally, continued attention will need to be paid to the impact of immunosuppression on HCV recurrence, as HCV remains the most common indication for liver transplantation in the United States.

Disclosure

No conflicts of interest were declared in relation to this paper.

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