

Immunosuppressive Strategies in Liver Transplantation for Hepatitis C

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Abstract

End-stage liver disease secondary to hepatitis C is the most common indication for liver transplantation in the USA and Europe. Its recurrence is almost universal after transplantation. In addition, the progression to fibrosis is accelerated compared to the non-transplant population. There is much debate over the most effective immunosuppressive modality and its role in the development of fibrosis in patients transplanted for hepatitis C. Use of all the major immunosuppressive classes is reported in the literature. There are few large comparative trials of immunosuppression in this patient population and there is often discordant data with regard to the best immunosuppressive therapy. Calcineurin inhibitors are effective and seem to be equivalent in the risk of redevelopment of hepatitis C and outcomes. The role of antiproliferative agents, such as mycophenolate mofetil or azathioprine, is not well defined. Although different groups have proposed different strategies, the adequate length and dose of steroid treatment is not clear. The use of steroid boluses and antibody therapy to treat acute rejection is associated with increased viral replication and severity of histologic changes and poor outcomes in the hepatitis C transplant patient. The growing thought on immunosuppression in the hepatitis C population is a low and stable regimen as opposed to short courses and rapid tapering of medications. There is little consensus as to the optimal regimen in patients transplanted for hepatitis C. (Trends in Transplant. 2010;4:78-85)

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Introduction

Hepatitis C virus (HCV) infection is the most common indication for liver transplantation in the USA and Europe^{1,2}. Recurrent hepatitis C after transplantation often behaves more aggressively. It has been reported that 20-40% of patients with recurrent hepatitis C will develop cirrhosis at five years³. Some risk factors for more severe recurrence include increased donor age, cytomegalovirus infection, previous treatment of acute rejection, pretransplant viral load, and HCV viral genotype (Table 1).

In order to prolong patient and graft survival, immunosuppressive agents must be used to prevent both acute and chronic rejection. Although most would agree that immunosuppression plays a major role in determining the aggressiveness of viral recurrence, very little is known about how to modify immunosuppression to slow the rate of HCV disease progression. Current strategies are based primarily on calcineurin inhibition therapy, with or without adjuvant agents. The role of sirolimus, which could have theoretical advantages in hepatitis C due to its antifibrotic effects, is not well defined. As it stands, there is no clear consensus on the optimal immunosuppressive regimen in liver transplantation for hepatitis C. Due to the conflicting data from various trials, we conducted a national and international survey of major transplant centers around the world to define the most prevalent management practices in this difficult group of patients. As expected, there are different approaches to immunosuppression in this population with regard to both maintenance and acute rejection treatment⁴. A report from the International Liver Transplantation Society Expert Panel was not able to recommend an optimal immunosuppression regimen since the existing data has not been able to show a clear advantage for any one approach³. The purpose of this article is to review the currently available information on benefits and

Table 1. Factors associated with disease progression after liver transplantation in patients with chronic hepatitis C

Donor-Recipient	Viral
Donor age greater than 50 years	Pretransplantation level of HCV RNA
Steatosis	Early
Race other than black	posttransplantation level of HCV RNA
Male gender	Possibly genotype 1, particularly 1b
Iron overload	Possibly quasispecies
Histocompatibility	Alcohol
Immunosuppressive medication	Coinfection with hepatitis B virus
Treatment of acute cellular rejection	Coinfection with HIV
Cytomegalovirus	

detriments of different immunosuppressive strategies in hepatitis C.

Calcineurin inhibitors

The calcineurin inhibitors are considered to be the foundation of modern immunosuppression. Both cyclosporine (CsA) and tacrolimus have been used successfully in liver transplantation. Several articles have been published regarding the utilization of calcineurin inhibitors and the difference between agents in the hepatitis C transplant population.

Watashi, et al. first described the effects of CsA on HCV in hepatocyte cell cultures. They discovered that CsA possessed suppressive effects on the HCV replicon, inhibiting replication and protein expression in a cultured human hepatocyte cell line. These effects appear to be independent of calcineurin inhibition⁵. Although their experiment was done *in vitro*, this was an early description of an immunosuppressive agent with anti-HCV properties, raising the possibility of its use in the hepatitis C liver transplant population.

In another study, Firpi, et al., in a combined *in vitro* and *in vivo* study, demonstrated

Table 2. Prevalent immunosuppressive strategies in liver transplantation for hepatitis C: results of a multicenter international survey

Phase	Strategy	No. centers (%)
Induction	None	64 (79)
	Antithymocyte antibody	3 (3.7)
	Basiliximab	14 (17.3)
Maintenance	Tacrolimus-based	70 (86.4)
	Cyclosporine-based	15 (18.5)
	Combination of tacrolimus, mycophenolate mofetil, and steroids	33 (41)
	Steroid-free protocols	6 (7.4)
	Rapid steroid discontinuation (1 week)	9 (11)
	Steroid discontinuation within 3 months	45 (56)
	Steroid discontinuation within 1 year	79 (98)

Twenty-seven (33.8%) centers use different immunosuppression protocol for HCV versus non-HCV patients.

From: Gedaly, et al.⁴

that CsA inhibited viral replication in a dose-dependent fashion. It has also been shown that CsA has a beneficial effect on interferon therapy. This paper also demonstrated that patients, when treated with interferon and ribavirin, gained a higher sustained virologic response with CsA (47%) versus the tacrolimus group (27%) ($n = 59$; $p = 0.03$). They suggested these effects may make CsA a beneficial choice in patients transplanted for hepatitis C⁶.

Charlton, et al. examined predictors of patient and graft survival in patients who underwent transplantation for chronic hepatitis C in 166 HCV-infected and 509 HCV-negative patients from three US centers. The main finding of this study was that high HCV RNA blood levels before transplantation predicted poorer graft and patient survival. The impact of induction immunosuppression also was examined. They observed no difference in either patient or graft survival comparing CsA- with tacrolimus-based regimens⁷.

Recently, Berenguer, et al. published a meta-analysis of several trials comparing tacrolimus with CsA in HCV-positive liver transplant patients. Unfortunately, their analysis of five trials ($n = 366$) could not demonstrate a

difference in mortality, graft survival, biopsy-proven rejection, corticosteroid-resistant rejection, or fibrosing cholestatic hepatitis. They concluded that more study was needed in this area to further elucidate the optimal immunosuppression in the hepatitis C patient⁸. Our recently published survey demonstrated that 85% of the centers use tacrolimus-based immunosuppression protocols⁴ (Table 2).

Sirolimus

Sirolimus is the newest agent added to the immunosuppression armamentarium. Its known antiproliferative effects make this agent an interesting option in the hepatitis C population. Unfortunately, its association with poor wound healing and hepatic artery thrombosis has limited its use.

Only small series have been reported on the use of sirolimus in liver transplant recipients. Samonakis, et al. published a case series in which two patients were converted from tacrolimus-based therapy to a sirolimus-based one. Interestingly, after conversion, both patients became HCV RNA negative without additional antiviral therapy⁹.

Vivarelli, et al. published a more recent case series with sirolimus in the hepatitis C population. These patients were converted from tacrolimus-based to sirolimus-based therapy within 15 days of liver transplantation without complication. This small case series of only six patients focused on the incidence of acute rejection. Two of the six died (one of sepsis 47 days after transplantation, and one of recurrent hepatitis C 143 days after transplantation). The remaining four patients were followed between 67 to 577 days after transplantation. There were three acute rejection episodes in this group of four. All were successfully treated with corticosteroid boluses. They concluded that sirolimus therapy was safe and effective for the prevention of acute rejection. As an interesting aside, three of these patients were converted for neurotoxicity and three for nephrotoxicity. Neurotoxicity resolved in all three, and two of the three with nephrotoxicity came off dialysis, while the third never required it¹⁰.

Analysis of histological recurrence of chronic hepatitis C and clinical outcomes after liver transplantation is dependent on the results of current trials.

T-cell proliferation inhibitors

The anti-metabolite class of immunosuppressives includes azathioprine and the mycophenolate salts (mofetil and sodium). These agents have been used as adjuvant therapy in combination with calcineurin inhibitors for many years in the liver transplant population.

Mycophenolate mofetil (MMF) is somewhat analogous to ribavirin in that it also is an inhibitor of inosine monophosphate dehydrogenase. Initially, MMF was mentioned to have antiviral properties because of its ribavirin-like effects, and early clinical trials suggested synergism with interferon α . Several authors

have proposed a direct effect of MMF, or an indirect benefit, while maintaining stable immunosuppression, citing the need for less treatment of rejection episodes. The data on the importance of MMF alone, or as an adjunct for patients undergoing transplantation for HCV, remain controversial.

In a large registry data trial, Wiesner, et al. compared outcomes in patients on triple immunosuppression therapy (tacrolimus, MMF, and prednisone) versus those patients maintained on dual therapy (tacrolimus and prednisone). They compared outcomes in 11,670 liver transplant patients of which 3,463 patients (29.7%) were transplanted due to hepatitis C. The group maintained on triple therapy had better patient survival (81.0 vs. 77.0% at four years; $p < 0.0001$), graft survival (76.4 vs. 72.9%; $p < 0.0001$), and lower rates of acute rejection (29.0 vs. 33.4%; $p < 0.001$). In the subset with HCV, the patient survival was significantly higher in the group treated with MMF (79.5 vs. 73.8%; $p = 0.002$), as was graft survival (76.4 vs. 72.9%; $p < 0.0001$). Cox regression demonstrated that MMF was independently associated with a reduction in the risk of death (HR = 0.77; $p < 0.001$). The risk of graft loss was also decreased with the addition of MMF (HR = 0.81; $p < 0.001$). This led the authors to conclude that triple immunosuppressive therapy improved long-term outcomes in liver transplant patients, even in those with HCV¹¹.

There is continued interest in mycophenolate for solid organ transplantation, particularly due to its lack of renal toxicity. Manrique, et al. performed a conversion study in which patients were switched to MMF monotherapy. Calcineurin inhibitor toxicity was the primary reason for the conversion. Predominant toxicities in this patient group were nephrotoxicity and hypertension. Forty-eight patients were converted to MMF monotherapy. Only four patients experienced acute rejection after the conversion. These patients were treated and there was no patient or graft loss in the study

group. The authors concluded that MMF monotherapy was safe. They did not study the recurrence of hepatitis C in their patient group, and noted that larger trials would be needed to assess hepatitis C recurrence in patients maintained on MMF monotherapy¹².

Kornberg, et al. also studied MMF in an attempt to modulate hepatitis C recurrence in the liver transplant recipient. In their study, patients were either maintained on their standard immunosuppression (CsA-based) or converted to MMF with a CsA taper. Patients in the taper group had a significant improvement in renal function, but showed marked progression of fibrosis. Conversely, the control group, with normal CsA levels, had worsening renal function, but a slower progression of fibrosis¹³. In the 12-month study period there were no rejection episodes in either group. The actual role of MMF and its long-term effects on hepatitis C recurrence have yet to be defined.

Corticosteroids

Corticosteroids still remain a valuable class of immunosuppressive agents. Many studies have been published on the effects of steroids on short- and long-term outcomes in liver transplant recipients; some of these have even focused on the HCV transplant population¹⁴⁻²⁰. There are varying opinions as to the best use of this class of agents.

Both the incidence and severity of recurrent hepatitis C have been related to steroids when used either as maintenance immunosuppression or in the context of treatment of rejection. A study from the Royal Free Hospital in London found that HCV RNA persisted at greater levels in patients exposed to a longer duration of steroid therapy. They also reported that HCV RNA levels at 12 months posttransplantation correlated strongly with the degree of fibrosis. Other studies have shown a strong

correlation between treatment of rejection and severe recurrence of hepatitis C. In the National Institute of Diabetes and Digestive and Kidney Diseases Liver Transplant Database study, treatment of acute cellular rejection increased mortality in HCV-positive patients (RR: 2.9; $p = 0.03$). Pulse steroid therapy for rejection markedly increased HCV RNA levels in the early posttransplantation period (seven days to four months). This also correlated with more aggressive recurrence of hepatitis and increases in hepatic fibrosis. Testa, et al. analyzed their single-center experience in 300 HCV-positive transplant recipients and found that histological recurrence of hepatitis C correlated with treatment of acute rejection, multiple episodes of rejection, steroid-resistant rejection, and cumulative steroid dose (for up to two years). Due to the link between steroid treatment of rejection and hepatitis C recurrence and disease progression, several groups started to use steroid withdrawal or complete avoidance.

Llado, et al. have published two studies on the complete avoidance of steroids in the hepatitis C transplant patient^{18,20}. In their 2006 study, patients received basiliximab induction and CsA maintenance, with or without steroids. At six months posttransplantation, there was no difference in biopsy-proven hepatitis C recurrence or acute rejection between the groups. However, there was an increased rate of diabetes and hypertension in the steroid group. Diabetic patients in the steroid group were more likely to develop bacterial infections as well. Patient survival was similar between groups. In this study, they concluded that steroid avoidance was safe and reduced infectious and metabolic complications¹⁸. Their 2008 study followed patients two years after transplantation. Again they showed a low risk of rejection in both groups. There was evidence of hepatitis C recurrence in 97% of patients in both groups. Bacterial and metabolic complications were more common in the steroid group. Interestingly, there was a significant

difference in the rate of grade 4 portal inflammation at two years that favored the steroid-free group. This did not, however, correlate with a significant difference in fibrosis between the groups at two years²⁰.

In comparison to the previous studies, Vivarelli, et al. studied rapid versus slow steroid tapering in hepatitis C transplant patients. Patients were divided into two groups. Group 1 had complete steroid withdrawal 90 days after transplant. Group 2 had complete steroid withdrawal 24 months after transplant. All but two patients had histologically confirmed hepatitis C recurrence during the study period. Group 1 showed significantly greater fibrosis at 12 months. Group 2 had greater fibrosis-free survival at one and two years. They concluded that a slow steroid taper reduced progression of recurrent hepatitis C posttransplantation¹⁴.

Kato, et al. have reported their experience with steroid-free immunosuppressive regimens. In their data, the only factor that was associated with an increased fibrosis stage was acute rejection episodes. The addition of MMF to the regimens decreased acute rejection rates for both groups at six and 12 months. Wound infections and diabetes were much more common in the steroid groups¹⁵.

To show the discrepancy among different centers, our survey demonstrated that while less than 10% of the groups used steroid avoidance, more than 50% of the scrutinized groups still used early withdrawal at three months. In 98% of the centers, steroids were discontinued after one year⁴.

Based upon these studies, there is a quandary as to the use of steroids posttransplantation. There is almost universal recurrence of hepatitis C after transplantation, regardless of the use of steroids, and although it seems to be relatively clear that they are associated with increase viral replication and progression of histologic changes after pulses of steroids

to treat rejection, it is less clear as to the appropriate length and doses of maintenance treatment that is associated with a less aggressive type of hepatitis C recurrence. One clear problem that all steroid groups experience is the increased risk of diabetes and infectious complications after transplantation and the sequelae from these diseases.

Antibodies

The polyclonal antibodies, lymphocyte immune globulin (ATG) and rabbit antithymocyte globulin (rATG) are agents that can be used both as induction and as treatment for acute rejection. The study and use of these agents has been reported in steroid-avoidance protocols²¹⁻²³. Published literature suggest that these agents are safe for the hepatitis C transplant population; however these same reports do not point to a clear advantage of using polyclonal antibodies in these patients²¹⁻²⁸.

There are several monoclonal antibodies in use for induction immunosuppression. The first of these is OKT3. Muromonab (OKT3) is an anti-CD3 receptor antibody with potent immunosuppressive effects. Early use of this agent showed that patients experienced more rapid and severe recurrence of the disease^{29,30}. It is largely accepted that OKT3 should be avoided if possible in the hepatitis C population.

The interleukin 2 (IL-2) receptor blockers basiliximab and daclizumab have been used for induction therapy in liver transplant patients. Their favorable side-effect profile and patient tolerability make them attractive agents in patients needing induction therapy. Much of the published literature on the use of these agents is in the steroid-sparing protocols^{15,17-18,20,31-35}.

Nelson, et al. published their experience with daclizumab in 2001. They found that those hepatitis C patients receiving daclizumab therapy

were more likely to have rapid recurrence of disease after transplantation³⁶. Interestingly, they also used a rapid taper of steroids in this population so that patients were steroid-free by four months posttransplantation. One could speculate that the faster onset of hepatitis C may be due, at least in part, to the rapid steroid taper as well as the use of daclizumab. There have been multiple studies since this time that have shown daclizumab to be safe in the hepatitis C transplant patient population. Rapid recurrence of hepatitis C was seen primarily in those patients with acute rejection episodes^{15,32,34}.

We found in our survey that only 3% of the centers used antithymocyte antibodies for induction and 17% IL-2 receptor blockers⁴.

Conclusions

There are multiple schools of thought regarding immunosuppression in the hepatitis C patient. To date, no one therapeutic modality has proven superior. From our review of the literature, a reasonable approach to immunosuppression would be a low and stable immunosuppressive regimen. Calcineurin inhibitor choice should be based on local practice and patient factors such as side effects and financial ability to purchase the medications. The data on HCV inhibition by CsA is exciting, but has not born clinical fruit at this time. Avoidance of steroids will alleviate some metabolic and infectious complications, but at the cost of earlier progression to fibrosis. This progression is much worse when the steroids are used in pulses to treat rejection. If steroids are used as part of the immunosuppression protocol they should be tapered slowly. The addition of MMF may have benefit, particularly at preventing acute rejection episodes and reducing the utilization of steroid pulses and antibodies. Low doses of combination therapy appear to be the best treatment option for the majority of patients.

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