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ORIGINAL ARTICLE

Prevalent immunosuppressive strategies in liver transplantation for hepatitis C: results of a multi-center international survey

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Summary

To determine current immunosuppression regimens and strategies for acute cellular rejection in hepatitis C virus (HCV) patients after liver transplantation (LT), questionnaires were sent to 264 LT programs worldwide. Surveys from 81 programs were reviewed. In 27 centers (33.8%) the immunosuppression protocol used in HCV differed from non-HCV patients. Tacrolimus-based immunosuppression is utilized in 70 centers (86.42%). Triple therapy using tacrolimus, mycophenolate mofetil and steroids is the most common regimen (41%). Six programs (7.4%) use steroid-free protocols. In nine centers (11%) steroids are discontinued within a week, 56% within 3 months, and 98% within the first year. At 75% of centers, mild rejection is treated by increasing baseline immunosuppression. Moderate rejection is treated by increasing baseline immunosuppression in 38% of centers, steroid bolus in 44%, and either in 16%. For severe rejection, 46% of centers give bolus steroid, and 16% administer antibodies. Among respondents, non-US programs use significantly more cyclosporine than US programs (35.6% vs. 2.8%, $P < 0.001$). Duration of steroid therapy is significantly shorter in US programs than non-US (10.8 vs. 29.4 weeks, $P < 0.001$). There is no consensus regarding the best immunosuppressive regimen and rejection treatments in HCV patients after LT. Our results reveal the most prevalent management practices in this difficult group of patients.

Introduction

Chronic hepatitis C virus (HCV) infection is the leading cause of end-stage liver disease representing roughly 40% of all liver transplants performed in the USA [1]. The data suggest that the incidence of HCV will rise substantially in the next couple of decades increasing the demand for liver transplantation (LT) [1]. However, HCV recurrence after transplantation is universal [2,3]. Interestingly, recurrent HCV after transplantation behaves more aggressively than it does before transplantation; 20–40% of patients with recurrent HCV will have cirrhosis at 5 years [4,5], compared to nontransplant patients where approximately 20% will develop cirrhosis at 20 years.

Risk factors for more severe recurrence include increased donor age, cytomegalovirus (CMV) infection, previous treatment of acute rejection, pretransplant viral load, and HCV viral genotype [6–8]. Several studies have reported older donor age to be a risk factor for premature graft loss and death [9–11]. The mechanism of CMV infection causing more aggressive disease is not well understood, but it appears to be independent of treatment for acute rejection. From the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) data, a pretransplant HCV viral load $>10^6$ copies/ml was

associated with decreased graft and patient survival, but the relationship of viral load to liver histology was not assessed [12]. More controversial risk factors include donor–recipient human leukocyte antigen (HLA) matching, cold ischemia time and the effect of specific immunosuppressive agents. Although most would agree that immunosuppression plays a major role in determining aggressiveness of viral recurrence, very little is known about how to modify immunosuppression so as to slow the rate of HCV disease progression. However, the consensus is that treatment of rejection episodes using steroid boluses and antibodies is associated with increased viral replication, greater fibrosis progression and higher risk of developing cirrhosis [7,13]. Therefore, knowing the impact of the treatment for acute cellular rejection on disease progression and outcomes, prevention becomes especially important.

Acute allograft rejection, in the presence of concomitant recurrent HCV, can be very difficult to diagnose since biopsy findings are often inconclusive. Particularly challenging are those patients who may have both processes occurring simultaneously. In these patients, deciding the most appropriate treatment strategy becomes especially important, since progression of recurrent HCV disease can be greatly affected by the administration of steroid boluses or other measures to treat acute rejection. Because of the increasing prevalence of HCV recurrence and its complicating effect on management decisions, we designed a questionnaire to assess current practices in the management of patients with HCV after LT, with a goal of identifying issues where consensus opinion is prevalent as well as issues which remain controversial. This is the first survey conducted to address post-transplant management and immunosuppression in HCV patients.

Patients and methods

In July 2007, letters of request for participation in surveys were sent to surgeons and hepatologists around the world (survey shown in Table 1). The survey was sent initially by postal mail, with a follow-up e-mail sent to nonresponders and additional centers outside the US. A total of 264 questionnaires were sent to the same number of liver transplant centers. All responses were entered into an Access 2003 database (Microsoft, Redmon, WA, USA). The results were then analyzed using STATA 9.0 for Windows (StataCorp LP, College Station, TX, USA). Fisher's exact test was used for dichotomized variables. Data were compared as US versus non-US programs and US versus European centers, to assess differences in various aspects of management. Differences were considered significant at $P < 0.05$ in all cases. Results are expressed as mean or median ± SD.

Table 1. Survey on hepatitis C immunosuppression and treatment.

1. Is your immunosuppression regimen in HCV patients different from the one used for non-HCV patients?
2. What is the current immunosuppression protocol for non-HCV patients in your program?
3. What is the current immunosuppression protocol for HCV patients in your program?
4. Do you employ early steroid withdrawal in your HCV patients? If yes, when do you plan to withdraw steroids?
5. Treatment options for mild rejection on biopsy-proven HCV recurrence with elevated LFTs.
6. Treatment options for moderate rejection on biopsy-proven HCV recurrence with elevated LFTs.
7. Treatment options for severe rejection on biopsy-proven HCV recurrence with elevated LFTs.
8. If you treat rejection by increasing immunosuppression, do you:
   - ○ Target higher FK or CsA levels?
   - ○ Restart or increase MMF?
   - ○ Restart or increase prednisone for a period of time and then taper without bolus?
9. Do you use biopsy in all cases with HCV and elevated LFTs after ruling out bile duct or vascular problems?

If not, what is your estimate on the percentage of patients in which you do biopsy?

10. Do you use preemptive treatment?
11. Treatment of HCV recurrence?
    - ○ Interferon
    - ○ Ribavirin
    - ○ Both
12. What would you estimate your response rate?
13. Do you consider retransplantation as an option in a patient with significant HCV recurrence who did not respond to treatment?

Results

Out of 264 centers, a total of 81 centers responded to our questionnaire (30.7% response rate). The majority of responses came from medium and high volume institutions. Of these 81, twenty-seven (33.8%) employ a different immunosuppression protocol in HCV versus non-HCV patients after transplantation (Table 2). Induction immunosuppression is used in 17 centers (21%) as follows: anti-thymocyte globulin in three centers (3.7%) and basiliximab in 14 centers (17.3%). Tacrolimus-based immunosuppression is employed in 70 centers (86.42%). Cyclosporine is the primary immunosuppressive agent in 15 centers (18.5%). Triple therapy using tacrolimus, mycophenolate mofetil (MMF) and steroids is the most commonly used regimen (41%). Steroid-free protocols are used in six programs (7.4%). In nine other centers (11%) steroids are discontinued within a week after transplantation; in 56% of the programs steroids are withdrawn within 3 months, 85% by 6 months and 98% of centers discontinue steroid use within the first year.

The Banff classification was used to facilitate the interpretation of the survey (mild, moderate, and severe

Table 2. Immunosuppression.

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, MMF 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.

rejection). Mild rejection is usually treated by increasing baseline immunosuppression (75% of centers, Table 3). Moderate rejection is treated by increasing baseline immunosuppression in 38% of centers, administering a steroid bolus in 44%, and either treatment in 18%. Severe rejection is treated with steroid bolus in 46% of centers, and antibodies (antithymocyte globulin, OKT3) in 16%. In 24% of centers, the most common treatment for severe rejection is either increasing baseline immunosuppression or administering a steroid bolus.

Respondents were asked to clarify their guidelines for increasing baseline immunosuppression if they employed this strategy for treating rejection. Ninety percent of respondents reported that they target higher levels of tacrolimus, and in 43% of cases, this is accompanied by increasing or restarting MMF. Only 9% will increase or restart the patient's steroids for treatment of rejection.

The questionnaire also investigated practices regarding utilization of liver biopsy in patients with HCV and elevated liver function tests (LFT) after vascular or biliary complications are ruled out. The vast majority of respondents (88%) stated that they perform a biopsy in all cases to make the diagnosis of HCV recurrence versus other causes of abnormal LFT. Among those who do not biopsy all patients with elevated LFT, 60% obtain biopsies in greater than 50% of these patients to reach a diagnosis. In addition, we asked respondents to speculate as to the number of times the biopsy was inconclusive in determining the diagnosis of HCV recurrence versus rejection. Out of 69 centers answering this question, 40 (58%) responded that the diagnosis is unclear in at least 30% of cases.

Preemptive therapy for HCV is utilized in only 11 programs, representing 13.7% of respondents. Of those 11, five centers utilize preemptive in more than 50% of their patients. Ninety-seven percent of respondents treat HCV recurrence with a combination of interferon and ribavirin. One center is involved in a trial which randomizes patients to receive either interferon alone or combination therapy; one center elects not to treat HCV recurrence. Seventy-eight percent estimate that clinical response rate is better than 30%. In 51 centers (63%), retransplantation is considered a valid option in patients with HCV recurrence.

US versus non-US centers

There were 36 US (44.4%) programs and 45 non-US programs (55.6%) that responded. Among non-US programs, 24 were from European centers (53.3%), five from Canada (11.1%), eight from Asia (17.8%), three from Australia (6.7%), one from Africa (2.2%), and four from South America (8.9%).

Interestingly, non-US programs appear to use significantly more cyclosporine than US programs in HCV patients (35.6% vs. 2.8%, $P < 0.001$). We also found that the duration of steroid therapy is significantly shorter in US programs compared to non-US programs (10.8 ± 1.5 vs. 29.4 ± 4.6 weeks, $P < 0.001$). Non-US centers tend to be less aggressive in treating mild rejection; only 5.6% will not treat mild rejection among US centers vs. 22.2% among non-US centers. Regarding the treatment of moderate rejection, 69% of non-US centers will treat it only by increasing baseline immunosuppression, compared to 33% of US centers ($P = 0.02$, Table 4).

Table 3. Treatment of rejection.

Rejection severity	Strategy	No. centers (%)
Mild rejection	Increasing baseline immunosuppression	60 (75)
Moderate rejection	Increasing baseline immunosuppression	28 (38)
	Steroid bolus	35 (44)
	Either increasing baseline immunosuppression or steroid bolus	14 (18)
Severe rejection	Steroid bolus	37 (46)
	Antibodies	12 (16)
	Either increasing baseline immunosuppression or steroid bolus	19 (24)

Table 4. US versus non-US centers.

	US centers *N* = 36 (44.4%)	Non-US centers *N* = 45 (55.6%)	*P*-value
Cyclosporine-based immunosuppression	1 (2.8%)	13 (35.6%)	<0.001
Duration of steroid therapy	10.8 ± 1.5 weeks*	29.4 ± 4.6 weeks*	<0.001
Mild acute rejection: no treatment	2 (5.6%)	10 (22%)	0.06
Moderate acute rejection	12 (33%)	31 (69%)	0.02

*Mean ± SD.

US versus European centers

The utilization of cyclosporine in patients transplanted for HCV is much higher among European respondents (38%) compared to US (2.8%, $P < 0.001$). The US centers are more aggressive in withdrawing patients from steroids compared to their European counterparts, at 10.8 ± 1.5 weeks versus Europeans at 28.6 ± 4.1 weeks ($P < 0.001$). European respondents are generally less aggressive in treating mild episodes of rejection than US respondents; in 5.6% of US centers mild rejection is not treated, as opposed to 33.3% of European centers ($P = 0.01$). While 86% of responding US centers increase patient immunosuppression to treat mild rejection in 86%, only 58% of European centers use this same strategy ($P = 0.03$). Tacrolimus or cyclosporine blood levels are increased by 94% and 79% of US and European respondents, respectively, to increase the baseline immunosuppression in their patients. In cases of moderate and severe rejection, US physicians are more aggressive in their treatment, using a steroid bolus in 66% and 75% of centers, respectively, versus 46% and 41% of European centers, respectively ($P = 0.01$ and $P = 0.01$, respectively). Interestingly, 38% of responding American centers would use antibodies to treat severe rejection, while no European respondents would.

Discussion

Hepatitis C is a significant cause of chronic liver disease, with nearly 4 million Americans and 170 million infected people worldwide [14]. Not surprisingly, end-stage liver disease caused by HCV has become a frequent indication for LT. Historically, the diagnosis of HCV was difficult. The availability of second-generation antibody testing for HCV, and more recently the advent of polymerase chain reaction (PCR) amplification of viral RNA, have greatly facilitated accurate diagnosis of HCV infection. However, on account of these improvements in diagnostic techniques, it has become evident that recurrence of HCV infection after LT is nearly universal, and often leads to progressive liver disease and allograft injury or loss [2,15].

Despite the global impact of HCV, many important questions remain unanswered, particularly with regard to prevalent immunosuppression management practices after LT. What is the most appropriate maintenance immunosuppression regimen for HCV patients? How should we treat acute rejection? How can acute rejection and recurrent HCV be differentiated clearly and consistently, and if this question cannot be answered, should it dictate an alternate therapeutic strategy? When is treatment indicated and for how long should the treatment be continued?

The role that increased immunosuppression plays in accelerating post-transplant viral replication and graft damage is unclear, although there is growing concern within the transplant community that a potentiating effect may exist. At present there is no clear answer regarding which immunosuppression protocol is most appropriate in this subset of patients. Most studies have shown that the severity of recurrent HCV is similar whether cyclosporine- or tacrolimus-based immunosuppression is used [7,16]. Several other studies initially reported MMF to possess antiviral properties, but subsequent studies have been unable to demonstrate this effect [17,18]. However, data support that the utilization of steroid boluses and/or antibodies to treat acute rejection is associated with poor outcomes in HCV patients after transplantation [7,13,19]. Interestingly, monoclonal or polyclonal antibodies do not seem to be harmful when used for induction of immunosuppression [5]. Newer immunosuppressive agents such as Sirolimus have not been fully studied in this regard and therefore conclusive recommendations cannot be established [20]. Based on available results, the utilization of pre-emptive therapy after transplant is not justified [21]. Pegylated interferon with ribavirin used in combination should be considered for treatment of recipients with histologically apparent recurrence of HCV [21,22].

Our survey revealed that induction is being used in 22% of the centers, and that basiliximab is the most common agent utilized for this purpose. Tacrolimus-based immunosuppression appears to be the most common maintenance regimen. Steroid use after transplantation in HCV patients is minimized early in 18% of centers, where they are either discontinued rapidly (within a week) or avoided entirely. The vast majority of transplant centers discontinue steroids within 3 months, while nearly every center stops steroids within the first year post-transplant

in their HCV patients. Treatment of mild acute cellular rejection in most centers involves increasing baseline immunosuppression by targeting higher tacrolimus levels. In some instances, MMF is restarted or increased in conjunction with the utilization of higher levels of tacrolimus. Moderate rejection is treated either by increasing immunosuppression or with administration of a steroid bolus. Most centers treat severe rejection with a steroid bolus. There appears to be a trend to avoid antibodies for treatment of acute rejection, even in severe cases.

Most transplant physicians prefer to perform liver biopsy in patients with HCV and elevated LFT, avoiding empiric steroid administration if possible. Even in experienced hands, biopsies frequently fail to establish a definitive diagnosis between HCV recurrence and acute rejection. Despite this, pre-emptive therapy does not appear to be used widely, perhaps on account of poor tolerance secondary to significant side-effects. Nearly all centers are currently using combined therapy with interferon or ribavirin, unless involved in a specific trial. As expected, management practices among responders demonstrate national and regional differences that, while relatively minor, highlight the scarcity of established guidelines and the absence of universal agreement.

Despite inherent limitations of survey-based data, we were able to uncover patterns of clinical practices of transplant centers worldwide when addressing one of the most vexing clinical problems: how to manage patients who have undergone LT for HCV. Our data have revealed disparity of treatment protocols for multiple clinical indications such as the utilization of increased baseline immunosuppression to treat acute cellular rejection, management of steroids as part of maintenance immunosuppression, and approach to induction therapy. Some of these practices, while experience-based rather than evidence-based, seem to make clinical sense. A consensus conference of experts would be beneficial in defining best strategies being used presently. Nevertheless, randomized studies will be needed to establish definitive guidelines for the management of this difficult group of patients.

Authorship

RG: designed study, collected data, analyzed results, wrote manuscript, approved final version. TMC: designed study, collected data, approved final version. PPM: edited manuscript, created tables, approved final version. HJ, TDJ and DR: edited manuscript, approved final version.

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