

Initial steroid-free immunosuppression after liver transplantation in recipients with hepatitis c virus related cirrhosis

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Abstract

AIM: Steroids can increase hepatitis C virus (HCV) replication. After liver transplantation (LTx), steroids are commonly used for immunosuppression and acute rejection is usually treated by high steroid dosages. Steroids can worsen the outcome of recurrent HCV infection. Therefore, we evaluated the outcome of HCV infected liver recipients receiving initial steroid-free immunosuppression.

METHODS: Thirty patients undergoing LTx received initial steroid-free immunosuppression. Indication for LTx included 7 patients with HCV related cirrhosis. Initial immunosuppression consisted of tacrolimus 2×0.05 mg/kg·d po and mycophenolate mofetil (MMF) 2×15 mg/kg·d po. The tacrolimus dosage was adjusted to trough levels in the target range of 10-15 µg/L during the first 3 mo and 5-10 µg/L thereafter. Manifestations of acute rejection were verified histologically.

RESULTS: Patient and graft survival of 30 patients receiving initial steroid-free immunosuppression was 86% and 83% at 1 and 2 years. Acute rejection occurred in 8/30 patients, including 1 HCV infected recipient. All HCV-infected patients had HCV genotype II (1b). HCV seropositivity occurred within the first 4 mo after LTx. The virus load was not remarkably increased during the first year after LTx. Histologically, grafts had no severe recurrent hepatitis.

CONCLUSION: From our experience, initial steroid-free immunosuppression does not increase the risk of acute rejection in HCV infected liver recipients. Furthermore, none of the HCV infected patients developed serious chronic liver diseases. It suggests that it may be beneficial to avoid steroids in this particular group of patients after LTx.

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INTRODUCTION

Liver diseases related to chronic viral hepatitis are the leading

indication for liver transplantation (LTx) worldwide^[1]. Hepatitis B virus and hepatitis C virus (HCV) infection account for the majority of liver diseases related to chronic viral hepatitis. In Europe, 8 422 patients received a liver graft for virus related cirrhosis between January 1988 to December 2000^[2]. Posttransplantation HCV infection is a relatively benign condition during the short-term follow-up and liver recipients reach survival rates similar to other indications. However, the natural history of posttransplantation HCV reinfection is variable. Almost all recipients became HCV seropositive during the first year after LTx. At 5 years posttransplantation, up to 30% of the recipients developed cirrhosis^[3,12]. The patients' immune status seems to be an important factor regarding the progression of fibrosis. The immunosuppressed liver recipients had a higher rate of fibrosis progression per year compared to patients without immunosuppression^[4].

The role of immunosuppressive treatment in the occurrence and severity of HCV reinfection has been discussed controversially^[5]. Since the first liver transplantation performed by Starzl in 1963, corticosteroids have been used traditionally for immunosuppression after organ transplantation due to the lack of other available immunosuppressive drugs^[6]. Nowadays, a variety of potent and selective immunosuppressive drugs are available, thus allowing avoidance of immunosuppressive drugs with unselective mode of action or unfavorable side effects^[7]. Corticosteroids have a well described spectrum of adverse effects including metabolic changes and an increased risk of cardio-vascular diseases. Also, corticosteroids have an unselective immunosuppressive mode of action. Furthermore, corticosteroids increased HCV replication *in vitro* and *in vivo*^[8-10]. After liver transplantation, high early HCV-RNA levels could be associated with more severe recurrence of hepatitis^[11]. Prieto *et al.* reported positive relationships between the number of rejection episodes, methylprednisolone (MP) boluses, treatment of rejection, cumulative dose of steroids and the development of HCV cirrhosis^[12]. These findings implicated that prevention of acute cellular rejection and avoidance of high-dose or maintenance steroids could be beneficial^[5], however, the experience with completely steroid-free immunosuppression after LTx is still limited.

Recently, we published a series of 30 patients receiving steroid-free immunosuppression that consisted of tacrolimus and mycophenolate mofetil (MMF)^[13]. Since the hypothesis that steroid-free immunosuppression might be particularly beneficial in HCV infected liver recipients, we analyzed this subgroup of liver recipients with regard to the risk of acute rejection, and development of serious HCV related liver disease in the graft.

MATERIALS AND METHODS

Patients

Thirty adult patients underwent LTx between June 1996 and January 1999. The detailed characteristics have been previously described^[13]. The indications for LTx included hepatitis C virus related cirrhosis in seven recipients. The HCV patients included 4 females and 3 males with a median (range) age of 58(43-62) years. HCV-RNA was seropositive prior to transplantation with a

median (range) viral load of $10^4(10^3-10^5)$ genome equivalent/mL. The serum HCV-specific RNA was detected by reverse transcription (RT)/polymerase chain reaction (PCR) as previously described by Mihm *et al.*^[14]. HCV genotype was classified as II (1b) in all seven patients according to Okamoto *et al.* and Simmonds *et al.*^[15,16]. Child-Turcotte-Pugh Score prior to LTx was Child A in 2, Child B in 2 and Child C in 3 patients. Four of the patients had a coexisting hepatocellular carcinoma.

Methods

Apart from an intravenous (IV) bolus of 500 mg MP before reperfusion of the graft, recipients received no further steroids. Tacrolimus (Prograf, Fujisawa GmbH, München, Germany) was started 6 h after reperfusion at an oral dosage of 2×0.05 mg/kg-d. Thereafter, tacrolimus dosages were adjusted to a target range of 10-15 μ g/L during the first three months and 5-10 μ g/L after the third month after LTx. Tacrolimus trough levels were measured by a microparticle enzyme immunoassay (Prograf-MEIA II, Abbott Laboratories, Chicago, IL, USA). MMF (Cell Cept, Hoffmann-La Roche, Grenzach-Wyhlen, Germany) was given orally starting from the first postoperative day (pod) at a body mass adjusted dosage of 2×15 mg/kg-d. Liver biopsies were performed routinely on d 7, after 6 mo, every year, and whenever clinically indicated. Acute rejection was defined as abnormal liver function tests, histological changes as graded by the Banff classification, and the necessity for therapy^[12]. Treatment of acute rejection consisted of IV-MP boluses of 500 mg over a period of 3-5 d with or without additional prednisolone tapering. Combined antiviral therapy consisting of interferon alfa and "low-dose" ribavirin was used in patients with HCV reinfection accompanied by chronic active hepatitis as described previously by Wietzke *et al.*^[17,18].

Statistical analysis

Actual survival was calculated by the Kaplan-Meier method.

RESULTS

Patient and graft survival

Twenty-two of the 30 patients receiving initial steroid-free immunosuppression have been alive after a median (range) follow-up of 1 386(44-2 037) d. Actual patient survival was 86.7% at 2 years and 73.3% at 5 years (Figure 1A). The actual patient survival of HCV-infected recipients was 85.7% at 2 years and 57.1% at 5 years, the difference was not statistically significant (Log-rank test (Cox-Mantel): $P=0.33$) (Figure 1B).

At present, four of the seven HCV infected liver recipients have been alive with a median (range) follow-up of 47(46-60)

mo after LTx. None of the deaths in the HCV patients was related to HCV reinfection. The causes of the 3 deaths were chronic graft dysfunction (CDF) on pod 164, heart failure due to preexisting toxic cardiomyopathy on pod 774, and a *de-novo* ovarian carcinoma on pod 950. One of the seven patients with HCV-related cirrhosis underwent successful retransplantation for primary nonfunction (PNF) on day 5 (Table 1).

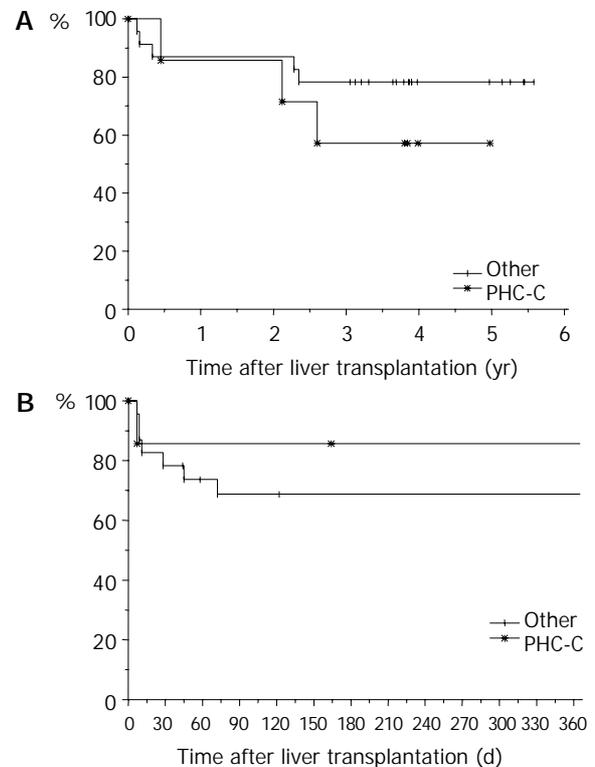


Figure 1 A: Actual patient survival according to primary indication (HCV related cirrhosis vs others) of liver recipients receiving steroid-free immunosuppression. B: Actual rejection free interval according to primary indication (HCV related cirrhosis vs others) during the first year after LTx in liver recipients receiving steroid-free initial immunosuppression.

Acute rejection episodes and immunosuppression

In total, 8 of the 30 liver recipients (26.2%) had an episode of acute rejection. The onset of acute rejection was between pod 7 and 72. The median (range) grade of acute rejection was 5.5(3-8) according to Banff classification. Low tacrolimus trough levels associated with diarrhea were observed in five of the eight recipients with acute rejection. Also, diarrhea was

Table 1 Characteristics of liver recipients with HCV-infection receiving initial steroid-free immunosuppression

| # | Gender (M/F) | Rge (yr) | Child Class | HCC | HCV genotype | HCV viral load | | | | Liver histology | Outcome (pod) |
|----|--------------|----------|-------------|-----|--------------|----------------|--------|--------|--------|-------------------------------|---------------------------|
| | | | | | | prior | 1 mo | 4 mo | 1 yr | | |
| 5 | f | 60 | C | no | II (1b) | 10^4 | 10^5 | 10^4 | 10^5 | | died (950), ovarian-ca |
| 9 | f | 62 | B | no | II (1b) | 10^5 | 10^5 | 10^6 | 10^5 | AR, hepatitis (+/-) | alive (1817), reLTx (5) |
| 12 | m | 57 | A | yes | II (1b) | 10^5 | 10^5 | 10^4 | | | died (774), heart failure |
| 13 | f | 59 | C | yes | II (1b) | 10^5 | 10^5 | 10^5 | | hepatitis (+/-), fibrosis (+) | alive (1456) |
| 19 | m | 58 | B | yes | II (1b) | 10^4 | 10^3 | | 10^4 | hepatitis (+) | alive (1402) |
| 20 | m | 46 | A | yes | II (1b) | 10^3 | | 10^4 | 10^4 | | alive (1389) |
| 25 | f | 43 | C | no | II (1b) | 10^4 | 10^4 | 10^5 | | | died, CDF (164) |

Abbreviations: # (patient number), HCC (hepatocellular carcinoma), HCV (hepatitic C virus), pod (postoperative day), yr (year), mo (mo), prior (prior to LTx), AR (acute rejection), +/-/+ / +/+ / +/+ / - (minimal/moderate/severe/reversed), reLTx (liver retransplantation), CDF (chronic graft dysfunction).

the predominant adverse effect when tacrolimus and MMF were given simultaneously. All acute rejection episodes completely resolved after IV-MP boluses and four of the patients with rejection episodes received additional steroid taper. In the further postoperative course, there was no graft loss due to rejection and all of these patients have been alive. Only one of the eight patients with acute rejection had HCV-related cirrhosis. This patient underwent retransplantation on pod 5 for PNF. Until retransplantation, immunosuppression was temporarily discontinued and the patient suffered from diarrhea, thus tacrolimus trough levels were low.

Only 3 of the 7 HCV patients received steroids after LTx, two in conjugation with tacrolimus first and then cyclosporine (CyA), and one for acute rejection. One patient was reconverted to tacrolimus after suspicion of CDF. MMF was intermittently discontinued in all 7 patients and withdrawn in 5 patients. The cause of MMF withdrawal was diarrhea in 3 patients and conversion to CyA in 2 patients. Maintenance immunosuppression in the HCV infected recipients consisted of tacrolimus monotherapy in 3 patients, tacrolimus/MMF in 2 patients, tacrolimus/prednisolone in 1 patient, and CyA/prednisolone in 1 patient.

HCV reinfection

All 7 HCV infected patients had HCV genotype II (1b). Recurrence of HCV-RNA in serum occurred within 4 mo after LTx in all seven liver recipients with HCV-related cirrhosis. Prior to LTx the median viral load was 10^4 (10^3 - 10^5) genome equivalent/mL. During the first four months, the viral load ranged from 10^3 to 6.5×10^5 genome equivalent/mL. The virus load was not markedly increased during the first year after LTx (Figure 2). Histologically, only 1 HCV patient had suspicion of minimal portal hepatitis in the most recent biopsy that occurred 15 mo after LTx and transaminases were within normal values (Table 1). Five months after LTx, another recipient had elevated transaminases (AST 55, ALT 109 U/L), suspicion of portal hepatitis and mild fibrosis in the graft. Combination therapy with subcutaneous interferon alfa-2a 3 MU three times per week and oral ribavirin 10 mg/kg body mass in three divided doses per day was given for 6 mo. At the end of treatment, the patient had transaminases within normal values (AST 9, ALT 12 U/L), and histological improvement without fibrosis, but positive serum HCV-RNA. A third recipient developed suspicion of minimal portal hepatitis and fibrosis associated with a reduction of small bile ducts. Liver histology improved after reintroduction of MMF. Initially, this patient underwent retransplantation for PNF and acute rejection was resolved.

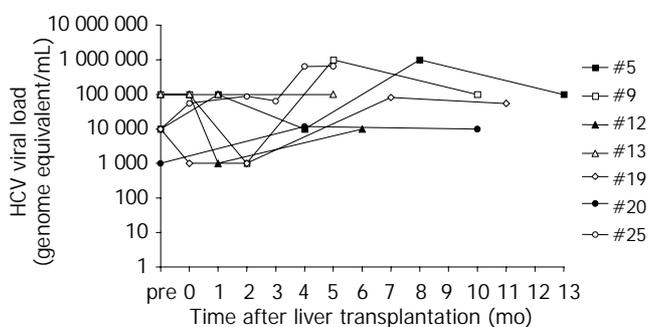


Figure 2 Serum virus concentration in seven HCV infected recipients during the first year after LTx. All patients received initial steroid-free immunosuppression.

DISCUSSION

Although steroids are known to increase HCV replication^[8],

they are given routinely for prophylaxis and treatment of rejection after solid organ transplantation. The potential risk of acute rejection must be faced against the benefit of steroid withdrawal. After LTx, HCV infection has been clearly identified as a risk factor for the development of early acute rejection^[19]. On the other hand, the presence, number, and treatment of acute rejections were found to be associated with the histologic recurrence of HCV infection after LTx^[20,21]. In 96 liver recipients, histologic recurrence of HCV infection occurred in 18% without acute rejection, 42% with one acute rejection episode, and 70% with more than one episode of acute rejection^[21]. In liver recipients, MP treatment for acute rejection was found to increase serum HCV RNA between 4 to 100 fold^[8]. OKT3, used for treatment of steroid-resistant rejection after LTx, was associated with more severe recurrences^[20]. The mutual relation between treatment of acute rejection and recurrence of HCV-infection after LTx sets the stage for a completely steroid-free immunosuppressive protocol.

Recently, it was clearly demonstrated that steroid-free immunosuppression after LTx was feasible and safe^[13,22-24]. The different immunosuppressive regimens consisted of CyA/azathioprine (Aza)^[23], CyA or tacrolimus monotherapy^[22], CyA/rapamycin, rapamycin monotherapy^[24], and tacrolimus/MMF^[13]. The reported rates of acute rejection were 65% for CyA and 66% for tacrolimus monotherapy^[22]. The combination of CyA/Aza resulted in 80% of acute rejection, but only 9% of acute rejections required treatment. Compared to patients receiving CyA/Aza/prednisone, the incidence and severity of rejection were similar in both groups but the dynamics of virus replication of HCV-RNA was faster among those treated with prednisone. The 2 year survival rate was 70.2% with prednisone and 78.3% without prednisone^[23]. The rate of acute rejection using rapamycin/CyA was 28% and with sirolimus monotherapy 75%^[24].

We reported that complete avoidance of corticosteroids after LTx could be performed without an increased risk of mortality, morbidity, and severe acute rejection. The rate of acute rejection with the use of tacrolimus in combination with MMF was only 26.2%^[13]. This rate of acute rejections might even be reduced, if underimmunosuppression were avoided. Low tacrolimus trough levels were observed in patients with diarrhea when tacrolimus and MMF were given simultaneously. Diarrhea could be avoided after introduction of a two hour dosing interval between tacrolimus and MMF administration^[13,25]. Therefore, the rate of acute rejections might be lower if tacrolimus and MMF are administered with a dosing interval.

In our present study, only 1 HCV patient developed acute rejection. This patient had a complicated clinical course with PNF, retransplantation, temporary discontinuation of immunosuppression, acute rejection, and received MP boluses as well as intermittent steroids until pod 255. Reinfection with HCV was noticed in all seven patients. Within 4 mo after LTx, all seven patients were HCV seropositive. Compared to the pretransplant HCV load, there was no significant increase during the first year after LTx. Also, liver histology was completely unsuspecting in 4 HCV patients. Three patients had suspicion of minimal portal hepatitis which was followed up by frequent biopsies in one patient. Another patient with supposed minimal portal hepatitis and additional mild fibrosis received combination therapy which improved transaminases and histology^[17]. Also, one patient with previous retransplantation developed portal hepatitis and fibrosis. MMF was reintroduced for reduction of small bile ducts, minimal portal hepatitis and fibrosis and resulted in histological improvement. None of the HCV infected patients developed serious chronic liver disease. However, one patient died of CDF which was related to underimmunosuppression after conversion to CyA for

suspicion of tacrolimus induced neurotoxicity. From our limited experience with the small number of patients, the avoidance of steroids did not alter the posttransplant HCV reinfection in serum and the histological alterations were mild despite all patients had HCV genotype II (1b). Feray *et al.* reported that HCV genotype II (1b) was a risk factor for recurrent hepatitis^[26,27]. However, the influence of HCV genotype II (1b) has been controversial. Gordon *et al.* reported a similar frequency of recurrent hepatitis with all HCV genotypes, but HCV genotype II (1b) was associated with a higher rate of cirrhosis^[28]. Thus, the avoidance of steroids seems to be beneficial for liver recipients with HCV genotype II (1b).

Hitherto, it remains unclear which immunosuppressive regimen is best for HCV liver recipients. MMF was discussed controversially in liver transplant recipients with HCV^[29]. In a recent prospective randomized trial comparing tacrolimus/prednisolone with tacrolimus/MMF/prednisolone in liver recipients with HCV, MMF had no impact on patient and graft survival, rejection or rate of HCV recurrence^[30]. However, MMF might reduce the frequency of acute rejection and therefore exposure to steroids^[31]. Our intention was to use a safe steroid-free immunosuppressive regimen. Tacrolimus is a potent immunosuppressive drug, but impairment of renal function might limit the use of tacrolimus especially during the early phase after LTx. Thus, we used a combination of tacrolimus and MMF which resulted in a low frequency of acute rejection^[13]. However, the combination of tacrolimus and MMF could cause diarrhea or other side effects that often required discontinuation or withdrawal of MMF. Thus, therapeutic drug monitoring of tacrolimus is an essential requirement for the combination of tacrolimus and MMF. Alternatively, anti-IL-2 receptor antibodies might have potential in steroid-free regimens. The use of anti-IL-2 receptor antibodies reduces the frequency of acute rejection after LTx, but there has been limited experience with HCV infection when anti-IL-2 receptor antibodies are given for induction of immunosuppression. Most recently, two immunosuppressive protocols using daclizumab have been reported with controversial results regarding HCV infection. Tacrolimus/MMF was compared with daclizumab/tacrolimus/MMF in a randomized open-label study and corticosteroids were eliminated 24 h after LTx in both arms. Steroids could be avoided safely after pod 1 and HCV recurrence was documented in 2 patients who did not receive daclizumab^[32]. In a group of 21 HCV infected liver recipients receiving daclizumab, MMF, and steroids for induction of immunosuppression, patients with HCV infection administered daclizumab were more likely to have an earlier onset of hepatitis, jaundice and greater histological activity compared with a well-matched HCV control group. Also, recurrent hepatitis progressed more rapidly in the daclizumab group. Nelson *et al.* concluded that daclizumab in combination with MMF might be associated with early recurrence of HCV and more rapid histological progression of disease in the early period after LTx^[33]. Also, triple and double immunosuppressive regimens had a higher rate of fibrosis and cirrhosis in HCV infected patients compared to monotherapy^[34,35]. These findings implicate that strenuous induction protocols should be avoided in HCV infected liver recipients.

As proposed by some centers, early withdrawal or avoidance of steroids in HCV infected patients could be beneficial. From our experience with the limited number of HCV infected liver recipients, initial steroid-free immunosuppression is safe, has a low risk of acute rejection without a need for high-dose steroids and high cumulative steroid dosages, which are likely to induce less severe HCV reinfection. Furthermore, none of the HCV infected patients developed serious chronic liver diseases. Therefore, it is high time to seriously reconsider the use of any steroids in liver transplantation especially for HCV-

infection patients and to prove this approach in a large randomized controlled trial.

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