

Recurrent Hepatitis C After Liver Transplantation: Immunosuppression and Histologic Course

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Abstract

Hepatitis C-related liver cirrhosis is the most common indication for orthotopic liver transplantation nowadays. However, recurrence of hepatitis C after liver transplantation in hepatitis C-positive graft recipients is almost universal.

Severity of graft hepatitis increases during the long-term follow-up and up to 30% of patients develop severe graft hepatitis and cirrhosis. In the past this led to an accelerated fibrosis progression rate, leading to decreased patient and graft survival in hepatitis C-positive patients. Several variables like viral genotype, donor age, rejection treatment, and cytomegalovirus disease have been shown to be associated with early and severe graft hepatitis. However, the impact of different immunosuppressive protocols including antibody induction therapy on histologic course and severity of hepatitis C recurrence is still unclear. It has been proven that stronger immunosuppressive regimens play an important role in fibrosis progression. To elucidate the role of different immunosuppressive strategies on the histologic course, a systematic review of the literature has been performed. However, it has to be pointed out that fibrogenesis is a multifactorial phenomenon. Therefore, defining the optimal immunosuppressive regimen may only one of several factors decreasing the severity of hepatitis C recurrence after liver transplantation. (Trends in Transplant 2007;1:69-75)

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Key words

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Recurrent hepatitis C after liver transplantation

The risk of death in recipients with hepatitis C virus (HCV) infection has increased when compared to other indications like alcoholic cirrhosis or Budd-Chiari syndrome. This is a consequence of recurrent disease in patients with HCV after orthotopic liver transplantation (OLT)¹. In contrast to hepatitis B virus (HBV)-related liver cirrhosis, recurrence of HCV after OLT is almost universal².

The natural history of HCV is generally considered to be slow; however, different factors causing a more progressive course have been identified in the past³. Former studies showed that progression of hepatitis C seems to be accelerated in immunocompromised patients⁴. Several pretransplant, peritransplant, and posttransplant variables such as HBV coinfection, viral load, or human leukocyte antigen (HLA) matching are evidently associated with disease progression after transplantation⁵. After transplantation, redistribution of virus arises from extrahepatic sources⁵. Molecular analysis has shown that postoperative viral strains are identical to isolates detected before transplantation⁶. Following liver transplantation, the viral load increases up to > 10-fold compared to pretransplant levels^{7,8}.

The recurrence of hepatitis C after OLT commonly occurs during the first posttransplant year. The majority of liver transplant recipients reveal histologic damage in liver biopsy specimen during this time⁹. Furthermore, from numerous data recently collected in HCV-positive patients after OLT, it has emerged that HCV recurrence as well as development of fibrosis are multifactorial and may depend upon several factors like pre- or post-hepatitis C viremia levels, renal function, HCV genotype, year of transplant, cytomegalovirus infection, and donor and recipient age¹⁰⁻¹⁵. A relationship between HCV viremia levels and genotype 1b has been suggested in the pathogenesis of severe recurrent hepatitis, but this remains controversial. In most studies, the incidence of recur-

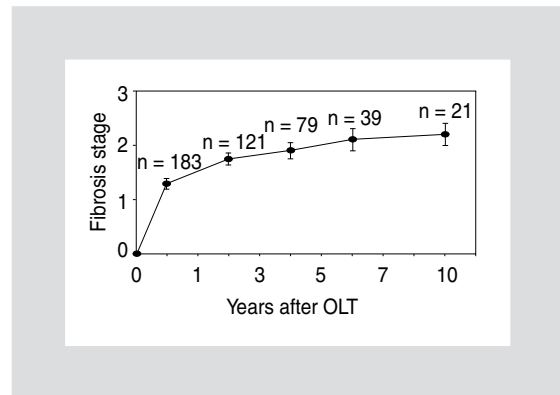


Figure 1. Mean fibrosis-stage progression evaluated by protocol liver biopsies at different time intervals in 183 recipients surviving more than one year after liver transplantation (OLT) with hepatitis C virus reinfection posttransplantation. Data were given as mean and standard error of mean (adapted from Neumann, et al.¹⁸).

rent hepatitis C is similar in the 1b and non-1b groups, but genotype 1b is associated with more severe histologic graft damage^{11,16}. A recent analysis of the United Network for Organ Sharing (UNOS) database delineated the inferior graft survival in HCV-positive patients after OLT and therefore underlined the impact of recurrent hepatitis C on outcome^{10,17}. Analysis from our own center showed that fibrosis progression during the course of the disease is not linear, but decreases after three years after OLT (Fig. 1)¹⁸. The primary immunosuppression was not associated with the development of fibrosis (Table 1).

Immunosuppression and viral activity

Liver damage due to HCV infection occurs in the context of an immune response in which the host immune response plays a critical role in controlling HCV replication and hepatocyte damage. Regulatory T-cells consist of phenotypically and functionally distinct CD4+ and CD8+ T-cell subsets, which are engaged in maintaining self tolerance and in preventing anti-nonself effector responses that may be harmful to the host; virus-specific CD8+ in the livers of patients with chronic HCV infection play a cardinal role in antiviral immune defences¹⁹. After liver transplantation and reinfection, when immunosup-

Table 1. Risk ratio (RR), confidence bounds (CB), and P values for immunosuppression possibly associated with fibrosis development (stage 1-4) within the first year after liver transplantation for hepatitis C¹⁸

Mode of immunosuppression	Fibrosis stage 1 - 4 RR (CB)	p value
Cyclosporin A vs. tacrolimus based	0.67 (0.45 - 1.25)	0.18
Additional ATG treatment (yes vs. no)	0.7 (0.3 - 1.35)	0.26
Treatment for rejection		
Single steroid pulse (yes vs. no)	1.2 (0.6 - 2.4)	0.45
Multiple steroid pulse (yes vs. no)	1.3 (0.4 - 4.0)	0.4
OKT3 treatment (yes vs. no)	1.1 (0.3 - 3.6)	0.9

pression modifies immune response, viral persistence and progression of recurrent infection may be related to an inappropriate helper T-cell response, whereas a vigorous T-cell response during early stages of reinfection could be an important mechanism to limit the allograft injury. Weston, et al. recently reported that emergence of regulatory T-cell responses and their presence correlated with mild histologic recurrence and excellent clinical outcome²⁰. Casanovas-Taltavull, et al. showed that patients transplanted for HCV cirrhosis, with sustained virologic response after therapy, as well as patients who spontaneously cleared HCV-RNA, displayed an immune response despite immunosuppression that might have contributed to the favorable outcome²¹. Another important characteristic of the HCV is the highly heterogeneous nature of the viral population, which has a role in the mechanisms of the transmission, persistence, and pathogenesis of HCV infection. A recent study has shown that in liver transplant recipients, selection of viral sequences was markedly impaired, especially early after transplantation; reduced sequence turnover correlated negatively with the outcome of graft infection²².

Acute rejection episodes and viral activity

Immunosuppression has to be divided in immunosuppressive induction protocols and re-

jection treatment. The incidence of acute and chronic rejection in HCV-positive patients has been reported to be higher than for other indications²³. However, the distinction between recurrent hepatitis C and allograft rejection is still a matter of discussion. A recent analysis by Regev, et al. showed that the inter- and intraobserver concordance of five experienced transplant pathologists to differentiate reinfection versus rejection is below 60%²⁴. Both the CD4+/CD8+ T-cell recognition of foreign major histocompatibility complex (MHC) in acute cellular rejection and the CD4+/CD8+ T-cell recognition of virally infected graft cells lead to recruitment of CD4+/CD8+ T-cells, mononuclear cell infiltrate and endothelialitis. Thus, viral infection and acute cellular rejection culminate in similar histologic pictures. The direct T-cell response to foreign MHC antigens has been thought to be the distinguishing feature of cell-mediated allogeneic immunity²⁵. Cell-mediated immunity seems to play a major role in controlling viral activity and determining the outcome of HCV infection. Sugimoto, et al. demonstrated that HCV persistence was associated with a global quantitative and functional suppression of HCV-specific T-cells²⁶. Spontaneous clearance in rare cases was coupled to a vigorous HCV-specific T-cell response. If bolus corticosteroid treatment is discontinued, the host cytotoxic immune response may recognize an even larger burden of infected cells. A repetition of this maneuver may culminate in accelerated graft destruction by recurrent hepatitis C²⁷.

If possible, the use of corticosteroid pulse therapy should be avoided in patients with recurrent HCV graft hepatitis. Additional mycophenolate mofetil (MMF) treatment could be a steroid-sparing alternative²⁸. Similar to steroid bolus treatments, the use of OKT3 or other polyclonal antibodies for rejection treatments have been associated with increasing viremia and more severe HCV recurrence.

Immunosuppression

Current immunosuppressive induction protocols consist of calcineurin inhibitors (cyclosporin A, tacrolimus), corticosteroids, mono- and polyclonal antibodies (IL-2-R antibodies), azathioprine and MMF. Immunosuppression maintenance in general consists of either calcineurin inhibitor (CNI) monotherapy or a combination therapy (CNI plus MMF).

Calcineurin inhibitors

Cyclosporin A (CsA) specifically inhibits HCV replication through blocking the viral RNA polymerase enzyme NS5B via cyclophilins^{29,30}. In contrast, as tacrolimus (TAC) inhibits calcineurin FK506-binding proteins and not cyclophilins, it does not exhibit antiviral activity³¹. The effect of CsA treatment on viremia in HCV-positive patients has been observed in non-transplanted patients. In a group of 10 patients, no changes of viremia were observed during application of 1.5-4 mg/kg CsA³². Although there are no data available for non-transplanted patients on TAC, in the posttransplant setting viremia in CsA- and TAC-treated patients with steroids are similar³³. Additionally, large studies could not show any differences in the long-term outcome of TAC- and CsA-treated patients². A recent study by Berenguer, et al. detected no differences between TAC- and CsA-treated patients regarding fibrosis at the first posttransplant year³⁴. These data can be confirmed by our own patient population where long-term graft

and patient survival figures were similar in patients on CsA and TAC. In contrast to CsA/TAC application, the use of high doses of steroids significantly increases the level of viremia in HCV-positive patients and is related to histologic injury³⁵. Different to this, new data showed that rapid tapering of maintenance steroid administration impairs graft survival in HCV-positive patients after OLT³⁶. However, to elucidate whether there are differences between TAC and CsA in regard to the histologic course, further prospective studies are needed.

To further investigate this issue, we performed a randomized trial of steroid-free immunosuppressive induction protocol with MMF and TAC in 60 patients. First results showed that the steroid-free induction therapy is safe and associated with a low incidence of rejections. Long-term data still has to show whether steroid-free immunosuppression induction protocols decrease the incidence and severity of recurrent graft hepatitis³⁷.

Mycophenolate mofetil

Mycophenolate mofetil blocks the *de novo* biosynthesis of guanine nucleotides, which are required for DNA synthesis. This results in an inhibition of lymphocyte proliferation, which may lead to a decrease of inflammatory activity. The use of specific inhibitors of the enzyme inosine monophosphate dehydrogenase (IMPDH) may provide an alternative treatment for patients with chronic HCV infection³⁸. The proposed independent antifibrotic effects of IMPDH inhibitors and described mitogenic responses in fibroblasts and endothelial cells may lead to a reduction of inflammation and fibrosis, as reported by Lau, et al.³⁹. Therefore, MMF might be an alternative treatment option in HCV patients after OLT because it has been shown to reverse acute rejection in HCV-positive recipients in the long term⁴⁰. Furthermore, MMF has been proposed to have some antiviral effects *in vitro* and *in vivo*⁴¹. This would predestine MMF as an optimal immunosuppres-

sant in HCV-positive liver transplant recipients. In contrast to these results, new data revealed an increase of HCV viremia after OLT when MMF was added to the immunosuppressive treatment⁴². Our own findings regarding MMF in combination with CNI taper showed a positive effect on fibrosis progression, graft inflammation, and alanine aminotransferase (ALT) levels, and may improve the clinical course of HCV after OLT; however, the antiviral properties of MMF are still unconfirmed²⁸. Recent data by Henry, et al. could demonstrate that MMF inhibits HCV replication *in vivo* and acts in synergy with CsA and interferon- α ⁴³.

mTOR inhibitors: (sirolimus)

Recently, a new potent immunosuppressant that blocks postreceptor signal transduction and interleukin-2-dependent proliferation have been developed and might open new possibilities in patients with HCV after OLT. Sirolimus, a macrocyclic lactone, is being investigated in large, multicentre trials and is proposed to have fewer properties to promote viral infections⁴⁴. Because of its potential to inhibit fibrogenesis, sirolimus may be sufficient to decelerate fibrosis progression in patients with recurrent hepatitis C after OLT. However, to date there are no data regarding the influence of sirolimus on recurrent HCV infection.

Azathioprine

Currently, few data concerning histologic course, mortality, and graft loss in patients who received CNI and corticosteroids alone or with azathioprine are available. However, azathioprine in combination with corticosteroids is known to be associated with increased HCV-RNA serum levels in non-transplant patients. A study by Broker, et al. found transaminases to be similar in patients with and without receiving azathioprine⁴⁵. In a recent retrospective analysis, Walter, et al. found that the use of azathioprine as part of an initial immunosup-

pressive regimen was associated with lower fibrosis progression⁴⁶. Further prospective randomized studies are necessary to elucidate the role of azathioprine in hepatitis C-positive graft recipients.

OKT 3

OKT3 treatment for steroid-resistant acute rejection results in a shorter time interval for graft hepatitis and an increased rate of cirrhosis (26.3 vs. 6%)⁴⁷. Whilst the type of CNI has no influence on histologic recurrence of HCV, cumulative exposure with steroids and OKT3 is associated with an increased number of graft losses. Diagnosis of rejection in HCV-positive patients after OLT has to be made by rigorous criteria. Every effort should be made to enroll HCV-positive patients into studies which contribute to the optimization of pre- and posttransplant management.

Antiviral treatment and immunosuppression

Although the role of immunosuppression on fibrosis progression is an important factor, the clinical and histologic course after OLT for hepatitis C is inseparably associated with antiviral treatment strategies. The recent introduction of new formulations of interferons (IFN), pegylated interferons (PEG-IFN), in the treatment of non-transplanted patients revealed promising results. These results are even superior when combining ribavirin and PEG-IFN⁴⁸. The optimal immunosuppression during antiviral therapy is not established and still a matter of discussion. A current analysis suggests that combination therapy with IFN α and CsA led to increased serum concentration of HCV core protein^{29,49}. Furthermore, combination therapy with IFN α and CsA has shown to be more effective than IFN alone in the treatment of HCV infection in non-transplanted patients⁵⁰. Results of antiviral therapy in hepatitis C patients have increased the interest to eradicate the virus immediately prior to trans-

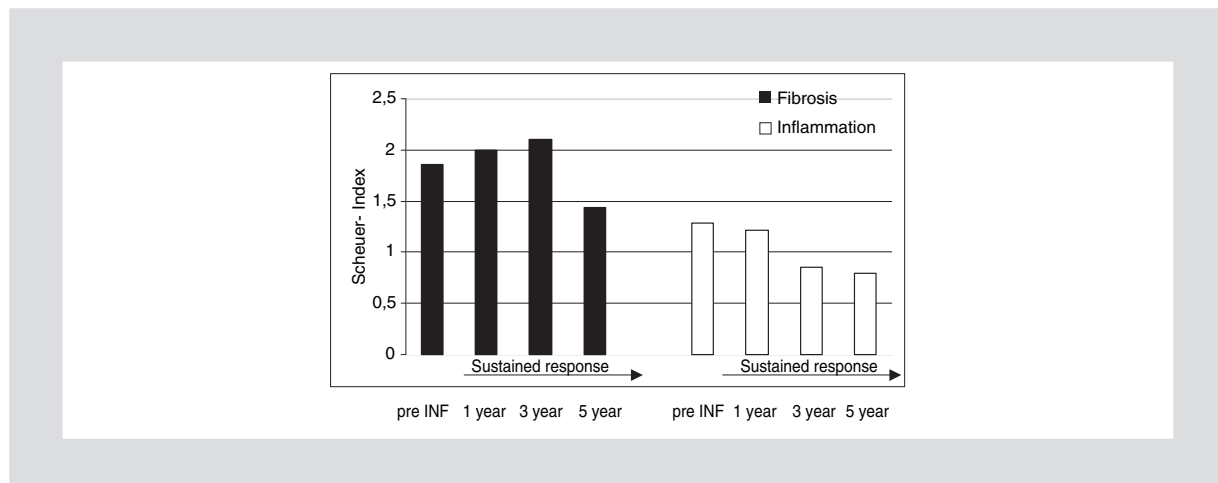


Figure 2. Course of fibrosis and inflammation scores pre interferon treatment and one, three, and five years after sustained virologic response ($n = 28$ after one year, $n = 19$ after three years, and $n = 17$ after five years) (from: Bahra M. Transplantation 2007;83:352-3).

plantation, similar to patients with HBV. Theoretically, IFN therapy should be most effective when administered immediately posttransplantation when viremia is lowest^{46,51}. In a recent study, patients received either IFN or no treatment after OLT. Interferon decreased the incidence of graft hepatitis significantly one year after OLT (27 vs. 54%)⁵². However, survival figures were similar in both groups after one and two years.

Our own results concerning the course of fibrosis progression in HCV-infected liver graft recipients with sustained virologic response after combination treatment (ribavirin plus IFN α) showed a deceleration of fibrosis progression. Therefore, a successful antiviral treatment seems to play a major role in prevention of graft cirrhosis in HCV-infected liver graft recipients⁵³. However, other variables such as type of IFN treatment (standard vs. pegylated), mode of immunosuppression, or episodes of acute cellular rejection had no influence on fibrosis progression in this analysis⁵³ (Fig. 2).

Summary

The impact of immunosuppression on the histologic course in patients with recurrent HCV after OLT is still unclear. However, optimized immunosuppressive protocols are needed to im-

prove the outcome in patients with HCV-related liver failure after OLT in the future. The type of CNIs seems to play a minor role in this context, whereas CNIs levels seem to modulate the histologic course. Novel agents like MMF and sirolimus have to be evaluated for their effects on viremia and development of graft hepatitis posttransplantation. Steroid pulse therapy in patients with recurrent hepatitis C should be avoided if possible. Once the diagnosis of recurrent graft hepatitis is made, antiviral treatment of HCV recurrence with IFN and ribavirin should be initiated. New treatment approaches with PEG-IFN may be promising to effectively reduce the complications of recurrent HCV after OLT and to decelerate fibrosis progression after OLT.

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