Prophylaxis and treatment of recurrent viral hepatitis after liver transplantation

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Abstract
Chronic hepatitis B or C can cause severe liver diseases such as liver cirrhosis and hepatocellular carcinoma (HCC). Both viral infections together especially hepatitis c virus infection (HCV) are the major indication for liver transplantation in Western Europe and the United States. Recurrence of hepatitis B virus (HBV) or HCV infection after orthotopic liver transplantation (OLT) plays a key role for the outcome after liver transplantation concerning patient and graft survival rates. Allograft dysfunctions, cirrhosis of the allograft and graft failure are major complications after recurrent viral hepatitis. The survival after liver transplantation for HBV-related liver disease changed dramatically during the last two decades with results today comparable with non-HBV-related liver transplantsations. Availability of immunoprophylaxis with hepatitis B immunoglobulin (HBIG) as well as nucleoside/nucleotide analogues like lamivudine or adefovir in the pre- and post-transplant setting conferred to significant better results due to an efficient prophylaxis and the possibility of therapy of HBV reinfection of the allograft. New drugs such as entecavir, tenofovir and telbivudine for the treatment of chronic hepatitis B infections may offer even more opportunities in the transplant setting. In contrast, despite recent achievements in the treatment of HCV infection with pegylated interferons and ribavirin, patients with HCV cirrhosis or after liver transplantation are difficult to treat. Sustained virological response (SVR) rates in prophylactic and therapeutic approaches of HCV reinfection after OLT are only low compared to the pre-cirrhotic HCV infection. Moreover, best treatment duration and dosage of recurrent HCV infection with pegylated interferon in combination with ribavirin remains to be defined.

Keywords: liver transplantation; hepatitis B; hepatitis C; recurrent viral hepatitis

Introduction
Hepatitis B (HBV) and hepatitis C (HCV) infections have a high incidences worldwide with about 300 and 170 million infected individuals worldwide. Chronic HBV and HCV infections can lead to severe liver diseases such as liver cirrhosis with progression to liver failure as well as hepatocellular carcinoma (HCC). As a consequence, orthotopic liver transplantation (OLT) is often the only therapeutic option. Fulminant liver failure in acute hepatitis B is a rare indication for liver transplantation compared to the chronic HBV infection. Due to the differences in prophylaxis and in the efficacy of therapeutic options for either HBV or HCV, the course of the diseases after OLT is completely different and will be discussed separately.

Hepatitis B
Hepatitis B virus infection is a common cause for liver cirrhosis and end stage liver disease as well as hepatocellular carcinoma. Indeed, there were twice as much deaths caused by HBV than by HCV reported by the world health organisation (WHO). In the year 2000, almost 600 000 people died of diseases following Hepatitis B infection within 400 000 due to primary hepatocellular carcinoma [1]. However, due to several reasons, HBV infection is not the mayor indication for liver transplantation compared to hepatitis C.

The role of Hepatitis B infection in the transplant setting has changed in the last two to three decades. In the 1980s HBV infection was considered a relative contraindication for OLT because of the complications with poor outcome after OLT. The rate of
allograft reinfection was almost 100% and lead rapidly to progressive liver disease and cirrhosis due to the lack of treatment options for HBV reinfection [2,3]. In the 1990s strategies to prevent reinfection by administering hepatitis B immunoglobulin (HBIG) profoundly improved the outcome after OLT [4,5]. In addition, availability of new antiviral drugs such as nucleoside analogues like lamivudine or nucleotide analogues like adefovir changed the outcome again.

In the last 10–20 years results after HBV-related liver transplantation are reported to be at least as good as or even better than liver transplantation for other diseases [6,7].

**HBV reinfection after OLT**

HBV reinfection of the allograft was the major cause for very poor outcome after OLT in the 1980s [2,3]. Immediate exposure to circulating particles provoke HBV reinfection [8,9]. A continuous latent source of HBV reinfection is extrahepatic reservoirs such as spleen or white blood cells. At highest risk for HBV reinfection are patients with high HBV levels and high HBV replication rates prior to OLT [10,11]. Accordingly, there is a decreased survival rate after transplantation in patients being hepatitis B envelope antigen (HBeAG) positive prior to OLT [12]. Patients with acute liver failure as a consequence of HBV infection, cirrhosis resulting from HBV/HDV coinfection and patients with low HBV viral load pre-OLT showed a lower risk for HBV reinfection of the allograft [11,13,14].

Viral replication seems to be higher under drug-induced immunosuppression after OLT. Especially, steroids are thought to play a role in HBV recurrence after OLT. It has been shown that viral replication was stimulated by steroids influencing the glucocorticoid responsive enhancer region of the HBV genome [13,14]. As a consequence it has been proposed that corticosteroids are rapidly removed from immunosuppressive regimen to minimize the risk of HBV recurrence. So far there are no studies to proof the better outcome under this regimen although many centres practice the early withdrawal of steroids in HBV-patients after OLT.

Different HBV genotype on recurrence rate have been discussed, but as shown in two recent studies, difference in the recurrence rate between different HBV genotypes were not observed [15,16].

**Prevention of HBV reinfection in allograft**

As mentioned above, high viral load in the pre-transplant setting seems to be a high risk for HBV reinfection after OLT. Therefore, antiviral treatment prior to transplantation was thought to diminish HBV recurrence rates after OLT. Perioperative treatment with lamivudine is considered to be effective in some studies [17]. Moreover, patients with active viral replication and liver cirrhosis showed a significant improved clinical outcome under treatment with lamivudine. A decrease of Child-Pugh scores and the expansion of transplant free time have been reported in those patients [18].

Passive immunoprophylaxis with hepatitis B immunoglobulin (HBIG) was first introduced in the early 1990s and reduced dramatically reinfection rates after OLT. Samuel et al. showed significantly reduced HBV recurrence rates and improved survival in hepatitis B patients receiving long term application of HBIG after OLT [11]. The results have been confirmed in many studies thereafter [19]. The duration of HBIG application is essential in HBIG monoprophylaxis. Short term application did not improve the outcome with constant recurrence rates after OLT.

Nevertheless, HBV recurrence was detected in 15–50% of patients receiving indefinite HBIG prophylaxis. HBV recurrence under ongoing HBIG prophylaxis was caused by escape mutations with reduced affinity to monoclonal or polyclonal anti-hepatitis B surface (anti-HBs) antibodies [20]. High dose HBIG prophylaxis with anti-HBs titers >500 U/l could reduce development of hepatitis B surface antigen (HBsAg) escape mutants, but not completely prevent the occurrence of mutations. 10–20% of patients show HBV recurrence even under high dose HBIG application. Due to additional therapeutic opportunities HBIG should therefore not be used as monoprophylaxis to prevent HBV recurrence.

Inhibition of HBV replication is another approach to prevent HBV reinfection of the allograft.

Lamivudine was the first inhibitor of HBV replication approved for treatment of chronic hepatitis B. It is a nucleoside analogue that inhibits competitively the reverse transcriptase and termination of proviral DNA chain extension. While short-term results of lamivudine monoprophylaxis, administered pre- and post- liver transplantation, showed excellent results with a 1-year recurrence rate of 10% and seroconversion to HBsAg negativity in 100%, recurrence rates of 50% in long-term follow up were seen [21]. Lamivudine resistant mutants, mainly the mutations within the tyrosine-methionine-aspartate-aspartate (YMDD) motif of the HBV DNA polymerase, lead to high recurrence rates in the long term follow-up. In addition, immunosuppression has a great influence on mutation rate: Lamivudine resistance was detected in 15% in immunocompetent patients within the first treatment-year compared to 45% in immunosuppressed patients [22,23].

Monoprophylaxis with lamivudine is only partially effective to prevent HBV reinfection. Occurrence of YMDD-mutant strains lead to HBV recurrence under ongoing therapy with lamivudine. As a consequence, monoprophylaxis with lamivudine can not be recommended as a standard regimen. Especially due to the fact that YMDD mutants occur more rapidly in immunosuppressed patients.

The combination of HBIG and lamivudine as prophylaxis in the transplant setting was used to
reduce HBV recurrence rates [24]. Due to the fact that both, HBIG as well as lamivudine in a monoprophylactic approach, show higher recurrence rates than in prophylaxis with HBIG and lamivudine in combination, the best results were obtained in combination prophylaxis with a higher efficacy in suppressing viral replication [38,39]. Furthermore tenofovir is highly effective in chronic HBV infections presenting YMDD-mutants [40]. They are under clinical investigation in non-transplant and partially in the transplant setting. They may play a role in the future in prevention of HBV recurrence after OLT in the future.

A different approach to prevent HBV recurrence is active hepatitis B immunization. Sanchez-Fueyo et al. reported the first successful active immunization in 14 out of 17 hepatitis B patients (82%) after OLT by using standard hepatitis B vaccines in low risk patients after initial HBIG prophylaxis (more than six months) [41].

In contrast, in another series including 17 patients with HBV only 12% developed sufficiently antibodies against HBV [42]. The use of new hepatitis B vaccines showed promising results: In a clinical trial 20 patients received recombinant HBV vaccine and two immunostimulators, 80% developed titres of anti-HBs >500 U/l [43].

In summary, initial combination prophylaxis with HBIG and lamivudine should be used in the transplant setting to avoid HBV recurrence. Lamivudine-resistant strains occur prior to transplantation, lamivudine should be used add-on with adefovir or the newer antiviral drugs. Occurrence of lamivudine resistance after OLT leads to triple therapy using HBIG, lamivudine and adefovir to reduce the risk of additional adefovir resistance (add-on). Here again entecavir, telbivudine and tenofovir may be new therapeutic options in the future. HBIG may be removed after 1-2 years in low-risk patients by closely monitoring HBV-DNA levels.

Despite efficient prevention by administering HBIG, lamivudine and adefovir, new antiviral drugs such as entecavir, telbivudine and tenofovir may become more important in the transplant setting. Recent improvements in vaccination against hepatitis B post-OLT are very promising with decreasing costs of prophylactic regimen as a consequence.

**Therapy of recurrent HBV infection**

Treatment of recurrent HBV infection depends on the circumstances leading to HBV reinfection after OLT. Therapy with Interferon alpha showed very disappointing results. Influence on HBV viral load or liver disease doesn’t seem to be consistent [44]. Higher viral loads under immunosuppressive regimens may cause the lack of efficacy. Furthermore, treatment with interferon alpha can lead to side effects such as neutropenia.

The use of lamivudine to treat recurrent HBV infection after OLT showed promising results comparable with results in the non-transplant setting with inhibition of viral replication and improvement of liver disease. In a series including 52 patients with HBV recurrence after OLT in one year follow-up
60% with undetectable HBV DNA and 31% lost HBeAg [45]. Unfortunately the risk of developing lamivudine resistance seems to be even higher under immunosuppression. In the same study lamivudine-resistant YMDD-mutants were detected in 27% of patients within one year of treatment [45]. Another risk for developing resistances against lamivudine seems to be a high viral load [21].

To treat lamivudine resistant HBV infections adefovir was used very successfully in recent years. It was not administered as a first line therapy in the transplant setting but as a very sufficient treatment for YMDD mutants with HBV recurrence after OLT. Since recent data showed a diminished risk for developing adefovir resistant mutants in a patients receiving lamivudine additionally, combination “add-on”-therapy is favourable.

The use of new antiviral drugs as therapeutical approach after HBV reinfection of the allograft is currently under investigation. However, entecavir is sufficient in suppressing HBV replication in OLT patients with lamivudine resistance. Recent data showed a higher risk for developing entecavir-resistant mutants in the presence of lamivudine resistant mutant. To clear safety and efficacy of entecavir in the post transplant setting more datas are needed. Furthermore, tenofovir is highly effective in lamivudine-resistant HBV-infection in the non-transplant setting, as mentioned above [40]. In the transplant setting, sufficient suppression of HBV replication by tenofovir in 7 out of 8 patients was reported in patients with lamivudine-resistant HBV reinfection after OLT [46].

In summary, depending on the circumstances of HBV reinfection different strategies are possible to be used: In patients with recurrent HBV due to missing prophylaxis lamivudine monotherapy is still used in most centres. Due to high lamivudine resistance rates in immunosuppressed patients primary combination therapy with lamivudine plus adefovir or entecavir as monotherapy are highly discussed and partially recommended. Additionally, it was shown that early removement of corticosteroids from the immunosuppressive regimen lead to improvement of the long-term course in patients with HBV reinfection after OLT [47,48]. Therefore, most centres withdraw steroids within 6 month after OLT if possible. Advantages of immunosuppression with either cyclosporin or tacrolimus HCV recurrence course are not clearly defined [14]. In patients with known lamivudine resistance the add-on combination therapy with lamivudine and adefovir to prevent development of adefovir resistant mutants seems to be the most favourable therapy at the moment. Due to the high risk of lamivudine resistance after OLT, entecavir or tenofovir as a first-line therapy after OLT should be discussed in the future. Moreover, promising preliminary results may make tenofovir an important drug in patients with lamivudine-resistance in the transplant setting.

Management of anti-HBe positive donor organs; prevention of de novo infection

Apart from recurrent HBV infection originating from the organ recipient, so called de novo infection can result from reactivation of virus from the donor organ. Organs from donor with past resolved HBV infection signified by antibody to HBV core antigen (anti-HBc) may carry latent HBV in the liver. It has been shown that 78% of patients receiving organs from HBsAg negative but anti-HBe positive organs developed hepatitis B infection compared with only 0, 5% of patients receiving organs from HBs-Ag negative and anti-HBe negative donors [49]. Anti-HBs-antibodies or anti-HBe-antibodies in recipients seem to diminish the risk of developing hepatitis B [50].

Even though naturally or vaccine-induced HBV immunity have a certain degree of protection against de novo infection [51], the risk should not be taken and prophylactic therapy is recommended.

In HBV-positive recipients the strategies described above are sufficient for reinfection as well as de novo infection. In HBV-negative recipients prophylaxis with either HBIG or lamivudine seems to be equal. However, lamivudine is mostly used due to costs and simple management [52,53]. There is no evidence for better outcome with combination therapy with HBIG and lamivudine.

Re-OLT after HBV reinfection of the allograft

The need for retransplantation for HBV-related graft failure has diminished markedly as a consequence of effective prophylaxis and therapy of HBV recurrence. Indeed, recurrent hepatitis B after OLT is reduced to less than 10 percent.

If retransplantation is needed, older studies showed a very poor outcome reflecting the missing antiviral drugs at that time. In a recent study with just seven patients a survival after OLT in 86% (6 patients) without HBV reinfection of the new allograft due to efficient antiviral therapy with HBIG and lamivudine has been demonstrated [54]. As a consequence, retransplantation should be considered in the HBV-related graft failure due to excellent opportunities to avoid reinfection after re-OLT.

Hepatitis C

Hepatitis C virus infection is the most common indication for orthotopic liver transplantation in Western Europe and the United States [55]. Approximately 170 million people are infected worldwide [56]. About 75–85% of people infected with hepatitis C develop chronic hepatitis, of which thirty percent develop liver cirrhosis with a risk of liver failure [57]. In addition, the risk for hepatocellular carcinoma is augmented in these individuals within 10–20 years of infection with hepatitis C [58].
Prevention of HCV reinfection after OLT

The most effective way to prevent recurrent HCV disease after OLT is viral elimination prior to transplantation. The benefit of reduction of viral load without eradication before organ transplantation is not clear regarding the fact of obligatory augmentation of HCV viral load after transplantation [66]. Efficacy of combination therapy with pegylated interferon (Peg-IFN) and ribavirin (RBV) is lower in patients with liver cirrhosis than HCV patients without cirrhosis. A study administering Peg-IFN plus ribavirin in non-cirrhotic HCV patients achieves a SVR of 42–46% for genotype 1 and 76–80% in genotype 2 and 3 [81, 82]. In patients with decompensated liver disease after application of standard interferon (IFN) 3MU 3x/week and RBV 1-1.2g/day SVR could be achieved in 42%; non-1-genotype 50% and genotype 1 12% [83]. 12 of 15 patients with SVR prior to transplantation did not show recurrence after OLT. In addition, side effects of the antiviral therapy are increased in those patients with the risk of decompensation of the cirrhosis during therapy. Only 17–25% of patients with liver cirrhosis or severe fibrosis are eligible for antiviral therapy prior to transplantation [83].

Another approach to prevent HCV recurrence after OLT is prophylaxis by using hepatitis C antibody therapy post-transplantation. Hepatitis C immune globulin (HCIG) delayed development of acute hepatitis C in chimpanzees, but did not prevent HCV infection [84].

The only published phase II study using HCIG (Civacir®) dosages of 75 mg/kg or 200 mg/kg to prevent HCV recurrence after OLT showed disappointing results: infection could not be prevented, lowering of RNA levels were not sustained [85]. As a consequence there is no role of HCIG in the transplant setting to prevent HCV reinfection. Currently monoclonal antibodies against epitopes in the envelop regions of HCV are tested in transplant patients.

In summary, the best prevention of HCV recurrence after liver transplantation is achievement of SVR prior to OLT. However, most patients in the transplant setting are not stable enough to undergo antiviral treatment before OLT. Due to disappointing results HCIG has currently no meaning.

Preemptive HCV therapy after OLT

Prophylactic therapy is mostly not feasible and rarely successful in preventing HCV recurrence as mentioned above. To increase the outcome in HCV patients after OLT by reducing the incidence of HCV recurrent infection with histological alteration of the liver, preemptive interferon therapy in the early period after transplantation is used. In clinical trials interferon (pegylated or conventional) as monotherapy or in combination with ribavirin was administered up to 6–8 weeks after OLT.

Sheiner et al. randomized patients up to 2 weeks after OLT to interferon monotherapy (3 MU
vs no treatment). While incidence of recurrent hepatitis was reduced significantly, HCV RNA levels were not changed [86]. Similar results were shown in a small study including 24 patients with a delayed onset of reinfection in the treatment group [87].

In another study 54 patients were randomized and treated within 3 weeks after OLT either with 180 μg peginterferon alfa-2a for 48 weeks or did not receive antiviral treatment. In the 24 week follow up, treated patients showed significant lower RNA levels and less histological changes than patients without treatment. Only two patients (8%) showed sustained virological response (SVR) in the treatment group. Rejection rate was similar in both groups (12 vs 21% \( P = 0.5 \) [88].

Preemptive treatment within 2–6 weeks compared standard interferon (IFN) with pegylated interferon (pegIFN) alpha-2b in doses of 3MU 3x/week or 1.5 μg/kg 1x/week and IFN or pegIFN in combination with ribavirin (600 mg to 1.2 g/day) for 48 weeks. SVR occurred in 9.1%, with most responders in the combination group.

But only 15% of patients received full-dose treatment for 48 weeks, dose reduction and discontinuation were necessary in 85 and 37%. 27% showed severe adverse events under therapy. In this study only 51 (41%) of 124 patients were clinically stable enough to participate in this study [89].

Early treatment of HCV recurrence was performed with the intention to prevent histological damages of the liver and to possibly achieve better virological response rates. Summarizing these studies SVR in preemptive interferon HCV therapy is very low and the histological benefit that could be expected out of therapy without SVR remains unclear. In combination with ribavirin SVR rates are higher, but not convincing. But only 40% are able to undergo preemptive treatment because of clinical and biochemical conditions. In over 50% dose reductions were necessary. Surprisingly, acute rejection was not seen more often under therapy than in control groups.

Post-transplant recurrent HCV treatment

Due to the poor efficacy rates of preemptive HCV therapy after OLT and the fact that only 40% of patients post transplantation are eligible to receive very early preemptive therapy, treatment of HCV recurrent disease is more common. Mostly indication to therapy is the histological evidence of recurrent HCV infection. Some centres take biopsies regularly after 6-12-24 month or regarding the clinical and biochemical course. Although, uniform concepts for histological analysis post OLT are missing. Most transplant centres treat recurrent HCV only if histologic liver injury is associated. There a no controlled trials to guide treatment of HCV after OLT.

Regarding recent studies, combination therapy with peg-interferon and ribavirin is superior to the monotherapy with either standard interferon or pegylated interferon. In some series using monotherapy with interferon low SVR rates in between 0–12% were detected [88,90,91]. Interestingly Chalsani et al. reported an improvement of histology and lower levels of HCV RNA after 48 weeks of therapy using Peg-IFN. Alpha-2a 180 μg 1x/week even though only 3 patients (12%) showed SVR [88]. Ribavirin monotherapy for an average of 23 month was analyzed in 18 patients after OLT. Decrease of transaminases was detected.

No change in histology or HCV levels have been seen [92]. Using combination with standard interferon and ribavirin better results were achieved, but SVR rates in between 7–30% (~21%) are still poor [79,93,94–101].

Samuel et al. treated patients with IFN 3MU 3x/week and ribavirin 800–1000 mg daily for 48 weeks; SVR rates of 21% are disappointing. In addition, he reported no histological improvement 6 month after therapy in all patients [93].

Comparable to patients with chronic HCV in the non-transplant setting pegylated interferon seems to be more efficient than standard interferon. An open labelled study with patients receiving Peg-IFN alfa-2b and ribavirin showed SVR rates of about 26% [63].

Due to severe side effects interruption of therapy was required in 38% [63].

Dumortier et al. reported SVR rates of 45% and an improvement of histology [102]. Those are uncontrolled series with small patient numbers and results may be too promising.

Neff et al. showed SVR 21–28% after therapy over 48 weeks. However relatively good results have been seen in a small study using triple therapy with IFN, RBV and amantadine for 48 weeks in post-OLT patients with previously nonresponse [103]. Due to increased side effects (e.g. anaemia, leucopoenia,) of the antiviral therapy after transplantation dose reduction or discontinuation is more likely. To avoid early termination of treatment with lower success rates as a consequence, growth factors such GM-CSF and erythropoietin are used. [63,104].

Patients present in up to 10% with a so called fibrosing cholestatic hepatitis (FCH). Rapid progression to liver failure typically with severe jaundice lead to extremely high mortality rate [70]. Due to the clinical situation therapeutic options are limited. In a series of seven patients receiving interferon alpha and ribavirin in combination for an average of 32 month only two survived. However, indefinite treatment seems to be beneficial in these patients who respond to treatment [105].

Summarizing, the results of antiviral treatment of HCV recurrence after OLT are still disappointing. However, application of pegylated interferon and ribavirin in combination shows the best outcome with the highest SVR rates and should be administered as standard therapy in this setting. But there are no guidelines, especially concerning duration and dosage of the antiviral treatment. Histological improvement after therapy without SVR
is controversial. A major problem leading to low SVR rates are increased side effects that make dosage reduction or discontinuation of the therapy necessary. Application of growth factors such as GM-CSF may help to reduce numbers of discontinuation with better outcome as a consequence.

Re-OLT after HCV reinfection of allograft

Re-transplantation as the only therapeutical option for patients with HCV-related graft failure is controversial due to the fact of inferior survival and limited availability of donor organs [59,66]. Survival after liver re-transplantation for recurrent HCV infection is reported to be significantly shorter than after re-transplantation for other causes of graft loss showing a 5-year survival of about 30% [106]. In a series randomizing 357 patients survival at 1.3 and 5 year was 57, 55 and 54% for HCV positive patients compared to 65, 63 and 61% in HCV negative recipients [107]. In series including few patients no statistically different survival rates haven’t been seen [108,109]. The clinical situation prior to retransplantation can explain different survival rates in clinical trials: in some series no different survival rates compared to other reasons leading to retransplantation have been detected when MELD score was less than 20 [110]. However, guidelines for retransplantation for HCV-related graft failure are difficult to create due to the inhomogeneity of cases and it still remains an individually based decision.

Conflict of interest statement. None declared.

References


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77. Sheiner PA, Schwartz ME, Mor E et al. Severe or multiple rejection episodes are associated with early recurrence of hepatitis C after orthotopic liver transplantation. *Hepatology* 1995; 21: 30–34

104. Wright TL. How can we identify better those with recurrent hepatitis C who will respond to therapy? What are the optimal treatment regimen and treatment duration? *Liver Transpl* 2003; 9: S109–S113

105. Gopal DV, Rosen HR. Duration of antiviral therapy for cholestatic HCV recurrence may need to be indefinite. *Liver Transpl* 2003; 9: 348–353


