

EASL Meeting Report

**Report of the Monothematic EASL Conference on
Liver Transplantation for Viral Hepatitis[☆]
(Paris, France, January 12–14, 2006)**

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1. Introduction

This EASL monothematic conference aimed to review in a 2-day meeting the most recent aspects of liver transplantation for viral hepatitis. Experts from Europe and overseas exchanged their views and expertise on the different aspects of liver transplantation and viral hepatitis, and presented the most updated information available at the time of the conference which was held in Paris, France, January 12–14, 2006.

1.1. Mechanisms of HBV infection

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The outcome of HBV infection is the result of complicated viral–host interactions that involve different actors, including the immune system, viral mechanisms, the liver microenvironment and the host anti-viral responses. For instance, HBV tolerance appears as the result of an “immune defect”, with a reduced T-cell-

dependent Th1 response. HBV is the prototype of the hepadnavirus family, sharing a distinctive strategy for replication. HBV replication occurs in the cytoplasm within viral capsids (core particles), where a terminally redundant RNA replication intermediate is converted, by the virally encoded RNA-dependent and DNA-dependent reverse transcriptase/polymerase, into a specific open circular (OC) duplex DNA without amplification. Transcription in the nucleus of the 1.1 genome-sized pre-genome RNA from the cccDNA is the critical step for genome amplification and ultimately determines the rate of HBV replication. A continued productive HBV infection requires a persistent population of transcriptionally active cccDNA molecules to ensure a stable source of pre-genome RNA for replication and the templates for mRNA synthesis and viral proteins production. HBV cccDNA has proven to be relatively insensitive to the therapeutic regimens based upon the use of antiviral drugs currently used to suppress HBV replication in chronically infected patients and the persistence of viral cccDNA is the basis for the rapid recurrence of HBV replication upon discontinuation of treatment. Recent studies have shown that cccDNA do decline after 48 weeks of treatment with adefovir dipivoxil or lamivudine plus pegylated interferon (from 1 to 2 logs) but it can be inferred, based upon a mathematical modelling, that it would take more than 14 years to completely clear a HBV-chronically infected human liver of intracellular cccDNA.

[☆] This Conference was organized by the EASL. Authors of the paper were members of the organizing committee. Didier Samuel was the chairman of the conference.

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Nuclear cccDNA molecules have been shown to be organized into a chromatin-like structure as a viral minichromosome that has been shown to consist of both histone and non-histone proteins, including the virally encoded core protein, the cellular acetyltransferases PCAF and CBP and the histone deacetylase 1 (HDAC1). It has been shown that HBV replication is regulated by the acetylation status of the cccDNA-bound H3/H4 histones. Accordingly, class I histone deacetylases inhibitors induced an evident increase of both cccDNA-bound acetylated H4 and HBV replication. Interestingly, histones hypoacetylation and HDAC1 recruitment onto the cccDNA in liver tissue correlates with low HBV viremia in hepatitis B patients. A similar epigenetic regulation of HBV transcription/replication cycle might be involved in the strong suppression of viral replication and gene expression that characterize the “occult” HBV infection, i.e., the presence of both integrated and episomal HBV genomes in the liver of HBsAg negative individuals with or without circulating antibodies to HBsAg (anti-HBs) and/or hepatitis B core antigen (anti-HBc). In the Mediterranean basin, about one-third of the patients with chronic hepatitis C carry such a cryptic infection, which is associated with advanced disease, cirrhosis and an increased risk to develop HCC. The mechanisms through which occult HBV infection may produce or contribute to liver damage are at present poorly defined. Recent studies on both humans and woodchucks convalescent from acute HBV and WHV infections have shown that the lifelong persistence of small amounts of replicating viruses induces a very mild liver necroinflammation that may last for life. Such “occult” HBV infection may become clinically relevant in the cases of immunosuppressed patients.

1.2. Treatment of HBV-cirrhosis

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The goal of treatment for patients with compensated HBV-cirrhosis is to prevent decompensation and hepatocellular carcinoma (HCC) and to reverse cirrhosis. For patients with decompensated cirrhosis, the main goal is to improve liver function, thereby obviating the need for liver transplant. Moreover, for patients who require liver transplantation, another aim of treatment is to decrease the risk of HBV recurrence post-transplant. In all these situations, the key is to maintain viral suppression and reduction in hepatic necroinflammation. Available treatments of hepatitis B include standard interferon (IFN) alfa, pegylated IFN alfa, lamivudine, adefovir, and entecavir.

IFN is not recommended for patients with decompensated cirrhosis because of the risk of hepatitis flares and infectious complications. However, clinical trials of IFN showed that patients with clinically and bio-

chemically compensated cirrhosis and adequate cell counts have a similar side effect profile as those without cirrhosis and the risk of hepatic decompensation is not increased. Long-term follow-up studies reported that patients with a sustained response to IFN have a lower risk of hepatic decompensation compared to those who did not respond. A beneficial effect of IFN on HCC development has been reported in some Asian studies but not in European or US studies.

Lamivudine suppresses HBV replication, normalizes ALT levels and reduces hepatic necroinflammation in patients with chronic hepatitis B. It is well tolerated in patients with cirrhosis including those with decompensation. A beneficial effect of antiviral therapy on the clinical outcome of patients with HBV-cirrhosis was demonstrated by the Asian trial in which lamivudine was found to significantly reduce the rate of disease progression, 7.8% vs. 18% ($p = 0.001$) and HCC development, 3.9% vs. 7.4% ($p = 0.047$) [1]. Lamivudine has also been shown to stabilize or improve liver function in patients with decompensated cirrhosis thereby obviating or delaying the need for liver transplant. However, clinical improvement is slow and may take up to 6 months [2]. Moreover, HCC can still occur even in patients with clinical improvement. For patients who are not transplant candidates, lamivudine can be a life-saving treatment, but a major concern is the risk of viral resistance, and the beneficial impact on clinical outcome is reduced in the case of viral resistance. Prospective studies to evaluate the efficacy of adefovir and entecavir in preventing or reversing adverse clinical outcomes in patients with HBV-cirrhosis have not been reported, but, based on data from lamivudine studies, it is anticipated that similar benefit can be observed. The major advantage of adefovir and entecavir is a lower rate of drug resistance (0% at 1 year, 29% at 5 years for adefovir). Entecavir is more potent but its long-term safety remains to be established. Antiviral efficacy of adefovir is variable and long-term use may be associated with a low risk of nephrotoxicity. Adefovir has been shown to be well tolerated and effective in suppressing lamivudine-resistant HBV in patients with decompensated cirrhosis with resultant clinical improvement [3]. Adefovir resistance is uncommon in patients who continued to receive lamivudine. The optimal antiviral strategy seems to be an association of different nucleos(t)ides analogues, in order to minimize the risk of viral resistance, viral breakthrough, and liver disease decompensation. Nevertheless, the best association is not known yet.

1.3. Timing of liver transplantation in patients infected with HBV

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HBV-induced liver disease represents 10% of the indications for liver transplantation in Europe and this has been very stable over the past 10 years. The timing of liver transplantation in the case of HBV infection depends on both the clinical and virological status of the patients. Therefore, a clinical score, involving these two different aspects of HBV liver disease, seems to be highly relevant [2]. In addition, rather than a score value at listing (MELD or others), the variation of this score during the waiting period seems to be the most relevant for the decision of transplantation.

It is well known that the presence of HBeAg and the detection of a high viral load (usually $>10^5$ copies/ml) pre-transplantation is associated with an increased risk of graft HBV re-infection [4–6]. Consequently, a consensus gradually emerged that suppression of viral load prior to transplantation should be an important independent goal. The development of the new nucleos(t)ide analogues has revolutionized the treatment of HBV. This also includes patients with end-stage HBV cirrhosis pending or already listed for liver transplantation. These well-tolerated anti-viral agents such as lamivudine and adefovir were shown to have a rapid and potent anti-viral effect. Thus, administration of lamivudine to HBV decompensated patients with a viral load $>10^5$ copies/ml is associated with successful suppression of viral load in 60–90% of patients prior to transplantation. However, severity of liver disease (as manifested by elevated bilirubin and serum creatinine levels as well as viral load) at time of treatment initiation is an important factor in predicting success of anti-viral therapy and delaying time of transplantation. Thus, clinicians who prescribe lamivudine to decompensated patients must differentiate between the anti-viral response, which often is rapid and impressive, and clinical improvement, which may take 6 months and longer to achieve. Regardless if both goals are achieved, suppression of viral load $<10^5$ copies/ml and preferably to 10^2 – 10^3 copies/ml remains an independent goal since a low viral load, pre-transplantation, reduces the risk of post-transplantation HBV re-infection [4,7]. Pre-transplant administration of lamivudine is not always effective and 20–25% of treated patients will not survive until transplantation. A major reason for lamivudine failure is the emergence of the YMDD mutant with an incidence of ~20% in the first year of treatment. Thus, lamivudine recipients must be monitored closely by quantitative HBV-DNA assays every 1–3 months and switched to another analogue, which is effective against YMDD mutants. It is likely that the new anti-viral agents such as adefovir, entecavir or tenofovir, which are effective against YMDD mutants, will enhance the options for successful pre-transplant therapy. The importance of combination as opposed to sequential therapy in prevention of breakthrough must also be clarified in the near future. Suppression of viral load and improvement of synthetic

liver functions may lead to removal of transplant candidates from the waiting list. Indeed the estimated 3-year survival in lamivudine recipients who survived 6 months of therapy with improved liver functions was 88% on continued treatment [2]. In conclusion, the impressive results in reversal of decompensation must be balanced on an individual basis against the risk of emerging breakthrough mutants as well as development of hepatocellular carcinoma and losing or delaying the option of liver transplantation. Thus, patients with HBV infection and discussion of liver transplantation should be referred to a transplant centre before the choice of anti-viral treatment.

1.4. Mechanisms of graft reinfection, and natural history

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The risk of HBV reinfection directly correlates with the viral load before OLT. If re-infection does occur in most cases, the course of the disease is enhanced compared to the situation before OLT. The progression of HBV-related liver disease is accelerated starting 2 months after OLT and may result in re-transplantation or death of the patients. In the absence of treatment, prognosis after liver transplantation is significantly poorer in the case of HBV infection. Factors associated with HBV recurrence are the status of viral replication at the time of transplantation and the type of liver disease (cirrhosis, fulminant hepatitis, HDV co-infection). When HBV-reinfection does occur, enhanced HBV replication is found, compared to the situation before OLT. Several molecular mechanisms are involved to explain increased HBV replication in these patients. 1. There is a glucocorticoid-responsive element in the HBV genome and glucocorticoids stimulate HBV-dependent transcription [8]. 2. Immunosuppression after OLT suppresses the virus-specific immune response. After OLT more frequently wild-type HBV is re-selected and this can result in a better replication fitness of the virus. 3. Mutations selected in the HBV preS region can result in a cytotoxic HBV strain, which is associated with fibrosing cholestatic hepatitis [9,10]. After OLT, the selection of cytotoxic HBV strains leads to a new histological picture that can be observed in the course of HBV-related liver disease and was described as fibrosing cholestatic hepatitis. These patients present with jaundice rapidly progressing to hepatic failure. Liver histology is characterised by cholestasis with an inflammatory infiltrate and fibrosis. Hepatocytes show a very prominent staining for HBsAg in the cytoplasm and it is thought that a direct cytopathic effect of viral proteins is the pathophysiological clue for this disease entity. After these observations were made in the early 1990s, new approaches were developed in order to block HBV-reinfection after OLT and these efforts resulted in effective prophylactic regimens.

1.5. General overview on HBV prophylaxis

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The spontaneous risk for HBV reinfection after transplantation is around 80%. Thus 20% of patients have a spontaneous disappearance of HBsAg, which was more frequent in patients transplanted for acute liver failure [4]. From a historical point of view, the first therapeutic breakthrough was the long-term administration of high doses of anti-HBs Ig (HBIG) that reduces drastically the rate of HBV recurrence. In the Paul Brousse series of 284 patients, the overall 10-year HBV recurrence rate was 27%, which was higher in patients with viral B cirrhosis (50%) than in those with fulminant hepatitis (0%) or with viral B-Delta cirrhosis (15%) [11]. Moreover, it was significantly higher in patients with viral B cirrhosis who were serum HBV-DNA positive before transplantation than in those who were HBV-DNA negative (80% vs. 27%). The advent of nucleos(t)ide analogues was the second breakthrough. Lamivudine alone without HBIG administration has been given as a prophylaxis. The medium-term results showed that HBsAg remained positive in the serum of a significant percentage of patients and that HBV DNA reactivation due to viral breakthrough was increasing with time to 40% at 3–4 years post-transplant [12]. Results of adefovir monotherapy post-transplantation are not yet available. The third breakthrough was the combination of HBIG with nucleos(t)ide analogue, which is able to reduce the recurrence risk to less than 10%, even in patients at high risk of HBV recurrence [6,13]. The result of these progresses during the past 15 years was that patients receiving adequate immunoprophylaxis have a similar 10-year survival rate to that of patients trans-

planted for other liver diseases [14]. Nevertheless, the excellent results of combined post-transplant prophylaxis and the high cost of HBIG have put in front the role of HBIG in these prophylaxis strategies. It has been suggested that the dose of HBIG in combination therapy can be reduced, and that IM HBIG can safely replace IV HBIG. There are ongoing studies on the possibility of discontinuation of HBIG after several weeks or months, with the introduction of HBV vaccine, or maintenance of nucleos(t)ide analogues. The future will probably see the emergence of a “à la carte” HBV prophylaxis taking into account the individual risk of HBV recurrence and the advantages and drawbacks of HBIG and/or antiviral therapy (Fig. 1).

1.6. HBIG prophylaxis – place and indications

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Hepatitis B immune globulin (HBIG) was the first therapy to show efficacy in preventing HBV reinfection in liver transplant recipients. The exact mechanism of action of HBIG is unknown, but it has been suggested that HBIG can bind circulating virus and prevent binding to receptors on hepatocytes, and that, in vitro, anti-HBs IgG can enter hepatocytes and bind HBsAg, and therefore prevent secretion of HBsAg and HBV virions from cells.

HBIG was used as prophylactic monotherapy until the mid-1990s, but with the availability of lamivudine and other safe and effective nucleos(t)ide analogues, the standard of practice quickly shifted to combination prophylaxis using oral antivirals (lamivudine, adefovir and entecavir) in combination with HBIG. The combination of HBIG and oral antivirals is attractive since these drugs have different mechanisms of action and

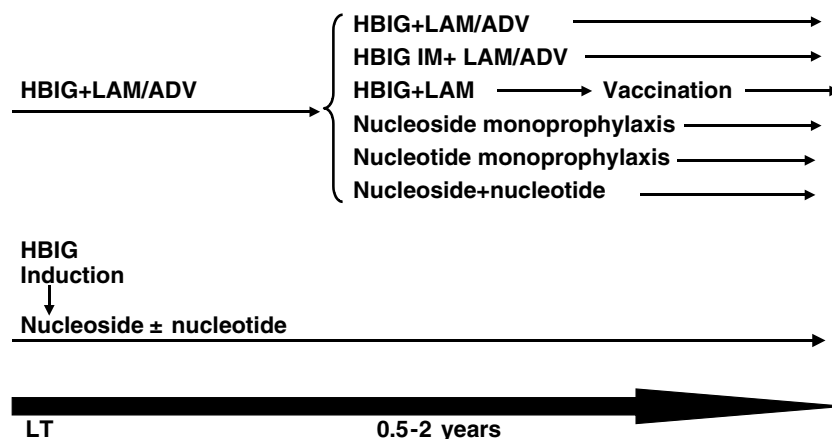


Fig. 1. Future strategies of prophylaxis of HBV reinfection post-transplantation. In the conference, there was an agreement to consider that an indefinite prophylaxis was necessary. The possibility to stop HBIG after several months or years post-transplantation can be envisaged only in non-replicators (HBV DNA < 10⁵ copies at LT) and with great caution in replicators (HBV DNA ≥ 10⁵ copies at LT). Adapted by Samuel from Seehofer and Berg Transplantation 2005;80:S120–S124.

different drug resistance patterns [6]. Indeed, though not compared head-to-head in randomized controlled trials, the outcomes achieved with HBIG in combination with antivirals appear superior to those achievable with HBIG or lamivudine monotherapies. Studies of the efficacy of combination prophylaxis using other antivirals (adefovir or entecavir) and HBIG have not been published but the efficacy of these agents would be expected to be at least comparable to those achieved with lamivudine and HBIG. Thus, HBIG is a central part of prophylaxis for LT patients and combination therapy using HBIG plus antivirals is the “standard” to which new prophylactic strategies will be compared.

Prior studies have shown that failure of HBIG prophylaxis during the early post-LT period was due to insufficient dosing of HBIG, and was more frequent in patients with high HBV replication. Anti-HBs titers associated with efficient prevention of re-infection were established during the HBIG monotherapy era and recently revisited in the combination therapy era. In patients on HBIG and concurrent lamivudine therapy, HBsAg neutralization was achieved with anti-HBs >300 IU/L during week 1 and >200 IU/L during weeks 2–12. However, the HBIG requirements during weeks 1–12 were higher in those patients who had HBV DNA levels >10⁵ copies/mL at the time of transplantation [15]. With the increasing availability of effective antivirals to suppress HBV DNA pre-LT, lower doses of HBIG may be needed in the early post-LT period.

The main limitations of HBIG as part of a long-term prophylactic strategy are its high cost, the need for parenteral administration, and the low risk for blood-borne infections. The emergence of mutations involving the “a” determinant of the HBV surface protein causing resistance to HBIG is a recognized complication of prolonged HBIG monotherapy but appears to be rare with combination therapy. The cost and safety issues have prompted studies of alternative anti-HBs agents and alternative treatment protocols using lower doses and shorter duration of HBIG. Alternative forms of antibody therapy studied include high-titer anti-HBs from plasma donors (economical but clinical experience limited), monoclonal antibodies (cost may still be issue, but presumably supply and safety not a concern), and vaccination (economical but antibody responses inconsistent). Lower dose protocols, including those using intramuscular HBIG, report efficacy rates of ≥90% in the first 1–2 years of follow-up, and are highly cost-effective [16]. Similarly, protocols using combination HBIG plus lamivudine for the first 1–6 months post-LT and then discontinuing HBIG report a low failure rate ~10% after 1–2 years follow-up [17,18].

In all studies of prophylaxis in the transplant setting, the risk of HBV re-infection has been related largely to the level of HBV replication at time of transplantation [7]. Thus, the available data suggest treatment strategies

should differ for patients with and without HBV replication before transplantation. Most experts recommend combination therapy of HBIG and antivirals for “replicators” or those with drug-resistant HBV infection. For “non-replicators”, discontinuation of HBIG after a defined period of time may be an option. However, the decision to stop HBIG must be tempered by the recognition that studies evaluating HBIG discontinuation in patients on combination therapy are limited to a few years of follow-up, and the risk of HBV recurrence may increase with time off HBIG. Additionally, there is evidence of HBV-DNA in serum, liver or peripheral blood mononuclear cells in HBsAg negative transplanted patients on HBIG or combination prophylaxis, suggesting that a persistent reservoir for re-infection exists in many patients [11]. Thus, a safer long-term prophylactic strategy may be to replace HBIG with a second antiviral agent or possibly by HBV vaccination.

In summary, HBIG combined with antiviral drugs is a highly effective form of prophylaxis in HBV-infected transplant recipients and this combination therapy remains the “standard”. Cost and the inconvenience of parenteral administration are the main limitations of HBIG prompting consideration of alternative agents and protocols. Replication status is the primary determinant of prophylaxis failure and as such should be the primary factor influencing current and future combination protocols.

1.7. Nucleos(t)ide analogues after transplantation

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The use of nucleos(t)ide analogues after transplantation has increased with time and is dependent upon recipient and liver graft parameters. In HBsAg-positive recipients, indefinite hepatitis B immunoglobulin (HBIG) immunoprophylaxis is required, and the adjunct of a nucleos(t)ide analogue is conditioned by pre-LT virological status. The cut-off between “replicators” and “non-replicators” is around 10⁵ copies/ml [7]: (1) In pre-LT active carriers (HBV DNA > 10⁵ copies/ml), nucleos(t)ide analogues are introduced in order to decrease viral load prior to LT. After surgery, combined prophylaxis with nucleos(t)ide analogues (lamivudine in lamivudine-sensitive patients, or lamivudine and/or adefovir in YMDD carriers) and HBIG led to less than 10% HBV recurrence. In this setting, the use of nucleos(t)ide analogues is essential and their withdrawal is not recommended in such patients; (2) in pre-LT inactive carriers (HBV DNA < 10⁵ copies/ml), combined prophylaxis with nucleos(t)ide analogues is also useful because this strategy is associated with very low risk of recurrence post-LT. If attempted, HBIG withdrawal should be considered at least 1–2 years after LT, and must be carefully monitored in patients treated with

both lamivudine and adefovir. The perspective of long-term prophylaxis with two analogues is promising, but requires comparative trials in the near future; (3) in inactive carriers with undetectable viremia, pre-LT requires HBIg prophylaxis alone without an analogue.

1.8. The role of the HBV vaccine

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The efficacious combination of HBIg and nucleos(t)ide analogues has long-term disadvantages in terms of cost, side effects and inconvenience for the patient. Thus, other strategies such as active HBV vaccination have been investigated. Studies have shown that conventional HBV vaccination of cirrhotic patients awaiting liver graft and of transplanted patients is disappointing due to relatively weak production of protective anti-HBs antibodies in these patients, who have an impaired immune system response related to the disease or to immunosuppressive agents. Therefore, alternative strategies of vaccination have been developed to overcome non-responsiveness: additional vaccine doses, double-dose vaccination, addition of pre-S-epitopes to HBsAg vaccine, DNA vaccines, use of more immunogenic adjuvants or immune-stimulating agents (e.g., GM-CSF).

Nonetheless, results of double-dose vaccination are difficult to analyze because the response rate in liver transplant patients, defined as anti-HBs antibodies higher than 10 U/l, is achieved in 20–80% of cases, and the only available study using a vaccine containing pre-S1, pre-S2 vaccines, showed only a 7% response rate. Anti-HBs antibodies titer higher than 100 IU/l was observed in less than 20% of the patients [19,20]. Promising preliminary results were found in studies using new adjuvants such as monophosphoryl lipid A (MPL) and Quillaja saponaria QS 21, which, in healthy adults, produced up to 10-fold-higher anti-HBs titers than standard hepatitis B vaccine. In a transplanted population, a better response rate, varying between 40% and 80%, was also observed but will require confirmation in a larger cohort of patients [21]. In a small cohort, a vaccine using MPL as adjuvant gave a low anti-HBs response. A difference observed among studies is the discontinuation or not of HBIg during vaccination. In the study from Berlin giving the best results of vaccine, the vaccine contains these 2 combined MPL and SQ21 adjuvant and HBIg were maintained during vaccination. The hypothesis is that starting the vaccine before discontinuation of HBIg favours the formation of antigen–antibody complexes. It increases the uptake of these immune-complexes through Fc-receptors of antigen presenting cells (APC), which might enhance

immune responses. Thus, results of vaccination are controversial and should be analyzed on large cohorts.

1.9. Treatment of HBV recurrence and the role of retransplantation

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The current prophylactic strategy which associates HBIg with nucleos(t)ide analogues is efficacious in reducing the risk of HBV recurrence. Nevertheless, HBsAg positivity after liver transplantation may occur due to failure of prophylaxis (HBsAg “escape” mutants, YMDD mutants, resistance to adefovir), donor-acquired infection (de novo infection) or acquired HBV infection (sexual acquisition post-LT).

Therapeutic management should be individualized: withdrawal of HBIg and the start of nucleos(t)ide analogues in HBsAg “escape” mutants, treatment with adefovir for YMDD mutants, and the addition of lamivudine in cases of adefovir resistance [22,23].

Most post-transplant HBV infections are associated with HBeAg positivity and high serum titers. The clinical outcome is unpredictable and may range from mild hepatitis to severe liver graft failure. Nucleos(t)ide analogues can achieve HBeAg and HBsAg seroconversion and improve liver function. De novo infection should be treated as early as possible after diagnosis with a combination of nucleos(t)ide analogues. Retransplantation for HBV recurrence is mostly historical and there is no current specific contraindication.

1.10. Liver transplantation and delta infection

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There has been a drastic decline in HDV infections in developed countries due to the control of HBV infection. The prevalence of Delta coinfection in HBV carriers in Italy declined from 25% in 1981 to 8% in 1997. Indeed, HDV requires obligatory helper functions of HBV, and can be transmitted only after prior HBV infection. Therefore, the efficiency of prophylaxis against HBV recurrence significantly decreases the risk of such recurrence following LT. For example, results of an experience by the group of Turin on 117 HDV carrier transplanted patients given prophylaxis with HBIg did not reveal any clinical recurrent HDV over a mean post-LT follow-up of 34 months, suggesting that current HBV prophylaxis can prevent HDV recurrence. Transient subclinical HDV reinfection (HDV RNA positive by PCR) was observed in only 5% of patients without any clinical consequence. Thus HDV infection does not appear as a current problem with the accurate control of HBV reinfection.

2. Liver transplantation and HCV infection

2.1. Mechanisms of HCV infection

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Hepatitis C virus (HCV) is a major public health challenge. In the course of HCV acute infection, about 20–50% of patients eliminate the virus, whereas 50–80% of patients will develop chronic infection leading to cirrhosis and ultimately to hepatocellular carcinoma within a few decades. HCV is a single-stranded ribonucleic acid (RNA) virus that belongs to the Flaviviridae family able to develop strategies to escape the immune system, generally unable to confer viral clearance, leading to progressive liver injury. Knowledge of its mechanisms of infection and persistence is limited by the absence of a simple productive cell culture system. The various components of the host innate and adaptive immune system are involved to different degrees in the outcome of HCV infection. Several lines of evidence suggest that HCV alters host defenses and innate immunity early during acute infection through a variety of complementary mechanisms, thereby facilitating the establishment of chronic infection. For example, HCV proteins counteract non-specific innate responses in blocking NK cell functions, particularly interferon (IFN) production, through inhibition of IFN signaling pathways. The humoral response is activated during HCV infection and a strong and specific neutralizing response has been recently described as being inversely correlated with HCV RNA kinetics [24]. Nevertheless, this capacity to induce protective immunity directed against HCV remains controversial, and the role, if any, of the neutralizing response in control of HCV infection or persistence is not clear.

The intensity, kinetics and specificity of the cellular response are also associated with the outcome of HCV infection. In acute infection, polyclonal, vigorous CD4+ responses coordinated with CD8+ T-cell responses directed against HCV epitopes predict recovery, and these multispecific responses persist for years after spontaneous resolution [25]. Conversely, impaired phenotypes and functioning of CD8+ T cells (CTL), and weak delayed or transient specific CD4+ cells, are observed in patients who subsequently develop persistent infection [26]. Moreover, this impaired cellular response is responsible for immune selection pressure on HCV, which promotes escape mutations contributing at least in part to HCV pathogenesis.

Pathogenesis of HCV-induced liver injury is mainly mediated by the immune system, and HCV itself does not seem to be cytopathic toward liver cells. The only demonstrated cytopathic lesion is HCV genotype-3-induced steatosis. Virus-specific T cells accumulate in the liver and destroy some of the infected cells. This intrahe-

patic T-cell response leads to partial viral control but also to progressive liver disease. It remains unclear whether or not HCV is fibrogenic and/or carcinogenic per se.

In summary, HCV persists and induces liver injury mainly due to a broad spectrum of functions on immunocompetent cells leading to an impaired immune response.

2.2. Treatment of HCV cirrhosis

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Recurrent HCV infection is associated with accelerated fibrosis progression leading to recurrent HCV-related cirrhosis and impaired long-term survival following LT. Therefore, treatment of HCV cirrhosis in candidates for LT is theoretically an attractive strategy for decreasing or suppressing viral replication prior to LT, leading to decreased risk of recurrence and enhancement of long-term survival. Moreover, eradication of HCV can stabilize and improve hepatic function.

In this setting of cirrhosis, clinical and biological abnormalities (renal failure, impaired liver function, thrombocytopenia, anemia) are frequent limiting factors and only around half of the patients can be administered antiviral therapy. The association of peginterferon–ribavirin appears to be more effective than monotherapy in terms of a sustained virological response (SVR). Predictive factors associated with virological response are almost the same as in non-cirrhotic infected patients (low viral load, genotype, early decrease in viral load, full dose treatment) and expected results of antiviral bi-therapy in terms of SVR are lower, between 20% and 40% [27,28]. Most patients require dose adjustments, and treatment withdrawal may affect 30% of cases. Side effects occur more frequently in such patients and some of these may be life-threatening, such as clinical decompensation and infection.

In summary, treatment of compensated HCV cirrhosis should be encouraged, along with continual laboratory and clinical follow-up, to detect severe adverse events. In patients with decompensated liver disease and the presence of predictive factors for SVR (genotype 2–3, genotype 1 low viral load), decisions should be individualized.

2.3. Natural history of HCV recurrence

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Early recurrent HCV infection based on the presence of HCV RNA in the serum and graft is almost universal (>95%) following LT. Recurrent liver disease occurs at various time points and displays a wide spectrum of histological findings [29–31]. Recent data indicate that

recurrent disease is associated with an increase in HCV-related fibrosis progression and impaired survival [32,33].

Recurrent acute hepatitis usually occurs 1 to 6 months post-LT, inducing subsequent liver injury. Recurrent hepatitis is very heterogeneous, but generally its natural history is more aggressive in transplant recipients than in immunocompetent patients. Severe progressive cholestatic hepatitis can occur early, 1 to 3 months post-transplantation, in fewer than 10% of cases. This rare but severe pattern of recurrence is characterized by a high serum bilirubin level ($>100 \mu\text{mol/l}$), very high serum HCV levels, central ballooning, paucity of inflammation, and cholangiolar proliferation without bile duct loss suggesting a direct cytopathic effect of HCV. Rapid progression to graft failure and death occurs without retransplantation. In most cases, recurrent infection is associated with chronic hepatitis. Serial liver biopsies showed that the course of fibrosis progression was accelerated, leading to cirrhosis in 8–30% of patients within five years. Recurrent HCV graft cirrhosis is also more aggressive than cirrhosis of the native liver, with a cumulative risk of complications of 65% over three years [33]. The true recurrence rate can be known only if routine biopsies are performed.

Taking into account all these features, recurrent hepatitis C has a negative impact on long-term post-transplantation survival. Other variables are involved in disease progression, such as the post-transplant immunosuppressive regimen, the use of marginal grafts, increasing age of the donor, pre-LT HCV RNA levels higher than 1 Meq/ml, early post-LT HCV RNA levels higher than 10 Meq/ml, prolonged ischemic time, CMV infection and HIV coinfection (Table 1). It has been suggested that transplantation in recent years was associated with higher severity of recurrence [34]. It could have been a confounding factor since the Valencia group described an improvement in the results in

Table 1
Factors associated with accelerated fibrosis progression

Donor older than 40–50 years
Pre-LT levels > 1 Meq/ml
Early post-LT levels >10 Meq/ml
Prolonged ischemic time
CMV infection
Rejection episodes
Over-immunosuppression
Boluses of Methylprednisolone
OKT3 Use
Rapid withdrawal of steroids before 3 months post-LT
HIV coinfection
“Retransplantation for HCV-graft disease?”
“LDLT ?”
“Genotype 1b?”

Adapted from M. Berenguer. LDLT, living donor liver transplantation; LT, liver transplantation.

patients transplanted in 2001–2003, using slow tapering in steroids, and a double immunosuppressive combination Calcineurin inhibitors and steroids, as well as limited use of steroids boluses [35].

2.4. Mechanisms of HCV reinfection of the liver allograft

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Several lines of evidence suggest that the immune response to HCV is compartmentalized and is responsible for liver damage associated with recurrent chronic hepatitis C. Two of the most important components of the immune response are cytotoxic T lymphocytes (CTL) and natural killer cells (NK), which kill HCV-infected hepatocytes. Cytokines play an important role in modulating the hepatic immune response. TH1 and TH2 refer to patterns of cytokines secreted by two subpopulations of CD4+ T cells that determine the outcome of responses to foreign antigens. TH1 cytokines (IL-2 and interferon (IFN)- γ) play a central role in cell-mediated immunity and in the killing of virus-infected cells; decreased expression of these cytokines might facilitate progression to chronic HCV infection. TH2 cytokines (IL-4 and IL-10) contribute to the humoral response.

Initial infection of the allograft may occur during reperfusion without inducing significant injury for several weeks. Initially, liver graft contains reduced numbers of HCV quasispecies, and the kinetics of the pattern of reinfection might be explained by a second non-serum infective compartment. Acute lobular hepatitis is characterized by higher levels of viral load, cellular proliferation and hepatocyte apoptosis than during the pre-LT period. At present, there is evidence for a non-specific/specific host inflammatory response involving TNF α /Fas pathways and T-cell responses (CD4+/CD8+) [36].

The severe form of progressive cholestatic hepatitis is associated with extremely high levels of HCV, the absence of a specific HCV response and a TH2 intrahepatic cytokine response (IL-10 and IL-4), suggesting a direct cytopathogenic effect of HCV within the liver graft (Fig. 2). Lastly, pathogenesis of liver injury during chronic recurrent hepatitis C is quite similar to the pre-LT period, with immune-mediated mechanisms involving an intrahepatic TH1 cytokine response responsible for liver injury (Fig. 3) [36].

2.5. Role of immunosuppressive therapy and rejection in HCV recurrence

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The progression of HCV infection is worse than in non-immunosuppressed groups. However, the role of immunosuppression as a co-factor in the more rapid

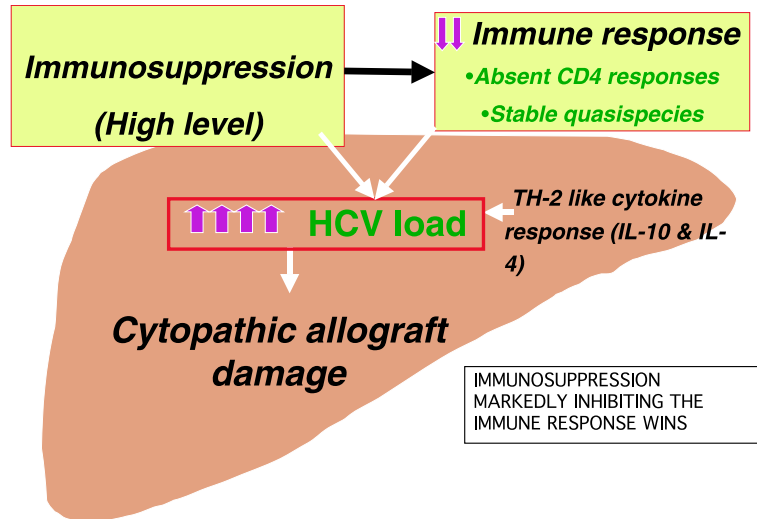


Fig. 2. Proposed pathogenesis of cholestatic hepatitis C on the graft post-transplantation (adapted from Ref. [36]).

progression of HCV infection is difficult to assert. HCV-infected transplant recipients experienced similar frequencies of acute cellular and steroid-resistant rejection as patients undergoing liver transplantation for other indications. However, the mortality risk was significantly increased for HCV-infected transplant recipients who developed early acute rejection compared with HCV negative transplant recipients. Antilymphocyte preparations but not IL-2 receptor blockers or alemtuzumab, used at induction for preventing rejection, are reported as being beneficial in some studies [37,38]. Cyclosporine in vitro has some antiviral effect [39] but there is no clinical evidence that HCV recurrence is less severe than with tacrolimus. Neither azathioprine nor mycophenolate mofetil has been shown to have a consistent effect on HCV recurrence [40]. Sirolimus long-term may have

some benefit as it has antifibrotic and potential antiviral effects. However, there are only preliminary reports on sirolimus and HCV recurrence. Repeated pulses of steroids [41,42] and OKT3 [43] use in acute cellular rejection are co-factors of graft loss due to HCV recurrence. So, many centres have used taper [44] or no maintenance steroid regimens to avoid steroids. These have not resulted in great improvement in HCV recurrence in these studies. First, the method of tapering off steroids seems to be important [45]. Slowly tapered off over time may prevent more aggressive forms of recurrent liver disease. Secondly, steroid withdrawal can be associated with substitution of other immunosuppressive drugs, which resulted in greater overall immunosuppression. In some studies, low dose prolonged steroid maintenance therapy shows less severe

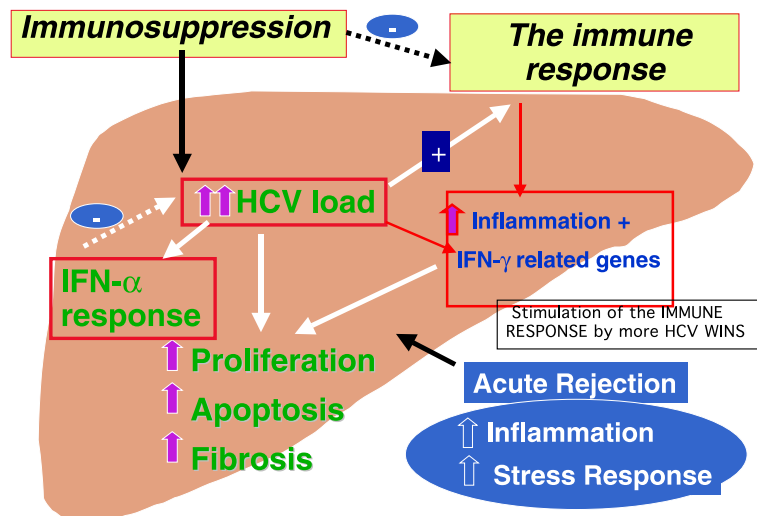


Fig. 3. Proposed pathogenesis of chronic hepatitis C on the graft post-transplantation (adapted from Ref. [36]).

recurrence of HCV. There are additional factors like CMV infection or HLA matching. Finally, the type of immunosuppression, the frequency of cellular rejection and its treatment need to be evaluated in the context of other factors such as donor age [46,47], which influence the progression of HCV recurrence after liver transplantation.

2.6. Pathology of rejection and HCV recurrence

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Liver biopsy continues to play an important role in the diagnosis and management of post-transplant HCV infection in the absence of other reliable diagnostic markers for graft hepatitis due to HCV. Histological features of HCV infection in the liver allograft are generally similar to those seen in the non-transplanted liver. Three stages can be distinguished. The early infection (0–2 months) is associated histologically with mild non-specific changes. The established infection (2–4 months) is associated with an acute hepatitis. The progressive damage (>6 months) is associated with a chronic hepatitis. However, the disease behaviour is more aggressive in the liver allograft with more severe degrees of necroinflammatory activity and more rapid progression to fibrosis. The risk of cirrhosis at five year ranges from 8 to 28% depending on the study. Histological findings in early post-transplant biopsies may be predictive of more aggressive disease behaviour. These include the severity of necroinflammatory activity (periportal and/or lobular), presence and/or severity of macrovesicular steatosis in day 1–28 biopsies and the presence of prominent hepatocyte ballooning and/or cholestasis. There are other predictive factors for severe disease: hepatitis activity index in first biopsies, hepatic stellate cell activation, hepatocyte proliferation and senescence. Atypical patterns of graft infection with HCV occur in a small proportion of cases. These include hepatocyte ballooning and a severe cholestatic syndrome resembling fibrosing cholestatic hepatitis B infection. There is a complex relationship between HCV and rejection in the liver allograft, including shared immunopathogenetic mechanisms of liver damage [48]. Overlapping patterns of inflammation can cause problems in the assessment of post-transplant biopsies. Histopathologic assessment should be used cautiously for the differentiation of recurrent hepatitis C from acute rejection. Many biopsies, which are difficult to interpret, have probably a dual pathology. HCV is best considered as the primary diagnosis. There are several other possible causes of chronic hepatitis in the liver allograft. Some of these may represent a form of late cellular rejection. The others are associated with de novo development of autoantibodies, possibly also reflecting an alloimmune graft response.

2.7. Alcohol and HCV

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There is a high prevalence of alcoholics among HCV liver disease patients. Thirty to 60% of HCV cirrhotic patients have a history of alcohol use. Before transplantation, some studies have reported that alcohol abuse in combination with chronic hepatitis C leads to an increased HCV-RNA level, accelerated progression of liver disease, increased risk of cirrhosis, and increased risk of hepatocellular carcinoma [49]. Alcohol abuse interferes with antiviral therapy increasing the rate of non-response to interferon therapy. That is why alcohol should be considered as a risk factor for HCV recurrence and for non-response to antiviral treatment after liver transplantation. It is important to search and prevent alcohol relapse after liver transplantation not only for alcoholic disease but also in HCV-infected patients. The severity of HCV histological damage must be interpreted cautiously in the presence of alcohol use [50]. Combined alcohol use and HCV might increase the risk of renal dysfunction, of neurological impairment, as well as of de novo solid tumors and Post-Transplant Lymphoproliferative Diseases as observed in the population of patients transplanted for alcoholic disease [51].

2.8. Treatment after liver transplantation

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In the absence of effective antibody preparations to prevent HCV re-infection [52], interferon (IFN)-based antiviral therapy administered pre-emptively or following established recurrent disease is the only available treatment strategy to achieve viral clearance or halt disease progression. The rationale to treat is shown by the fact that SVR is associated with reduced activity and a stable or reduced stage of fibrosis [53,54]. The rationale for using pre-emptive therapy is to administer antivirals as soon as possible after liver transplantation at a time when viral load is relatively low [55], histological disease is absent or minimal and is based on the high rates of viral clearance observed after treatment of acute HCV infection in non-liver transplant patients. The disadvantages of this strategy are: a low applicability (35%) during the immediate post-liver transplantation period due to poor general conditions, persistent cytopenia, renal dysfunction, ongoing bacterial infection and the increased risk of severe side effects, including acute cellular rejection, leading to frequent discontinuation of therapy or dose reductions [56]. The results of pre-emptive therapy have been disappointing with SVR of 7–13% with IFN [57,58], 16–33% with INF-ribavirin [59]

and 9% with pegylated IFN [60] in reported controlled clinical trials. Because of its unproven efficacy, the preemptive therapy is recommended only in special circumstances such as patients with a low Meld score before transplantation or following re-transplantation for HCV-related allograft. The most applicable and accepted strategy is to treat with pegylated IFN plus ribavirin patients with cholestatic HCV recurrence and those with chronic hepatitis and rapidly progressive fibrosis. The pathological staging of liver fibrosis cannot be estimated using surrogate markers. The protocol liver biopsies are still recommended before treatment. The results of antiviral therapy for established HCV recurrence have been poor with SVR of 12.5% with IFN [61], 21% with IFN plus ribavirin [62] and 9% with pegylated IFN alone [60] in reported controlled clinical trials. In non-randomized trials, the combination Peg-IFN plus ribavirin is the most effective achieving SVR between 30% and 45% [63,64]. These disappointing results are not unexpected for a number of reasons. Firstly, liver transplantation recipients overexpress variables predictive of non-response in immune competent patients such as older age, infection with genotype 1, high viral load, failed antiviral therapy pre-liver transplantation and more advanced liver fibrosis. Secondly, liver transplantation recipients frequently have comorbidities that increase the side effects of IFN and ribavirin and thus preclude full-dose therapy. Even mild degrees of renal dysfunction may exacerbate the risk of ribavirin-induced haemolytic anaemia. The additive effects of IFN with preexisting hypersplenism and the myelosuppressive effects of immunosuppression may result in severe neutropenia and thrombocytopenia. For these and other reasons, dose reductions or discontinuation of IFN or ribavirin is required in up to half of treated patients. Lastly, immunosuppression may impair the immunomodulatory effects of IFN. The advantages of initiating therapy 6–24 months after liver transplantation when compared to the preemptive strategy are the need for less immunosuppression, improved clinical status, lower risk of acute rejection and cost savings. In contrast, higher viral loads and more advanced fibrosis are disadvantages of delayed therapy that may have a negative impact on viral clearance. Some cases of acute and chronic rejection have been associated with the use of interferon. The rate of rejection during IFN-based therapy is controversial [61,65]. There are no solid data to support the use of ribavirin monotherapy either preemptively or after disease recurrence. The potential benefit of maintenance therapy with ribavirin following discontinuation of IFN remains unproven. Therefore, the decision to treat should balance the side effects of treatment and disease progression (fibrosis stage ≥ 2) as assessed by annual protocol liver biopsies in absence of new antiviral agents with greater efficacy and a better safety profile.

2.9. How to improve the results of antiviral therapy

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In comparison with immunocompetent patients, the results of antiviral therapy after liver transplantation seem rather disappointing. However, the exact difference in efficiency is unclear, as most data originate from uncontrolled retrospective series, often including an unclear proportion of patients who already received antiviral therapy prior to transplantation. One of the central problems is the high incidence of side effects (mainly thrombocytopenia and anaemia), eventually requiring interruption or discontinuation of antiviral treatment. The risk-benefit of using growth factors (e.g., erythropoietin, G-CSF) has not yet been established. Although they facilitate the use of the optimal doses of IFN and ribavirin, the cost and complexity of therapy is significantly increased. There are lacking reports on optimized protocols, effect on viral clearance and the cost efficiency. The treatment with recombinant thrombopoietin may be indicated in case of thrombocytopenia, but there are no studies in liver transplantation. Daily high-dose induction therapy with IFN must be evaluated. Efforts have to be made in the use of ribavirin substitutes that do not cause haemolysis (e.g., virmidine). The latest reports favour the use of individualized treatment protocols according to viral dynamics in immunocompetent patients. A similar approach appears reasonable after transplantation. Especially the substantially elevated viral load in transplanted patients may point out the need for longer treatment duration. A long-standing discussion is the optimal moment to initiate treatment after liver transplantation. New variants of interferon (e.g., albuferon) shall probably not substantially change therapeutic efficacy after liver transplantation. Similarly, the success of therapeutic vaccination appears questionable during immunosuppression therapy. On the other hand, inhibitors of HCV protease have proven to be potent suppressors of HCV replication. This holds prospects for both prevention and therapy of recurrent hepatitis C after liver transplantation.

2.10. Maintenance therapy and long-term benefit of antiviral treatment

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The most ambitious goal of therapy is to eradicate HCV infection. If this aim cannot be reached, the primary objective becomes the prevention of complications. The best strategy to prevent severe complications of chronic hepatitis C in immunocompetent patients is to

halt fibrosis progression. Several studies have shown the benefit of maintenance therapy with pegylated-IFN, particularly in patients with rapid progression rates or high risk factors. Considering the aggressive course of hepatitis C in transplant recipients, it is imperative to validate effective strategies to slow down this unfavourable course. Re-treatment with pegylated-IFN plus ribavirin in non-responder transplant patients could be the first strategy. The improvement of fibrosis was observed in treated patients with or without SVR [53,54]. Prolonged maintenance therapy should probably delay progression of fibrosis and reduce the risks of cirrhosis and retransplantation but there are no published data. The best maintenance therapy is probably the association of pegylated-IFN plus ribavirin but the problem is the quality of life under this therapy. The role of ribavirin levels and its relevance is discussed. The ribavirin monotherapy could be effective supportive preliminary data.

2.11. Retransplantation (Retx) for HCV recurrence

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In those patients with allograft failure to HCV, consideration of ReTx is the only option, but historically, this practice has been associated with significantly decreased survival rates, longer hospital stays and higher costs when applied non-selectively. For example, patients with HCV-related graft failure have not worse survival than other causes of graft failure in HCV-infected ReTx recipient. Patients undergoing ReTx for allograft cirrhosis HCV have poor outcomes vs. ReTx for cholestatic HCV recurrence. The true question is not whether to perform ReTx for HCV, but rather what is an acceptable survival rate for ReTx in the era of MELD [66–68]. Rosen thinks that 1-year survival drives utility for reTx for HCV and changes to current allocation system will need to take place. ReTx needs to be performed at a lower MELD score than for a first transplantation [69]. Maximal utility achieved with MELD = 21 because it drops off after MELD 28. Others questions are without answers: Should patients undergoing living donor transplantation be given priority for ReTx? What is the acceptable survival for ReTx?

2.12. Liver transplantation and hepatocellular carcinoma

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The incidence in the general population of hepatocellular carcinoma (HCC) is evaluated from 5 to 15 cases/10⁵ inhabitants. In cirrhotic patients the 5-year incidence of HCC is 15–20%. This incidence is increasing, due to a rising incidence of viral hepatitis. HCC is the fifth most common neoplasm in the world and the leading cause of

death among cirrhotic patients. Risk factors for developing HCC include male sex, age, increased AFP concentration, viral etiology, ethanol intake, portal hypertension, iron deposition, dysplasia, and irregular regeneration.

2.12.1. Risk factors for HCC recurrence after transplantation

HCC recurrence rate and survival of patients with HCC treated by orthotopic liver transplantation (OLT) depend on tumor stage. The most powerful predictor of recurrence in the absence of extrahepatic spread is macro- or microscopic vascular invasion and this runs in parallel to tumor size and number. However, the relationship is non-linear and a significant proportion of tumors under 5 cm have unfavorable histology (vascular invasion and/or high grade). Except for tumor size and vascular invasion, few risk factors have been demonstrated to influence prognosis.

2.12.2. Assessment before transplantation

Detection of arterial hypervascularity in lesions larger than 2 cm in diameter by non-invasive imaging (ultrasonography, spiral computed tomography (CT) or magnetic resonance imaging (MRI)) is diagnostic for HCC. Diagnosis of lesions smaller than 2 cm in diameter is difficult and serial ultrasound examination every 3 months is recommended for lesions <1 cm in diameter, and fine needle aspiration biopsy is recommended for lesions between 1 and 2 cm, accord to European Association of the Study of the Liver (EASL) consensus guidelines [70]. The clinical value of fine needle aspiration biopsy as a diagnostic tool is limited by high false positive rates and the risk of tumor seeding. The rationale to propose 3-D MRI angiography (MRA) as the best radiologic technology for HCC staging has been proposed recently. This technology detects all nodules above 20 mm in size and a high proportion of nodules between 10 and 20 mm and is significantly better than triphasic helical CT. There is no effective method for detecting tumors less than 1 cm in diameter [71].

2.12.3. Exclusion and therapy on the waiting list

On the waiting list, 25% of candidates, because of HCC progression in a majority of cases, will be excluded if the waiting list is longer than 12 months. Recurrence rates of HCC after transplantation range between 5% and 15% even when the tumors are relatively limited in extent (within the so-called “Milan criteria”) corresponding with solitary HCC <5 cm or with up to 3 nodules smaller than 3 cm. In addition to the risk of recurrence, other factors used to justify pretransplant treatment of HCC include long waiting times at some centers and attempts to “downstage” HCC. A variety of treatments as chemoembolization, radiofrequency, resection or “multimodality therapy” for HCC have

been used prior to transplant. If this therapy may diminish the risk of exclusion on the waiting list and the risk of recurrence after liver transplantation, the most effective strategy should be based on the increase of donation either from cadaveric or from living donors. Many controversial issues exist in liver transplantation for HCC: Who are the optimal candidates? Should the criteria be expanded? How should diagnosis/staging be done? Should HCC receive priority? Who should be excluded from the waiting list? What is the impact of HCV reinfection? What is the role of immunosuppression?

2.13. Viral hepatitis recurrence in living donor liver transplantation (LDLT)

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The question is “do LDLT HCV infected recipients have a worse outcome than deceased donor liver transplant (DDLT) recipients?” The specific features of LDLT are: a vigorous hepatic regeneration, LD graft cells have better functional state due to low cold ischemic time, LD grafts received a relative larger viral inoculum, the size of the graft is smaller which leads to a relative excess immunosuppression and reduced antiviral defenses. The potential advantages of LDLT are the possibility to attempt antiviral therapy pre-LT, a shorter cold ischemic time, and a younger donor age. The potential disadvantages are HLA homology between donor and recipient, HCV replication in proliferating hepatocytes, a greater “relative immunosuppression”, and more technical problems (vascular, biliary). Some studies have shown a higher viral recurrence rate, an earlier viral recurrence, a higher cholestatic hepatitis rate, and a higher accelerated viral kinetic in LDLT [72,73]. However, other studies have not shown any difference in survival, severity and prevalence of HCV recurrence. At the Mayo clinic Arizona, a histological comparison at 2 years did not show any difference in severity of recurrence between 15 LDLT and 52 DDLT recipients. Limited data are available in LDLT for HBV patients, it does not indicate a worse outcome than DDLT. Thus data are not sufficient to conclude to a difference in severity of viral recurrence in LDLT, however, the interaction between hepatocyte proliferation and viral replication requires further studies.

2.14. Indications and results for liver transplantation in HIV-infected patients

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Jean-Charles Duclos-Vallee, Centre HepatoBiliaire, Inserm Unit 785, Hopital Paul Brousse, France.

Life expectancy in HIV-infected patients has increased due to the efficacy of highly active antiretroviral therapy (HAART). The overall prevalence of HCV co-infection is high, rising to 50–90% among intrave-

nous drug users. In Europe, according to the data of EUROSIDA, 34% of the HIV positive patients are HCV positive. End-stage liver disease is an emerging problem in these patients. An increasing number of coinfecting subjects will develop decompensated cirrhosis or hepatocellular carcinoma. The kinetics of progression of fibrosis is particularly high in HIV-HCV co-infected patients. Thus, a high number of HIV-infected patients will die as a consequence of viral hepatitis [74,75]. HCV-related disease is now the leading non-AIDS cause of death in HIV-infected persons in the developed world. Concerning the HBV/HIV coinfecting patients, the mortality is high (14.2/1000) in comparison with the HBV-infected patients (0.8/1000) and the HIV-infected patients (1.7/1000) [76]. Moreover, the incidence of fulminant hepatitis is higher in HIV/HCV coinfecting patients. For all these reasons, there is a strong demand to offer liver transplantation to HIV-infected patients [77].

The published literature of the results in HIV-infected persons in the era of HAART is limited. However, recent reports from the US and Europe have shown that liver transplantation in HIV-infected patients is feasible [78–80]. Recently, it has been shown that the cumulative survival of 24 HIV-infected liver allograft recipients compared to age- and race-matched HIV negative recipients was similar ($p = 0.365$): The 1-, 2-, and 3-year survival were 87.1%, 72.8%, and 72.8% among HIV-infected patients versus 86.6%, 81.6% and 77.9% among HIV-negative recipients [79]. Five predictors of poor survival have been individualized: post-LT HAART intolerance ($p = 0.044$), post-LT CD4 < 200 cells/ml ($p = 0.005$), post-LT HIV viral load > 400 copies/mL ($p = 0.016$) and HCV infection ($p = 0.023$).

Two main problems appeared during the post-LT period: (1) the severity of HCV recurrence on the liver graft which may imply starting HCV therapy early after LT. (2) A mitochondrial toxicity may also induce severe disease on the graft. In our experience two patients died because of a mixed toxicity due to HCV infection on the liver graft and mitochondrial toxicity due to nucleoside analogues [80]. LT can be performed in HIV-HCV co-infected patients with controlled HIV infection. However, the management of HCV recurrence on the liver graft and HAART toxicity must be optimized.

2.15. Donors at risk of viral transmission

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The number of patients on the waiting list has increased exponentially, while the number of donors remained fairly constant. Thus many strategies to expand the donor pool have been developed as the use of marginal donors such as older donors, grafts with

steatosis, and donors with evidence of prior exposition to Hepatitis C and B viruses.

2.15.1. Donor HCV positive

HCV-related cirrhosis is a main indication for liver transplantation in Europe and the United States. Therefore, the use of HCV-infected grafts in selected HCV+ recipients may represent a way of expanding the donor pool. HCV-positive donors account for about 2% of the liver donors in Spain and between 6% and 12% in USA. Of course a small proportion (between 20% and 40%) of these grafts will be suitable for liver transplantation because of the presence of an underlying chronic liver disease. However, patient survival at short and mid-term has been similar between recipients of HCV+ grafts and HCV-negative grafts in all studies. With regard to recurrent hepatitis C, the rate and severity of recurrent hepatitis C – assessed by serial protocol biopsies – as well as 4-year and 5-year patient and graft survival rates were similar between both groups [81]. So, based upon the available data, it can be concluded that the use of HCV positive infected grafts in HCV-positive recipients seems justified and safe in the mid-term.

2.15.2. Donors HBsAg-negative/anti-HBc-positive

The prevalence of anti-HBc positive in organ donors is related to the prevalence of HBV infection in the general population. Therefore, it is low – about 7% – in most western countries but very high – between 50% and 60% – in areas where HBV infection is endemic. Moreover, the prevalence of anti-HBc positive appears to increase with age and now old donors are common on the waiting list. De novo hepatitis B infection may appear and the reported transmission with anti-HBc positive donor ranges between 17% and 94% from the different studies [82–86]. Recipients who are anti-HBc positive alone have a 10–15% risk of de novo HBV infection. Several studies have confirmed the presence of HBV-DNA in the liver in about 50% of anti-HBc positive donors. In contrast, serum HBV-DNA is positive in very few of them, about 5%.

To minimize the risk of HBV infection, the best approach is the selective allocation of anti-HBc+ grafts to appropriate recipients: (1) Patients undergoing transplantation for HBV cirrhosis because they are going to receive HBV prophylaxis anyway. (2) Recipients who are anti-HBs+ alone or with associated anti-HBc positivity. In these cases, HBV prophylaxis does not seem necessary. (3) Recipients who are anti-HBc+ alone. The need for a specific HBV prophylaxis in this subgroup is unclear at the present time. (4) Anti-HBc+ grafts may be offered to selected naive recipients with advanced end-stage cirrhosis and/or HCC. No consensus exists concerning the prophylaxis of HBV infection in this subgroup. However, most centres administer passive immunoprophylaxis (HBIG administration) in these

cases or lamivudine treatment or both [84–86]. In conclusion, if donor anti-HBc must be used, large prospective studies with long follow-up are needed to determine the real efficacy of the different prophylactic strategies and a consensus must be adopted.

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