Tratamiento e historia natural de la hepatitis crónica C en pacientes coinfectados por VIH-1

Javier Murillas Angoiti

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Tesis Doctoral

TRATAMIENTO E HISTORIA NATURAL DE LA HEPATITIS CRÓNICA C EN PACIENTES COINFECTADOS POR VIH-1

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ANEXO 1:PUBLICACIONES

Towards Individualized Antiviral Therapy of Patients Infected with Hepatitis C Virus Genotypes 2 and 3

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Abstract

Pegylated interferon alpha in combination with ribavirin administered for 24 weeks has been approved as standard antiviral treatment in patients with HCV genotype 2 and 3 infection in many countries. Thereby, high sustained virologic response rates of approximately 80% are achieved, similar to those previously reported with a treatment duration of 48 weeks. Recently, the possibility to further reduce treatment duration to achieve better tolerability and lower side effects without compromising the sustained virologic response rates was investigated in three clinical trials. In the different studies, reduction of treatment duration to 12, 14 or 16 weeks in patients with an early virologic response defined as undetectable HCV-RNA (< 50-600 IU/ml) at week 4 of therapy was associated with similar sustained virologic response rates (82-90%) as compared to the standard treatment duration of 24 weeks (80-91%). Furthermore, in HCV genotype 2 infected patients overall, even higher sustained response rates as compared to those infected with HCV genotype 3 were detected (80-92% *vs.* 66-73%). Genotype 2/3 infected patients without an early virologic response at week 4 should be treated for at least 24 weeks. The results of the three studies have to be confirmed by larger ongoing studies before a general change of the therapy guidelines. Furthermore, it has to be determined in future trials whether on the basis of unfavorable response predictors (e.g. liver fibrosis, elevated γ-glutamyltransferase, high HCV-RNA concentration at baseline, and genotype 3) duration of therapy has to be extended beyond 24 weeks.
In HCV genotype 2/3 infected patients with failure to treatment with (pegylated) interferon-alpha and ribavirin, no standard treatment exists. In current studies, the value of different treatment options including repetition of interferon-alpha plus ribavirin combination therapy, triple therapies, and direct antiviral drugs such as protease and polymerase inhibitors are investigated. (Hepatology Reviews 2006;3:3-10)

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Key words

HCV. Interferon-α. Ribavirin. Protease inhibitors. Treatment duration.

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Introduction

Hepatitis C Virus (HCV) is a small enveloped RNA virus that belongs to the family of *Flaviviridae*[1]. Due to the lack of a proofreading activity of the viral RNA-dependent RNA polymerase, HCV exhibits a highly variable genome and clusters in several distinct genotypes. Today, at least six different genotypes and more than 50 subtypes have been reported with different geographic distributions[2]. In western countries, genotypes 1, 2, and 3 are primarily found, with a predominance of genotype 1. Genotype 4 is widely distributed in North Africa and the Middle East, whereas genotype 5 is found in South Africa, and genotype 6 in Hong Kong and more recently in Australia.

Therapy for HCV infection was first reported in the late 1980s when patients with so-called non-A non-B hepatitis were treated with interferon (IFN)[3]. At that time, treatment consisted of 3-6 million IU of standard IFNα as monotherapy, typically three times a week administered subcutaneously for 24 to 48 weeks. After isolation and characterization of HCV, it became obvious that sustained virologic response (SVR) rates (defined as non-detectable HCV-RNA 24 weeks after cessation of therapy) were markedly different according to the HCV genotype. In large multicenter studies, SVR rates were 2 and 7% for patients infected with genotype 1 treated for 24 and 48 weeks, respectively. In contrast, for patients infected with genotypes 2/3, SVR was achieved in 16% (24 weeks) and 29-33% (48 weeks)[4,5].

The introduction of combination therapy with IFNα and the nucleoside analog ribavirin for 48 weeks in the late 1990s substantially improved treatment outcome with mean SVR rates of 41%. However, differences between genotype 1 and genotype 2/3 infected patients remained evident. SVR rates for patients with genotypes 1/4/5/6 were 28-36% compared to 61-79% for patients with genotype 2/3 infection[4-7]. The development of pegylated (PEG) interferons with a sustained absorption, a slower rate of clearance, and a longer half-life than unmodified IFNs, led to a further improvement of SVR rates, especially for patients infected with genotype 1[6,7]. Again, SVR rates were significantly higher in genotypes 2 and 3 (76-82%) as compared to genotype 1 infected patients (42-52%). At present, two types of PEG-IFNα are approved for the treatment of chronic hepatitis C: PEG-IFNα-2a and PEG-IFNα-2b, which differ in size and form of the linked polyethylene glycol molecule (40 *vs.* 12 kDa). Due to pharmacokinetics, the 40 kDa PEG-IFNα-2a is given independently from body weight with 180 µg, whereas for the 12 kDa PEG-IFNα-2b, a dose of 1.0-1.5 µg per kg body weight is approved. Both PEG-IFNs are injected subcutaneously once a week.

The reasons for the markedly different virologic response rates between genotype 1 and genotype 2/3 infected patients are unknown. Several HCV proteins (core, envelope [E] 2, non-structural [NS] 3, NS5A) have been associated with IFNα resistance mechanisms *in vitro,* and sequencing of the respective HCV genes showed a potential importance of amino acid variations within the E2 and NS5A proteins in correlation with sensitivity to IFNα-based therapy[8].

Current Antiviral Standard Therapy of Patients with HCV Genotype 2/3 Infection

In the first pivotal trials using PEG-IFNα in combination with ribavirin, antiviral therapy was administered for 48 weeks, independent of the HCV genotype. Patients with genotype 2/3 infection treated with PEG-IFNα-2b or PEG-IFNα-2a plus ribavirin achieved SVR rates of 82 and 76%, respectively, confirming the favorable results achieved by standard IFN plus ribavirin treatment[6,7]. Subsequent studies therefore investigated the possibility of reducing the duration of therapy from 48 to 24 weeks for patients with genotype 2/3 infection without compromising the antiviral efficacy. It was shown that similar SVR rates (78-81%) were achieved in patients treated for 24 weeks compared to those treated for 48 weeks[9,10] (Figs. 1 and 2). Treatment-emergent serious adverse events, as well as adverse events leading to treatment discontinuation or dose reduction occurred at rates less than half of those observed with 48 weeks of treatment. Consequently, the 24-week treatment with PEG-IFN plus ribavirin has been established as standard of care for first-line therapy in genotype 2/3 infection[11].

As in combination with PEG-IFNα-2a, a uniform dosage of 800 mg ribavirin per day independent of body weight has been proven to be as effective as a body weight-adapted ribavirin schedule; this regimen was approved for treatment of genotype 2/3 infected patients[9]. Based on study results for approval of the 24-week treatment schedule for PEG-IFNα-2b, a dosage of ribavirin of 800-1400 mg per day based on body weight was determined[10].

While in previous studies genotype 2/3 infected patients were always reported together, in the above studies, differences in the SVR rates were detected for patients infected with genotypes 2 and 3 (Fig. 1). In general, patients infected with genotype 2 tend to have an even more favorable outcome compared to those infected with HCV genotype 3 (93 *vs.* 79%). By analyses of patient characteristics before initiation of antiviral therapy, apparent differences between genotypes 2 and 3 could mainly be attributed to a subgroup of genotype 3 infected patients with a high baseline HCV-RNA concentration of more than 6 x 10^5 IU/ml in one study[10]. In this subgroup, a relapse rate of 23% after the cessation of treatment was observed more frequently as compared to relapse rates of 5-8% in the remaining groups[10]. Furthermore, a histologically proven liver steatosis more frequently found in genotype 3 infected patients has been shown to be a significant prognostic factor for SVR. Although fibrosis has not been identified as an independent, negative, predictive factor for SVR in HCV genotype 2/3, it is worthwhile to note that patients who have no fibrosis achieve higher SVR rates as compared to those who have cirrhosis or bridging fibrosis (97 *vs.* 75%).

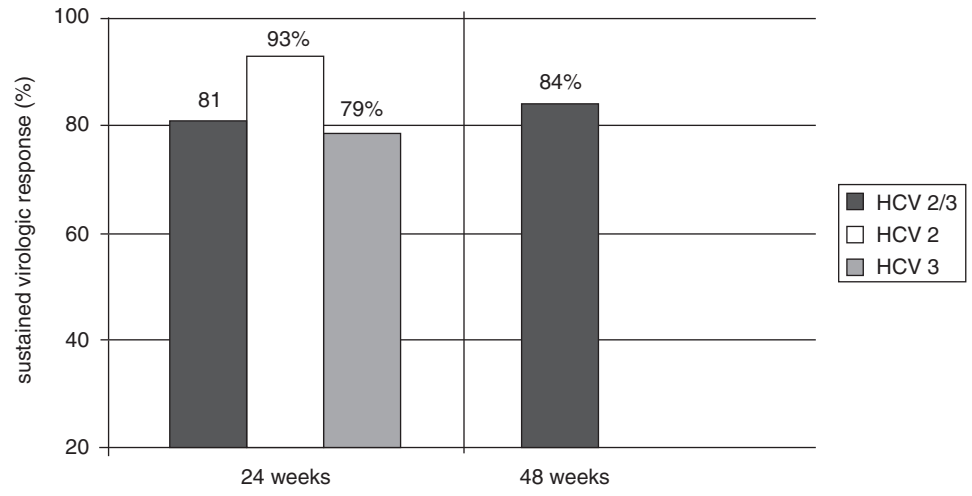

Figure 1. *SVR rates for treatment duration of 24 weeks (Zeuzem, et al.[10]) according to HCV genotypes 2/3, and treatment duration of 48 weeks (Manns, et al.[6], historical control).*

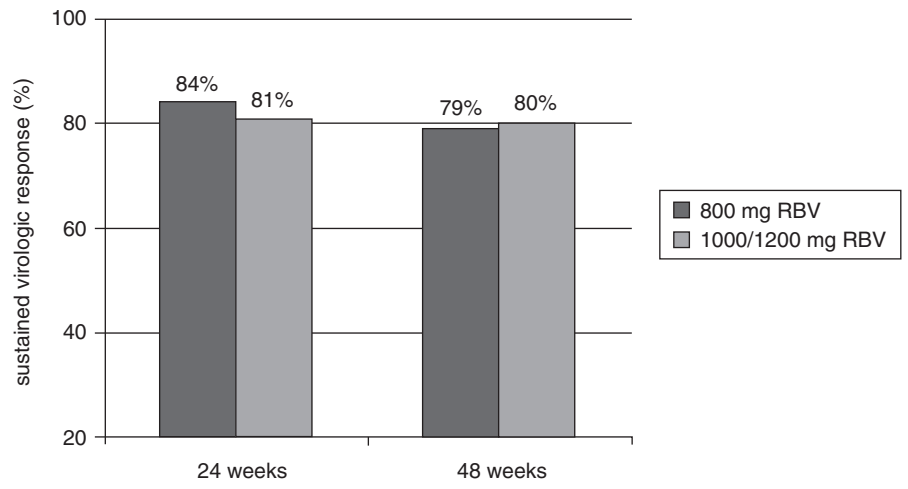

Figure 2. *SVR rates (Hadziyannis, et al.[9]) according to ribavirin (RBV) dosage and treatment duration (24* vs. *48 weeks).*

Towards Individualized Treatment Duration in Patients with HCV Genotype 2/3 Infection

Recently, three independent studies investigated whether treatment duration of PEG-IFNα-2a / 2b plus ribavirin in patients with genotype 2/3 infection can be further reduced from 24 weeks to 16, 14, and 12 weeks without compromising the SVR rates[12-14]. The rationale for these studies was mainly based on the observation that shorter treatment durations are associated with better tolerability and lower rates of premature discontinuation of therapy. In all three trials, HCV-RNA was assessed at week 4 after initiation of therapy, as in many previous studies early virologic response had been shown to predict treatment outcome[15,16].

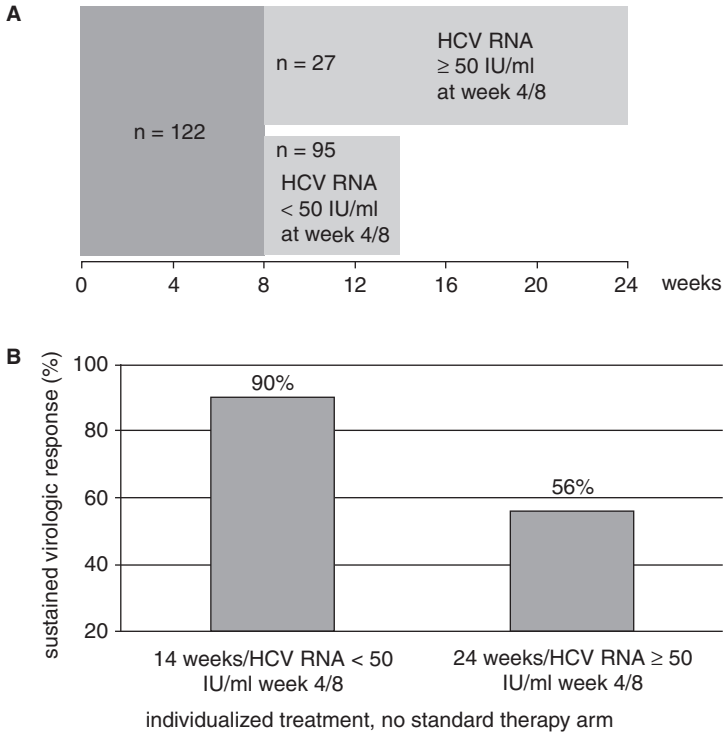

Figure 3. *Treatment regimen of the nonrandomized study by Dalgard, et al.[12]* ***(A)****. SVR rates according to treatment duration and presence or absence of an early virologic response (HCV-RNA < 50 IU/ml at week 4 and 8)* ***(B)****.*

In a first published nonrandomized trial, 122 therapy-naive Norwegian patients were treated with PEG-IFNα-2b 1.5 µg/kg body weight and ribavirin 800-1400 mg adjusted to body weight[12]. Patients with an early virologic response, defined as undetectable HCV-RNA (< 50 IU/ml) at weeks 4 and 8 after initiation of treatment, were treated for 14 weeks (n = 95). The remaining patients received 24 weeks of treatment (n = 27) (Fig. 3A). A control group receiving standard treatment of 24 weeks, independent of early virologic response at weeks 4 and 8, was not included in this study. The overall SVR was comparable to previous studies (82%). Patients with an early virologic response achieved SVR in 90% of cases, whereas patients without early virologic response at week 4 showed SVR rates of only 56% (Fig. 3B). Interestingly, all patients that were HCV-RNA negative already at week 2 (n = 36), achieved SVR. As there was no control arm in this study, no data on SVR rates of patients with early virologic response who received standard therapy are available. In this study, independent factors associated with SVR included younger age, treatment according to protocol, undetectable HCV-RNA at treatment week 4, and lower viral load at baseline. Indeed, patients with genotype 3 and an HCV-RNA concentration less than 6 x 10^5 IU/ml had higher SVR rates as compared to those with a higher HCV-RNA concentration (98 *vs.* 79%). When only patients who underwent a pretreatment liver biopsy were included in the analyses (n = 93) the absence of fibrosis was the sole factor associated with favorable treatment response. In turn, those patients who relapsed after 14 weeks of treatment (n = 9) were likely to have advanced bridging fibrosis or cirrhosis. There was no difference in SVR rates compared to HCV genotypes 2 and 3. However, there were only 23 patients with genotype 2 enrolled in the trial. The authors stated that shortening of antiviral therapy in patients with genotype 2 and 3 may be possible in those with an early virologic response, but should be restricted to patients who do not exhibit bridging fibrosis or cirrhosis.

In a second study, 283 patients were randomized to receive antiviral treatment with PEG-IFNα-2b 1.0 µg/kg body weight and ribavirin 1000-1200 mg for 24 weeks (standard-duration group, n = 70) or, according to early virologic response at week 4 (variable-duration group, n = 213) for either 24 weeks (HCV-RNA positive at week 4, HCV-RNA ≥ 50 IU/ml, n = 80) or 12 weeks (HCV-RNA negative at week 4, HCV-RNA < 50 IU/ml, n = 133) (Fig. 4A)[13]. In the standard-duration group the

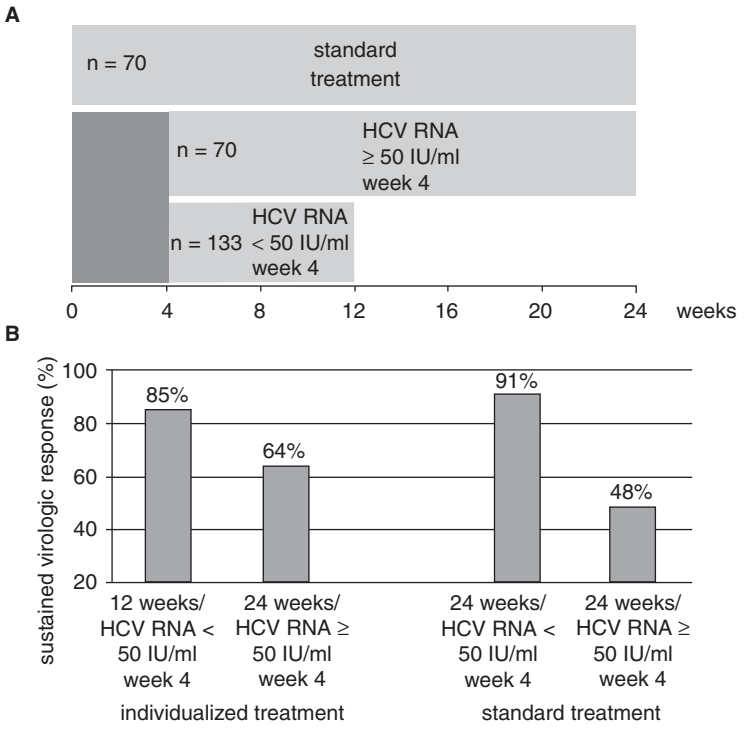

Figure 4. *Treatment regimen of the randomized study by Mangia, et al.[13]* ***(A)****. SVR rates according to individualized and standard treatment. In the individualized treatment arms, SVR rates are shown according to treatment duration and the presence or absence of early virologic response (HCV-RNA < 50 IU/ml at week 4). In the standard treatment arm, all patients received treatment for 24 weeks and SVR rates are shown according to the presence or absence of early virologic response* ***(B)****.*

SVR rate was 76% as compared with 77% in the variable-duration group. Patients in the variable-duration group who were HCV-RNA negative at week 4 achieved SVR in 85% of cases as compared to 64% in those who did not show an early virologic response. In the standard-duration group, SVR rates were 91 and 48% with regard to the presence and absence of early response, respectively (Fig. 4B). In this study, no independent baseline factor was significantly associated with early virologic response or virologic relapse. The overall rate of SVR was 80% among patients with genotype 2 and 66 % among those with genotype 3 ($p < 0.001$). However, as SVR rates were similar in patients with genotype 2 and 3 who had an early virologic response and who were treated for 12 or 24 weeks, the authors concluded that, in patients with either genotype who have undetectable HCV-RNA at week 4, the reduced duration of 12 weeks is sufficient.

A third study reported virologic response rates for 153 patients treated with PEG-IFNα-2a 180 µg per week plus ribavirin 800-1200 mg/day based on body weight[14]. Patients with undetectable HCV-RNA after four weeks of treatment (rapid virologic responders, < 600 IU/ml) were randomized for a total duration of 16 (n = 71) or 24 weeks (n = 71). Patients without rapid virologic response at week 4 were treated for 24 weeks (n = 11) (Fig. 5A). The SVR rates in early responders who were treated for 16 and 24 weeks were similar at 82 and 80%, respectively. Patients with detectable HCV-RNA at week 4 cleared the virus in only 36% of cases (Fig. 5B). Generally, patients with genotype 2 infection had higher SVR rates as compared to patients with genotype 3 infection (92 *vs.* 73%). The infection with HCV genotype 2 was confirmed as an independent factor for SVR in a multivariate analysis. Other factors associated with SVR were low γ-glutamyltransferase levels at baseline and low pretreatment HCV-RNA concentrations. Interestingly, when only those patients who showed an early virologic response (n = 142) were stratified by pretreatment HCV-RNA concentration (≤ 800,000 IU/ml, > 800,000 IU/ml), it was shown that patients with genotype 2 achieved SVR in 100 and 93% of cases, respectively, independent of treatment duration. However, in patients with genotype 3 infection, treatment outcome was different with regard to the pretreatment HCV-RNA concentration. SVR was observed in 85% of the patients with low pretreatment HCV-RNA concentrations, whereas only 59% of the patients with high HCV-RNA concentrations were sustained responders ($p = 0.003$). Consequently, the authors stated that a 16-week treatment duration is sufficient for patients with HCV genotype 2 infection (irrespective of the pretreatment HCV-RNA con-

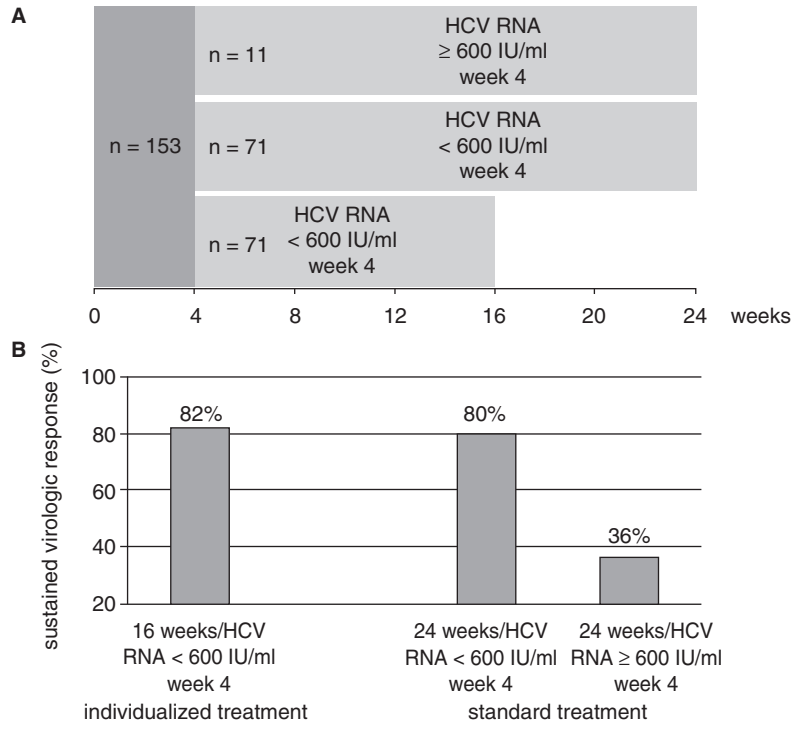

Figure 5. *Treatment regimen of the randomized study by von Wagner, et al.[14]* ***(A)****. SVR rates are shown according to individualized treatment arm and standard treatment arms. In the standard treatment arms, SVR rates are shown according to the presence or absence of an early virologic response (HCV-RNA < 600 IU/ml at week 4)* ***(B)****.*

centration) and those infected with genotype 3 and an HCV-RNA level ≤ 800,000 IU/ml at baseline who achieved an early virologic response at week 4. However, as results were less conclusive in patients with genotype 3 and high pretreatment HCV-RNA levels, the authors suggested that additional larger studies may be required for this patient group.

In summary, the results of these preliminary trials are encouraging for physicians and patients, as shortening of the treatment duration in the majority of patients infected with HCV genotypes 2 and 3 seems to result in similar SVR rates when compared to the current standard duration of 24 weeks of treatment.

The study results reported by Mangia, et al. and von Wagner, et al. confirm the more favorable outcome of patients with HCV genotype 2 infection that had already been observed in previous studies investigating standard treatment duration of 48 *vs.* 24 weeks[9,10].

However, several open questions need to be answered in the future. Compared to the former trials, the role of steatosis as an important factor influencing treatment outcome particularly in HCV genotype 3 infection has not been assessed so far in those patients that undergo shorter treatment durations[10]. Furthermore, Mangia, et al. reported that, independent of the HCV genotype, patients with an early virologic response can be treated for 12 weeks, whereas von Wagner, et al. convincingly showed that patients with genotype 3 infection and high pretreatment HCV-RNA levels exhibit less favorable SVR rates despite an early virologic response. It has to be noted that in the Mangia trial, patients with HCV genotype 2 infection were predominantly included. For patients without early virologic response at week 4, the SVR rates were significantly lower in all three trials, so that in this patient group even an extension of the present standard therapy duration of more than 24 weeks needs to be investigated in future trials[17]. Although not statistically significant, the relapse rates of patients who were treated for 12 weeks and 16 weeks were higher as compared to the relapse rates of those treated for 24 weeks (10 and 12% *vs.* 4 and 5%, respectively) despite an early virologic response at week 4. Furthermore, in two of the three trials, advanced fibrosis was associated with reduced virologic response rates.

Recently, results of the ACCELERATE trial were presented at the annual meeting of the European Association

for the Study of the Liver (EASL 2006) in Vienna (Shiffman et al. J Hepatol 2006, abstract 734). In this large study, 1469 patients infected with HCV genotype 2 and 3 were randomized to receive treatment with PEG-IFNα-2a and 800 mg ribavirin for 16 or 24 weeks. The overall sustained virologic response rates were significanlty greater with 24 rather than with 16 weeks of treatment (76 *vs.* 65%) challenging the results of the three discussed pilot studies. Particulary, in patients with genotype 2 infection, 24 weeks of treatment resulted in higher sustained response rates than 16 weeks (82 *vs.* 65%).

Presently, it is therefore too early to change the recommendations for standard therapy of patients infected with genotypes 2/3 on the basis of these studies. Moreover, as shortened treatment duration in these trials ranged from 12 to 16 weeks, it seems to be necessary to determine the optimal treatment duration with regard to therapy outcome and cost-effectiveness. However, the results of future studies may permit, presumably separately for genotypes 2 and 3, the establishment of individualized treatment duration based on pretreatment HCV-RNA concentration and early virologic response after four weeks of treatment.

Patients with Nonresponse or Relapse to Antiviral Therapy

Although approximately 80% of patients with HCV genotype 2/3 achieve SVR to the current standard therapy, there are still a substantial number of patients with either nonresponse or virologic relapse. In the former patients, HCV-RNA remains detectable in the blood even during the course of treatment. In patients with virologic relapse, HCV-RNA is negative during IFNα-based treatment, but becomes detectable thereafter.

Whereas guidelines for the first-line therapy of patients with chronic hepatitis C are based upon numerous studies with large numbers of patients, optimal therapy of nonresponders and patients with virologic relapse is less well established[11,18]. However, on the basis of therapy improvement in the last few years, there is general agreement of a renewed antiviral therapy with PEG-IFNα plus ribavirin in patients who failed to have a SVR to standard IFN monotherapy, and this is also currently under investigation in nonresponder and relapse patients to standard IFN plus ribavirin treatment. Two large international trials are currently investigating virologic response rates in patients with nonresponse (HALT-C) and patients with nonresponse or relapse (EPIC-3) to standard IFN, with or without ribavirin[19,20]. In both trials, patients receive at least 48 weeks of treatment with either PEG-IFNα-2a (HALT-C) or PEG-IFNα-2b (EPIC-3) in combination with ribavirin, irrespective of the HCV genotype. Interim analyses of patients with genotypes 2/3 from the HALT-C and EPIC-3 trials showed SVR rates of 59 and 56%, respectively. In the EPIC-3 trial, previous relapsers to standard IFNα plus ribavirin have higher SVR rates (63%) as compared to previous nonresponders (47%). Moreover, increasing liver fibrosis is associated with reduced SVR rates.

In the EPIC-3 and HALT-C trials, patients without virologic response at week 12 or 20, respectively, receive a maintenance therapy with low-dose PEG-IFNα, with the aim of reducing fibrosis progression. Results from these therapy arms are not yet available.

Ongoing studies address the treatment of patients infected with HCV genotypes 2/3 and relapse or nonresponse to PEG-IFNα plus ribavirin.

Future Antiviral Strategies in Patients with HCV Genotype 2/3 Infection

A large number of new antiviral enzyme inhibitors (directly targeting for example the HCV NS3 protease or the virus-encoded NS5B RNA-dependent RNA polymerase) are currently under clinical investigation in phase I/II studies. They are expected to fundamentally expand the treatment options for patients infected with chronic hepatitis C. However, due to the variable amino acid sequences of the NS3 and NS5B proteins, the antiviral efficacy of antiviral enzyme inhibitors may be different between HCV genotypes. Indeed, in an early proof-of-principle study of the NS3 protease inhibitor BILN-2061 it was shown that antiviral efficacy was less pronounced and more variable in patients with HCV genotype 2/3 infection compared with previous results in patients with HCV genotype 1[21,22]. A lower affinity of BILN-2061 for the NS3 protease of HCV genotypes 2 and 3 has been suggested as a major contributor to these findings. Therefore, the need for antiviral compounds that specifically target the protease or polymerase of HCV genotypes 2 and 3 may be evaluated in the future, especially for patients with nonresponse to PEG-IFNα and ribavirin combination therapy.

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Does Interferon Improves Portal Hypertension?

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Abstract

Hepatitis C virus infection is a major health problem worldwide, mainly due to the frequent development of advanced liver disease, cirrhosis, and its complications. Most of these complications are associated with the development of clinically significant portal hypertension with variceal bleeding, ascites, bacterial infection, and hepatorenal syndrome. Recently, the use of combined therapy with pegylated interferon and ribavirin has been evaluated and validated in compensated cirrhotic patients. In addition, several large-scale cohort studies are evaluating the long-term efficacy of antiviral therapy on the prognosis of compensated cirrhosis. However, the impact of antiviral therapy on portal hypertension has not been assessed. This review provides some preliminary data suggesting that antiviral therapy decreases portal pressure at the end of therapy and may decrease the incidence of portal hypertension related events. These findings provide a rationale for the development of future trials aimed to evaluate the long-term effects of antiviral therapy in portal hypertension associated to hepatitis C virus cirrhosis. (Hepatology Reviews 2006;3:11-5)

Key words

Portal hypertension. Hepatic venous pressure gradient. Antiviral therapy. Hepatitis C.

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Introduction

It is clearly established that chronic hepatitis C virus infection (HCV) is the major cause of cirrhosis and its complications in the western world[1]. In addition, HCV cirrhosis is the main indication for liver transplantation, indicating the importance of advanced HCV chronic infection. The progression rate of HCV infection is variable, but it is estimated that about 30% of patients progress to liver cirrhosis after 20 years of infection[2]. The presence of cirrhosis implicates the distortion of liver architecture and the presence of vascular abnormalities, inducing an initial increase in intrahepatic vascular resistance, followed by complex functional abnormalities of intrahepatic and splanchnic vascular beds, leading to portal hypertension. Once portal hypertension has developed, the risk of severe complications such as variceal bleeding, ascites, bacterial translocation, hyponatremia and renal failure appears, leading to a marked worsening in prognosis. Therefore, portal hypertension is a principal therapeutic objective in the management of chronic liver diseases.

The actual management of HCV infection is based on combination therapy with pegylated interferon (PEG-IFN) and ribavirin. Although the principal aim of this antiviral therapy is to obtain a sustained virologic response (SVR), defined by the absence of viral replication six months after stopping therapy, several recent reports have suggested an additional beneficial effect of combined antiviral therapy on liver histology with a significant reduction in fibrosis besides the viral response[3,4]. In addition, the combination of PEG-IFN and ribavirin in compensated cirrhosis is relatively safe, without showing a significant increase in severe adverse effects compared to noncirrhotic patients. On the other hand, other physiologic and pharmacologic properties of interferon (IFN), besides its antiviral effect, may have an influence on liver inflammation and inflammatory mediators. Therefore, it is possible to speculate about the potential role of IFN-based antiviral therapy in the pathophysiology of portal hypertension.

In this review we analyze the available data regarding the possible effects of IFN-based antiviral therapy on portal hypertension.

Does Antiviral Therapy Decrease Portal Pressure?

Several papers have clearly shown that the increase of portal pressure, usually estimated by the hepatic venous pressure gradient (HVPG), has a central role in the development of complications of cirrhosis[5-7]. The importance of portal pressure is also clearly demonstrated when analyzing the existence of several threshold values of HVPG for the development of different manifestations of this syndrome. Thus, the decrease of HVPG is an important end-point when treatment of portal hypertension is considered.

Only three studies have evaluated the effect of antiviral therapy on portal pressure.

The first of these studies evaluated the effect of six-month, isolated, non-pegylated IFN administration on portal pressure in chronic hepatitis C cirrhotic patients. In this small placebo-controlled trial, end-of-treatment HVPG was significantly lower than baseline HVPG in IFN-treated patients, while it had increased in placebo-treated patients (Fig. 1). Unfortunately, this study had to be interrupted

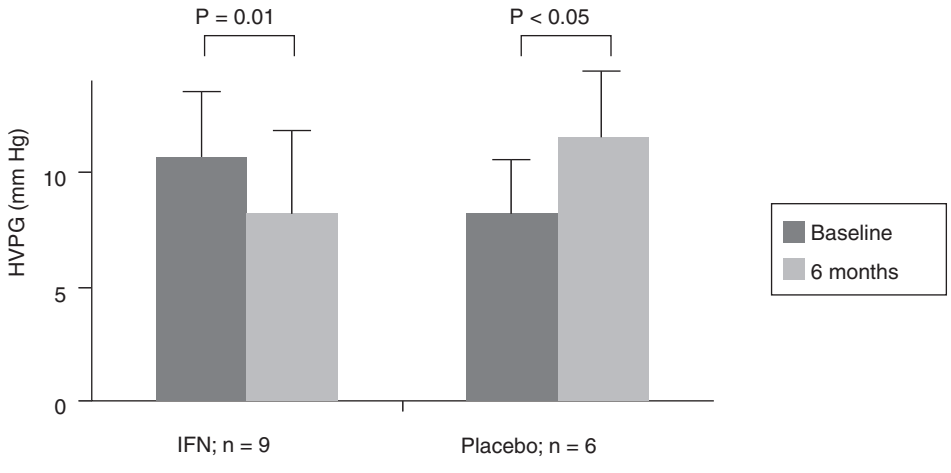

Figure 1. *Effects of non-pegylated interferon and placebo on portal pressure.*

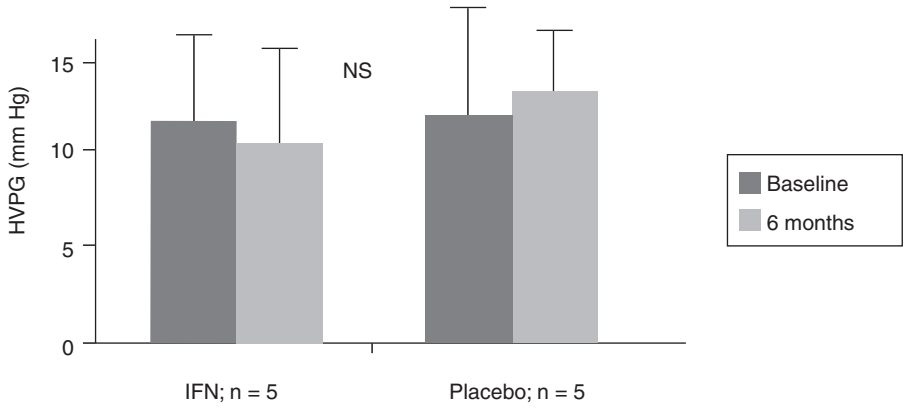

Figure 2. *Effects of non-pegylated interferon and placebo on portal pressure.*

due to the impossibility to assign patients to the placebo group due to ethical considerations[8].

The second evidence regarding the portal pressure decreasing effect of antiviral therapy comes from a sub-analysis of a large, randomized, placebo-controlled trial designed to evaluate the outcomes of cirrhotic patients who were administered isolated non-pegylated IFN for six-months[9]. Repeat measurements of the HVPG before and after treatment were only available in 10 out of 99 patients, five in the active and five

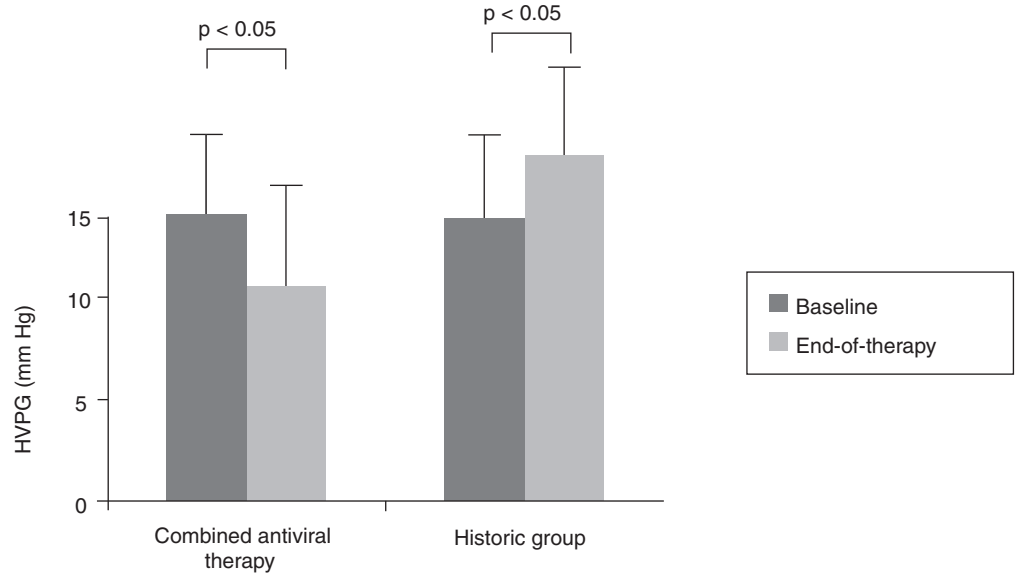

Figure 3. *Effects of combined antiviral treatment (pegylated interferon plus ribavirin) on portal pressure. Antiviral therapy was administered 24-48 weeks according viral genotype.*

in the placebo arm. In this study no effects of antiviral therapy could be detected, probably due to the small sample size (Fig. 2).

The last published study up to now was presented in the last AASLD meeting in Boston in October 2004[10]. This is an open study in which blind evaluation of HVPG measurements performed immediately before and after a 24-48 month course of combined antiviral therapy according HCV genotype was performed in patients with compensated F3-F4 chronic hepatitis C and portal hypertension. The presence of portal hypertension was assessed by an HVPG value > 5 mmHg. Baseline and end-of-treatment liver biopsies were also done. Interestingly, a significant decrease in mean HVPG was observed after antiviral therapy (Fig. 3); this effect was observed in all patients except one who underwent a sudden increase of ALT during therapy. The decrease of HVPG seemed to be related to a decrease in inflammatory activity. In fact, the reduction of HVPG was greater in those patients with normal ALT at the end of therapy. These findings are markedly different from those observed in a historic group of cirrhotic patients in which two different hemodynamic studies were performed after a mean time period of 12 months. In this particular group, paired HVPG measurements showed a significant increase on portal pressure. In addition, only 10% of these patients had a spontaneous decrease of portal pressure.

In summary, there is some evidence suggesting that antiviral therapy may decrease portal pressure immediately after antiviral IFN-based therapy. There is no data regarding the long-term effect of antiviral therapy in portal pressure. However, it seems that the effect might not be maintained in the long term, as suggested by the fact that a third hemodynamic measurement, performed in six non-sustained viral responder patients one year after stopping treatment, showed a significant increase of HVPG. Further studies are needed to determine whether the early portal pressure reducing effect of antiviral therapy is maintained in the long term, especially in sustained viral responders.

Is the Magnitude of Change on Portal Pressure after Antiviral Therapy Relevant?

Several reports[6,7] have clearly suggested that the achievement of an adequate portal pressure reduction after pharmacologic treatment of portal hypertension decreases the probability of developing severe manifestations of end-stage liver cirrhosis such as variceal bleeding, spontaneous bacterial peritonitis, hepatorenal syndrome, and even death. This threshold reduction of portal pressure has been estimated as an absolute reduction of HVPG values to < 12 mmHg, or as a decrease > 20% of baseline value after treatment, and therefore this adequate response is considered as the goal of treatment of portal hypertension.

The magnitude of the decrease of HVPG after antiviral therapy has been only assessed in one study[10], in which 80% of patients with severe portal hypertension, as defined by a baseline HVPG value > 12 mmHg, had a clinically relevant decrease of portal pressure at the end of treatment. Therefore, it is possible to speculate that if the portal pressure decreasing effects of antiviral therapy were maintained in the long term, antiviral therapy could provide an effective prevention of complications of portal hypertension. However, it is very important to emphasize that the effects of antiviral therapy on portal pressure have been assessed only in a very small number of compensated cirrhosis and that no clinical end-points have been assessed. Therefore, there is not enough evidence to recommend the use of antiviral treatment in the management of clinical events related to portal hypertension such as variceal prevention and bleeding, etc. In addition, the effect of antiviral therapy in decompensated cirrhosis has not been assessed. Further studies are needed to evaluate whether the long-term use of antiviral therapy may delay the appearance and decrease the severity of manifestations of portal hypertension.

Is the Effect of Antiviral Therapy on Portal Pressure Translated to Clinically Relevant Variables?

The description of the probable effect of antiviral therapy on portal pressure is a very important finding from a pathophysiologic point of view; however there is limited data regarding the effects of antiviral therapy on clinical manifestations of portal hypertension. A recent randomized study (COPILOT study) was performed in a relatively large number of previous non-responders to combined antiviral therapy, hepatitis C virus compensated, cirrhotic patients[11] with either continuous PEG-IFNα-2b (1.5 μg.kg/week) or colchicine (0.6 mg bid) as a potentially anti-fibrogenic drug. Patients underwent an extensive follow-up, including clinical assessment and repeat liver biopsies, and ultrasonographic and endoscopic examinations, as well as clinical outcomes, were evaluated. Interestingly, the number of patients who had variceal hemorrhage during follow up was lower in the IFN group (11 out of 42 in the colchicine-treated group *vs.* 1 out of 26 in the IFN group). In addition, the cumulative probability of being free of clinical manifestations of portal hypertension was significantly greater in the IFN-treated patients. This study suggests that, irrespective of its antiviral effect, continuous antiviral therapy could have a potential role in the prevention of complications of portal hypertension. Unfortunately this large study does not include hemodynamic measurements that could provide relevant information regarding pathophysiologic aspects. Again, these results are clearly preliminary and should be confirmed by this mentioned study and other ongoing large-scale trials.

Future Investigations

The existence of a possible effect of antiviral therapy on portal pressure and also in the clinical manifestations of portal hypertension is an exciting field that should be exten-

sively studied in the coming years. First, it is crucial to evaluate whether cirrhotic patients who undergo sustained viral response also have a sustained reduction in portal pressure and also whether the magnitude of this effect is relevant in terms of hemodynamic response and clinical end-points such as variceal bleeding, development of ascites etc.

Another important issue to consider is the design of possible strategies of long-term IFN-based therapies aimed not to virologic end-points but to variables related with clinical manifestations of portal hypertension. Duration, dosage, adverse events and costs of this therapeutic approach are critical. It is important to emphasize that an adequate monitoring of these therapies should include the evaluation of changes in portal pressure. In fact it has been suggested that due to the fact that HVPG measurement could represent overall architectural changes and vascular distortion of a greater volume of liver parenchyma, it may allow a more thorough estimation of liver damage[12]. The possibility to expand adequately dosed PEG-IFN monotherapy to patients with some degree of decompensation of liver disease should be cautiously evaluated.

Finally, the mechanisms implicated in portal pressure decreasing effects should be elucidated. One may speculate that, as combination therapy has anti-inflammatory, antifibrotic and immunomodulatory properties besides its antiviral activity, its beneficial effects may not be limited to inhibition of viral replication. Clearly, further studies are required.

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Liver Transplantation in HIV-Infected Patients: Update in 2006

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Abstract

The prognosis of HIV infection has dramatically improved in recent years with the introduction of combined antiretroviral therapy. Currently, liver disease is one of the most important causes of morbidity and mortality, even more so given the high rate of hepatitis C virus (HCV) coinfection in countries where drug abuse has been an important HIV risk factor. Survival of HIV-coinfected patients with end-stage liver disease (ESLD) is poor and shorter than that of the non-HIV-infected population. One-year survival of HIV-infected patients with ESLD is only around 50-55%. MELD score and Child-Turcotte-Pugh classification are useful for assessing the severity of liver disease in these patients and can be used to establish their prognosis and to indicate liver transplantation. HIV infection is no longer a contraindication to transplantation, which is becoming standard therapy in most developed countries. The HIV criteria used to select HIV-infected patients for liver transplantation are quite similar in Europe and North America. Current criteria state that having had an opportunistic infection (e.g. tuberculosis, candidiasis, *Pneumocystis jirovecii* pneumonia) is not a strict exclusion criterion. However, patients must have a CD4 count above 100 cells/mm^3 and a plasma HIV-RNA viral load which is suppressible with antiretroviral treatment. More than 150 orthotopic liver transplantations in HIV-infected patients have been published in recent years and the short and mid-term survival was similar to that of HIV-negative patients. The main problems in the posttransplantation period have been recurrent HCV infection (the principal cause of posttransplantation mortality) and the pharmacokinetic and pharmacodynamic interactions between antiretroviral and immunosuppressive agents. There is little experience with the treatment of recurrent HCV infection. Preliminary studies show rates of sustained virologic response ranging from

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15-20% in HIV/HCV coinfected recipients. Liver transplantation in HIV/HBV coinfected patients has a good prognosis because HBV recurrence can be successfully prevented using immunoglobulins and anti-HBV drugs. Finally, this field is evolving continuously, and the indications for liver transplantation or the management of coinfections may change in the future as more evidence becomes available. (Hepatology Reviews 2006;3:16-29)

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Key words

End-stage liver disease (ESLD). HIV-1-infection. Hepatitis C virus infection. Hepatitis B virus infection. MELD score. Child-Turcotte-Pugh classification. Liver transplantation. Mortality. Prognosis.

Introduction

HIV-related mortality has declined dramatically since 1996 in Europe and the USA with the widespread use of highly active antiretroviral therapy (HAART). Conversely, end-stage liver disease (ESLD), mainly caused by hepatitis C virus (HCV), is becoming an important cause of death among HIV-1-infected patients[1]. Orthotopic liver transplantation (OLT) is the only therapeutic option for patients with ESLD[2]. However, until a few years ago, infection with HIV was an absolute contraindication to any type of transplant. The prognosis and the fear that transplant-associated immunosuppression could speed up the progression to AIDS or increase the risk of opportunistic infections meant that OLT was ruled out[3]. The spectacular improvement in prognosis observed in HIV-infected patients after the introduction of HAART in 1996 has meant that transplantation has now been reconsidered in patients with ESLD. This paper does not aim to provide an exhaustive review of the matter at hand, which has already been amply studied in other recent reviews[4-8]. Our main objective is to define the criteria to select HIV-infected patients for OLT, taking into account that this field is evolving continuously and the indications for OLT or management of these patients may change as more evidence becomes available.

Experience of OLT in HIV-Infected Patients in the HAART Period (1996-2006)

Initial attempts at OLT in HIV infected patients before the introduction of HAART regimens (pre-1996) provided very poor results (Table 1). Putting together the most important case series published[9-12], three-year survival was only 44% (Table 2). Most patients died because of HIV-disease progression, with graft function being normal in many cases. However, since the introduction of HAART in 1996, HIV-infected recipients of liver transplantation have improved their short and mid-term survival. Accumulated experience in North America and Europe in the last 10 years has shown that more than 150 OLT cases were performed[5,6,13-25]. Survival was > 70% in most series, with different periods of follow-up. In more than two-thirds of cases, the primary indication of OLT was HIV/HCV coinfection. Although cases came from different institutions, the criteria used for liver transplantation were quite similar. In general, candidates did not have a prior history of opportunistic infections, CD4 counts > 100 cells/µl, and undetectable plasma HIV-RNA on HAART (or available drugs for successful treatment in the post-OLT period)[6,7]. In a multicenter and multinational retrospective study performed by Ragni, et al., including 23 HIV-infected patients who underwent OLT, survival at three years was 73 and 79% (p = NS) for HIV-infected and non-infected recipients, respectively (Table 2)[13]. Similar rates were seen for graft survival. In all cases published in the HAART era, the main cause of death was due to hepatitis C recurrence. Furthermore, survival of HIV-infected recipients in the HAART era was almost 30% higher than in the pre-HAART era[9-12]. Therefore, at present, HIV infection is no longer a formal contraindication to transplant.

In Spain, the OLT program in HIV-infected patients started in January 2002[25]. To date, 50 liver transplantations have been performed in 48 patients, of whom 90% were HIV/HCV coinfected. There were 10 deaths (20%) after a median follow-up of 12 months (range 5-24 months).

Table 1. *Liver transplantation in HIV-infected patients: main series of cases (≥ 5) before and after HAART*

Author (Reference)	Year	Country	No. of cases	Viral coinfection	Follow up (months)	Outcome (patients alive)
Before HAART (pre-1996)						
Tzakis, et al.[9]	1990	USA	15	Not available	29	7 (47%)
Bouscarat, et al.[11]	1994	France	11	HCV, 9 cases HBV, 2 cases	53	4 (36%)
Gordon, et al.[12]	1998	U.K.	6	HCV, 6 cases	14	0 (0%)
After HAART (1996-2006)						
Prachalias & Boyd[16]	2001	U.K.	7	HCV, 4 cases	3-25	0 (0%)
				HBV, 3 cases	3-33	3 (100%)
Bouscarat, et al.[17]	2002	France	7	Mostly HCV	13	5 (71%)
Roland, et al.[18]	2002	International	19	Mostly HCV	10.5	15 (79%)
Ragni, et al.[13]	2003	International	24	HCV, 15 cases HBV, 7 cases	17	18 (75%)
Neff, et al.[21]	2003	USA	16	HCV or HVB	12	14 (87.5%)
Fung, et al.[6]	2004	USA	29	HCV, 26 cases	18	20 (69%)
Norris, et al.[15]	2004	U.K.	14	HCV, 7 cases	12	2 (29%)
				HBV/OH, 7 cases	19	7 (100%)
Radecke, et al.[20]	2005	Germany	5	HCV, 3 cases	23	2 (40%)
Vogel, et al.[22]	2005	Germany	7	HCV, 4 cases	24	6 (86%)
Duclos-Vallee, et al.[23]	2005	France	7	HCV, 7 cases	22	5 (71%)
Grossi, et al.[24]	2005	Italy	23	HCV, 72%	6	18 (78%)
Miró, et al.[25]	2006	Spain	50	HCV, 96%	12	40 (80%)

Magnitude of ESLD in Europe and North America

According to current estimates, there are around 540,000 HIV-infected patients in Western European countries[26]. Prevalence of HCV and HBV coinfection in European HIV-infected patients was 33 and 9%, respectively[27,28]. So the estimated number of HCV and HBV coinfected patients is around 180,000 and 49,000, respectively. In a cross-sectional study performed in Spain[29], 8% of coinfected patients had clinical or histologic criteria of cirrhosis and 17% of them met the Spanish criteria to be admitted in an OLT waiting list. Therefore, the potential number of candidates for OLT in Europe would be around 3,100 (Table 3).

According to these studies[26,29], in Spain there are 77,000 HCV-coinfected individuals and 7,000 HBV-coin-

Table 2. *Three-year survival of patients with and without HIV-infection who underwent liver transplantation before and during the HAART period*

	Before HAART[9-12] (pre-1996)	During HAART period (1996-2004)[13]	
	HIV-infected patients (n = 32)	HIV-infected patients (n = 24)	Non-HIV infected patients (UNOS) (n = 5,225)
Survival			
– 1 year	69%	87%	87%
– 2 years	56%	73%	82%
– 3 years	44%	73%	79%

HAART: Highly active antiretroviral therapy; UNOS = *United Network for Organ Sharing.*

Table 3. *Estimated number of HIV-infected patients who could be candidates to be evaluated for OLT in Europe and North America*

	Spain[29]	Western Europe [26-28]	North America[6]
HIV-infected patients	140,000	540,000	1,125,000
HCV coinfection	77,000 (55%)	33%	28%
HBV coinfection	7,000 (5%)	9%	9%
Patients with liver cirrhosis*	6,700 (8%)	≈18,000	≈33,000
OLT candidates**	≈1,142 (17%)	≈3,060	≈5,700

*Among coinfected patients: among patients with cirrhosis.

fected patients among a total number of 140,000 HIV-infected patients[15,18]. Using the same calculations, the potential number of candidates to be evaluated for liver transplantation would be around 1142 cases (Table 3).

Criteria for Including HIV-Infected Patients in the Liver-Transplant Waiting List

Liver Disease Criteria

Criteria concerning liver disease are the same as for the non-HIV-infected population, the main indication for OLT in HIV-infected patients was ESLD caused by HCV coinfection. Less frequent indications were HBV coinfection (either acute or ESLD) and liver cancer. The British HIV Association, together with the UK and Ireland Liver Transplantation Center, has recently published a Consensus Guideline reviewing the liver disease criteria as well as the HIV-infection criteria[30]. In this guideline, indications for liver transplantation include acute liver failure, decompensated liver disease (with ascites, encephalopathy –it is important to exclude HIV-related dementia–, or variceal bleeding difficult to manage with standard therapies, and poor liver function, e.g. albumin < 30 g/l, INR > 41.5 and elevated serum bilirubin > 450 mmol/l) and hepatocellular carcinoma (HCC) detected during regular tumor surveillance. Criteria for liver transplantation are: no more

Table 4. *Spanish criteria for OLT in HIV infection[31]**

A. HIV-infected patients who do not fulfil the criteria for HAART
– CD4 lymphocyte count > 350 cells/mm^3.

B. HIV-infected patients who fulfil the criteria for HAART
– No AIDS-defining opportunistic infection except tuberculosis, oesophageal candidiasis or *P. jirovecii* pneumonia.
– Must have a CD4 lymphocyte count > 100 cells/mm^3†.
– Undetectable viral load in plasma HIV-1 RNA <50 copies/ml at the time of the transplant or effective and durable therapeutic options for HIV infection during the posttransplant period.

C. Other criteria and criteria related to risk behaviour
– Abstinence from drugs (heroin, cocaine) for at least two years.
– No consumption of alcohol for at least six months.
– Favorable psychological/psychiatric evaluation.
– Understanding of the techniques and responsibilities involved in OLT.
– Social stability.
– Women must not be pregnant.

*Patients already included on a waiting list for OLT who no longer fulfill the previously mentioned criteria are temporarily excluded and re-included when they fulfill the criteria again.
†Patients who have suffered from tuberculosis, esophageal candidiasis or *P. jirovecii* pneumonia (PCP), must have a CD4 lymphocyte count of >200 cells/mm^3.
HAART: Highly active antiretroviral therapy; OLT: Orthotopic liver transplantation.

Table 5. *HIV criteria for OLT in some European countries and the USA*

	Spain[31]	Italy[24,¶]	U.K.[30]	USA[34]
Previous C events:				
– Opportunistic infections	Some*	None in the previous year	None after HAART-induced immunologic reconstitution	Some†
– Neoplasms	No	No		No
CD4 cell count/mm^3	> 100‡	> 200 or > 100 if decompensated cirrhosis	> 200 or > 100 if portal hypertension	> 100
Plasma HIV-1 RNA viral load BDL on HAART§	Yes	Yes	Yes	Yes

BDL: Below detections levels (< 200 copies/ml).

*In Spain, patients with previous tuberculosis, *Pneumocystis jirovecii* pneumonia (PCP) or esophageal candidiasis can be evaluated for OLT.

†In USA, PCP and esophageal candidiasis were not exclusion criteria.

‡Patients with previous OIs should have > 200 CD4 cells/mm^3.

§If PVL was detectable, post-OLT supression with HAART should be predicted in all patients.

¶Grossi PA and Carosi G, Personal communication.

than three tumor nodules, no nodule greater than 5 cm in diameter, absence of macroscopic portal vein invasion, and absence of recognizable extrahepatic disease[30].

HIV-Infection Criteria in Spain

In Spain, a multidisciplinary Task Force[31] has recently defined the following clinical, immunologic and virologic criteria (Table 4).

Clinical Criteria

Ideally, patients should not have suffered previously from AIDS-defining diseases as they may then have a greater risk of reactivation. However, the improved prognosis post-HAART means that some authors are in favor of withdrawing exclusion criteria for some opportunistic infections that can be efficaciously treated and prevented, such as tuberculosis, candidiasis and *Pneumocystis jirovecii* pneumonia[5,7,20].

The Spanish Task Force considered that the experience with other HIV-infected opportunistic infections and tumors (e.g. Kaposi sarcoma) is still too limited to make any recommendations.

Immunologic Criteria

All groups agreed that the CD4+ lymphocyte count should be > 100 cells/mm^3 for OLT[5-7,19]. This figure is lower than used for kidney transplantation (i.e. CD4 > 200 cells/mm^3) because patients with cirrhosis often have lymphopenia due to hypersplenism, which leads to a lower absolute CD4+ count, despite high CD4 percentages and good virologic control of HIV.

Virologic Criteria

The essential criteria for OLT is that the patient must be able to have effective and long-lasting antiretroviral therapy during the posttransplant period[5-7,31]. The ideal situation is one in which the patient tolerates HAART before transplantation and is ready for the transplant with undetectable plasma HIV viral load by ultra-sensitive techniques (< 50 copies/ml). Nevertheless, this is not always possible for several reasons:

1) In some patients with ESLD, it may be difficult to maintain an undetectable HIV viral load in plasma because they often experience intolerance or toxicity related to antiretroviral drugs, which must then be stopped. In these cases, and to avoid resistance, it is better to save antiretroviral therapy for the posttransplant period.

2) Some patients remain viremic with HAART. In these cases, it is mandatory to carry out antiretroviral sensitivity testing (genotypic or phenotypic resistance testing)[32] to ascertain the real therapeutic options. The evaluating team and HIV experts will have to evaluate whether the patient has effective and durable rescue therapy.

3) Some patients do not have an indication for HAART as they are long-term non-progressors (LTNP) or do not have immunologic criteria (CD4+ lymphocyte count > 350 cells/mm^3) or clinical criteria to start HAART and, therefore, they have viremia that is detectable in plasma. In this setting, it is unknown whether and when (pretransplant or posttransplant) it would be beneficial to initiate HAART in order to reach an undetectable HIV viral load in plasma.

Other Criteria

Furthermore, to include an HIV-infected patient on the OLT waiting list, the candidate must have a favorable

Table 6. *Five-year survival of HIV-infected patients with end-stage liver disease (ESLD)[36,37]*

	Miro[36]	Pineda[37]	
	HIV-infected patients	HIV-infected patients with HCV coinfection	HCV monoinfected patients (control group)
No. of cases	104	180	1037
Survival			
– 1 year	57%	54%	74%
– 2 years	41%	40%	61%
– 3 years	30%	ND	ND
– 5 years	ND	25%	44%

ND: No data available.

psychiatric evaluation. Patients who actively consume drugs will be excluded. In Spain, it is recommended a consumption-free period of two years for heroin and cocaine[31] and six months without addiction for other drugs (e.g. alcohol). Patients who are on stable methadone maintenance programs are not excluded from transplantation and can continue on such programs after the transplant[33]. Finally, as is the case with any transplant candidate, HIV-infected patients must show an appropriate degree of social stability to ensure adequate care in the posttransplant period.

HIV Criteria in Other European and North America Countries

Most liver transplant groups from Europe and North America are using similar HIV criteria as summarized in table 5[24,30,31,34]. We would like to point out that currently to have a previous opportunistic infection is not a strict exclusion criteria in itself. On the other hand, a CD4 cell count > 200 cells/mm^3 is the cut-off used in Italy and the UK unless patients had decompensated cirrhosis or portal hypertension, respectively. In these scenarios, they use the same CD4 cell threshold used in Spain and the USA (e.g. 100 cells/mm^3).

Special Considerations in HIV-Infected Patients

OLT in HIV-infected patients is a complex scenario that requires a multidisciplinary approach[5-7,31]. Sites wishing to carry out transplants in HIV-positive patients must have a multidisciplinary team which can periodically evaluate these patients during the pre- and posttransplant periods. The team should include members from the liver transplant team (medical and surgical), specialists in infectious diseases and HIV, a psychologist/psychiatrist, an expert on alcoholism and drug abuse, and a social worker.

Controversial Issues in the Pretransplant Period

Waiting list mortality in HIV-infected patients with ESLD is very high. This is because survival of HIV-infected patients with decompensated cirrhosis is much lower than in HIV-negative patients[36-38]. Pineda, et al.[37] have recently shown in a multicenter case-control study performed in Andalusia (Spain) that the outcome of cirrhosis after the first decompensation in HIV/HCV coinfected patients is much worse than in the HCV-mono-infected population. Survival at one, two and five years for coinfected and mono-infected populations was 54 and 74%, 40 and 61%, and 25 and 44%, respectively (Table 6)[37]. In another study[38], the same group of investigators identified as independent predictors of a poor outcome in HIV/HCV coinfected patients the severity of liver disease (Child-Turcotte-Pugh [CTP] classification, or developing hepatic encephalopathy as the first hepatic decompensation) and the level of cellular immunosuppression (< 100 CD4 cells/mm^3). On the other hand, HAART was associated with reduced mortality[38]. Concerning the antiretroviral therapy, these patients should follow the general recommendations[39-41] and their liver function must be closely monitored in order to detect hepatotoxicity. Furthermore, some antiretroviral drugs may be contraindicated in cirrhotic patients (i.e. didanosine) and their dosing should be adjusted according to the degree of hepatic impairment (Table 7)[41-44].

In our experience, we have followed the evolution of 104 HIV-infected patients with cirrhosis after their first hepatic decompensation or HCC[36]. Median survival time of our cohort was 17 months, similar to the Merchante cohort (13 months)[38]. We included HCV-infected and non-infected patients and we did not find significant differences in survival according to the etiology of cirrhosis, suggesting that HIV-infected patients have an overall poor outcome regardless of the nature of their liver disease. Furthermore, MELD score was the only factor independently associated with mortality. This is of relevance because during the last years MELD has been increasingly used to establish the prognosis of patients

Table 7. *Dosing of antiretroviral agents according to the degree of hepatic dysfunction in cirrhotic patients*[41-44]

Drug name	Hepatic impairment
NRTIs	
Abacavir (ABC)	Mild hepatic impairment (Child-Pugh score 5-6): 200 mg BID. To enable dose reduction, Ziagen® Oral Solution (10 ml BID) should be used. Moderate to severe hepatic impairment: the safety, efficacy, and pharmacokinetic properties of abacavir have not been established, therefore ABC is contraindicated.
Didanosine (ddI)	Usual dose. Close monitoring is required for evidence of toxicity. Some authors do not recommend its use in cirrhotic patients. Didanosine should not be coadministered with ribavirin during hepatitis C therapy.
Emtricitabine	Usual dose (no data available, but based on the minimal hepatic metabolism it is unlikely that a dose adjustment would be required).
Lamivudine (LAM)	Usual dose.
Stavudine	Usual dose.
Zalcitabine	Usual dose.
Zidovudine (ZDV)	A decrease in ZDV oral clearance by 32, 63, and 70%, was observed, respectively, in patients with mild, moderate-to-severe liver disease, or biopsy-proven cirrhosis, compared to control subjects. Some authors suggest 200 mg BID in patients with severe liver disease. Frequent monitoring for hematologic toxicities is advised.
NRTIt	
Tenofovir	Usual dose
NNRTI	
Efavirenz (EFV)	Mild-to-moderate hepatic impairment: usual dose. Patients should be monitored carefully for dose-related adverse events, especially nervous system symptoms. Severe hepatic impairment: EFV must not be used. In the single patient studied with Child Pugh grade C half life was doubled. Limited data showed a fourfold increase in EFV AUC in two patients with liver disease (one of them with cirrhosis).
Nevirapine (NVP)*	Mild-to-moderate hepatic impairment (Child-Pugh ≤7): usual dose. However, patients with moderate hepatic impairment should be monitored carefully for dose-related adverse events (in a study with four patients with moderate hepatic impairment (Child-Pugh B), NVP AUC increased by 41%). Severe hepatic impairment: should not be used. NVP should not be used for HCV coinfected patients (risk of increased fibrosis and fibrosis progression rates). An increased risk of hepatotoxicity was observed in women with a baseline CD4 count > 250 cells/mm^3 and men with > 400 cells/mm^3.
PI	
Amprenavir (APV)	APV (unboosted): Child-Pugh 5-8: 450 mg BID. Child-Pugh 9-12: 300 mg BID. Consider TDM when possible. Some authors recommend APV 600 mg BID or 1200 mg QD in moderate-to-severe hepatic impairment, as changes in the AUC for APV are similar to those produced when boosting by RTV in the absence of liver impairment. APV boosted with RTV: no data. Concomitant administration should be used with caution in patients with mild and moderate hepatic impairment and is contraindicated in patients with severe hepatic impairment. Avoid Agenerase® oral solution due to the risk of propylene glycol accumulation and toxicity.
Atazanavir (ATV)	Moderate hepatic impairment/Child-Pugh B (7-9): a dose reduction to 300 mg QD should be considered for patients who have not experienced prior virologic failure. Some authors recommend unboosted ATV 400 mg QD for treatment-experienced patients. Severe hepatic impairment/Child C (> 9): should not be used. ATV boosted with RTV: no data (use with caution if mild hepatic impairment; should not be used if moderate-severe hepatic impairment).
Fosamprenavir (FPV)	FPV (unboosted with RTV): Mild-to-moderate hepatic impairment (Child-Pugh 5-8): 700 mg BID. Severe hepatic impairment (Child-Pugh > 9): should not be used. FPV/RTV: limited data. Should be used with caution in patients with mild or moderate hepatic impairment and is contraindicated in those with severe hepatic impairment.

Table 7. *Continued*

Drug name	Hepatic impairment
PI	
Indinavir (IDV)	IDV (unboosted with RTV) Mild-moderate hepatic impairment: 600 mg TID. Severe hepatic impairment: no data. Consider TDM when possible. IDV boosted with RTV: some HCV/HBV-HIV coinfected patients may need dose reductions, usually IDV/RTV 400/100 mg BID, or even IDV/RTV 200/100 mg BID.
Lopinavir/r (LPV/RTV)	Mild-to-moderate hepatic impairment: usual dose. An increase of approximately 30% in LPV exposure has been observed, but is not expected to be of clinical relevance. Severe hepatic impairment: no data are available. According to the manufacturer, LPV/RTV should not be given to these patients. Pharmacokinetic studies showed conflicting data. A small study compared LPV AUC between HCV or HBV coinfected HIV patients (n = 26; n = 7 cirrhotic) and HIV infected controls. No statistically significant differences were observed. In contrast, a 71% increase in LPV AUC was observed in patients with moderate hepatic impairment, compared to those with normal hepatic function. Consider TDM when possible.
Nelfinavir (NFV)	Usual dose. Hepatic impairment significantly increases (↑49-69 % AUC) the levels of nelfinavir. Nevertheless, data do not indicate increased toxicity.
Ritonavir (RTV)	Mild-to-moderate hepatic impairment: usual dose. Severe hepatic impairment: should not be given.
Saquinavir (SQV)	Mild hepatic impairment: usual dose. Moderate hepatic impairment (SQV ± RTV): has not been studied. Use with caution. Severe hepatic impairment: avoid use.
Tipranavir (TPV)	Limited data. Mild hepatic impairment: usual dose. Moderate hepatic impairment: TPV/RTV use has to be considered on an individual basis with close patient monitoring. Severe hepatic impairment: avoid use.
Fusion inhibitors	
Enfuvirtide (T-20)	No data available, but based on information that this drug does not have either hepatic or renal metabolism, it is unlikely that a dose adjustment would be required. Some authors recommend their use in liver transplantation.

AUC: area under the plasma concentration time curve; BID: twice daily; HBV: hepatitis B virus; HCV: hepatitis C virus; NRTIs: nucleoside analogs; NRTIt: nucleotide analogs; NNRTI: nonnucleoside reverse transcriptase inhibitors; PI: protease inhibitors; QD: once daily; TID: three times a day.

*The first 18 weeks of treatment is a critical period which requires close monitoring. The risk of hepatic events is greatest in the first six weeks. Women and patients with higher CD4+ cell counts are at increased risk of hepatic adverse events. However, the risk continues past this period and monitoring should continue at frequent intervals throughout treatment. Monitoring of hepatic tests should be done every two weeks during the first two months of treatment, at the third month, and then regularly thereafter. Liver test monitoring should be performed if the patient experiences signs or symptoms suggestive of hepatitis and/or hypersensitivity.

with cirrhosis and, consequently, to indicate liver transplantation.

In our experience, once the HIV-infected patient with ESLD is included in the transplant waiting list, mortality of HIV-infected patients remained very high (67%). This occurred mainly because in our centre, as in most other Spanish centers, prioritization for organ allocation was predominantly established on the basis of the time in the waiting list. In comparison, the annual mortality rate for non-HIV-1 infected patients while on the liver transplant waiting list in our center ranged between 8 and 12% in recent years. High mortality rates of HIV/HCV coinfected patients with ESLD waiting for liver transplantation has been previously reported in two studies[45,46]. In one of these studies[46], mortality rates during pretransplant evaluation among HIV-positive (n = 58) and HIV-negative (n = 1359) patients were 36 and 15%, respectively ($p < 0.001$).

For these reasons, physicians attending cirrhotic HIV-infected patients should prospectively follow these patients and they should evaluate them early for OLT after the first clinical decompensation of the liver dis-

ease: i.e. ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, gastroesophageal variceal bleeding and/or jaundice. Similarly, patients whose cirrhosis is associated with HCC should also be evaluated. Both prevention and effective treatment of these complications may improve the likelihood of patient survival until OLT[47,48].

Organ transplantation in HIV-infected patients has raised ethical problems which have not yet been completely resolved. However, currently most groups agree that HIV-infected patients should receive the same treatment as other patients and be included on waiting lists under the same conditions[49].

The pretransplant evaluation of donor and recipients should be the same as for non-HIV-infected patients. With respect to the type of donor to be used in HIV-infected patients, most solid organ transplants were carried out using cadaveric donors. In recent years, and as a consequence of the increased demand for organs, the number of living donors has increased. Nevertheless, the benefits of this technique have yet to be demonstrated in the HIV-infected population.

Issues to Consider in the Posttransplant Period

After OLT, patients and physicians start a new and complex clinical situation. Patients must receive a large quantity of medication, and this can compromise adherence. In addition to HAART, which they may be accustomed to, they must take immunosuppressive drugs and the habitual prophylaxis against opportunistic infections and other medications to manage complications that frequently develop after OLT (e.g. diabetes, hypertension). Patients on methadone programs must continue with this. HCV coinfected patients may require therapy with interferon (IFN) and ribavirin.

In this new scenario, what are the current data regarding the course of HIV infection, immune suppression and allograft rejection, pharmacologic interactions among the different type of drugs used and the course of HCV and HBV infection recurrence?

HIV Infection and Antiretroviral Therapy

Patients usually follow the same HAART regimens that they took during the pre-OLT period, but these regimens can be changed in the post-OLT period on an individual basis in order to choose the easiest regimen to adhere to, with lower potential for pharmacologic interactions with immunosuppressive agents and anti-HCV drugs, and lower liver toxicity. In any case, we should follow the general recommendations for antiretroviral therapy in adults[39-41] and liver function must be closely monitored in order to detect hepatotoxicity. Furthermore, HIV-infected patients should have a lot of support at all times and understand the importance of correct adherence to all their treatment schedules.

We have solid data showing that HIV-infected patients did not have an increased risk of postoperative complications or a higher incidence of opportunistic infections or tumors than HIV-negative patients[5-8]. CD4 cell counts remain stable and plasma HIV viral load undetectable as long as HAART can be administered. Furthermore, immunosuppressive drugs (e.g. calcineurin inhibitors, mycophenolic acid, prednisone) can reduce HIV replication in two ways: first, by reducing the immune activation induced by HIV; and, second, because calcineurin inhibitors and mycophenolic acid have direct anti-HIV activity[6,7]. Furthermore, mycophenolic acid enhances abacavir action against HIV[50].

Immunosuppression and Rejection Issues

There are no specific immunosuppressive regimens for HIV-infected patients, and each centre uses the same regimens as for HIV-negative patients. As mentioned previously, the use of standard immunosuppressive therapy in patients with well-controlled HIV infection did not increase their susceptibility to opportunistic infections or malignant conditions[5-8]. Therefore, HIV-infected patients should follow the same prophylaxis protocols as the general population. In some studies, the rates of allograft rejection were higher than in the HIV-negative population. The cause of this phenomenon is unknown, and it is particularly noticeable in kidney transplants[51,52], suggesting that HIV does not protect against allograft rejection. At present, the best regimen of immunosuppression in HIV-infected recipients is unknown.

Pharmacologic Interactions

There are important pharmacologic interactions between antiretrovirals and immunosuppressive or anti-HCV drugs that may be clinically relevant[40-44,53-64] and these are summarized in table 8.

Cyclosporine A, tacrolimus and sirolimus are metabolized in the liver using cytochrome P-450, whereas mycophenolate mofetil undergoes glucuronization in the liver. Antiretrovirals can act as inhibitors or inducers of these enzymatic systems. When they act as enzyme inhibitors (e.g. protease inhibitors [PI]), they increase concentrations of these immunosuppressants and can lead to toxicity. For this reason, doses must be markedly reduced (e.g. tacrolimus 1 mg/week in patients taking Kaletra®)[56-58]. These interactions have caused some episodes of acute rejection in patients who stopped protease inhibitors while taking calcineurin-inhibitors. On the other hand, when antiretrovirals act as enzyme inducers (e.g. nonnucleoside reverse transcriptase inhibitors, [NNRTI]), they reduce drug levels and can trigger rejection, and so doses of most immunosuppressive drugs must be increased[59]. Therefore, it is important to know very well the possible drug interactions and closely monitor the levels of immunosuppressive drugs. In addition, there are important, overlapping, acute and chronic toxicities between

Table 8. *Drug interactions between antiretroviral agents and immunosuppressive drugs*

Drug	Mycophenolate mofetil (MFL)	Cyclosporin A (CyA)	Sirolimus (SRL)	Tacrolimus (TCL)
Abacavir	Both abacavir and mycophenolate are eliminated mainly by glucuronidation. However, clinically important drug-drug interactions have not been reported.			
Amprenavir	Theoretically, based on elimination pathways, pharmacokinetic drug-drug interaction is unlikely.	Risk of increased drug levels/toxicity of immunosuppressive drugs. Markedly lower doses of immunosuppressive drugs may be required. TDM of CyA, SRL and TCL is recommended.*		
Didanosine	Theoretically, based on elimination pathways, a pharmacokinetic drug-drug interaction is unlikely.			
Efavirenz	Theoretically, based on elimination pathways, pharmacokinetic drug-drug interaction is unlikely.	Minimal interactions with EFV and CyA or TCL are expected. Some patients needed an initial CyA dose of 350-450 mg b.i.d, followed by a maintenance dose of 250-400 mg b.i.d. TDM of CyA, SRL and TCL is recommended.		
Indinavir	Theoretically, based on elimination pathways, pharmacokinetic drug-drug interaction is unlikely.	Risk of increased drug levels/toxicity of immunosuppressive drugs. Markedly lower doses of cyclosporine and tacrolimus may be required. Some patients needed an initial CyA dose of 75-100 mg b.i.d., followed by a maintenance dose of 75 mg b.i.d. TDM of CyA, SRL and TCL is recommended.*		
Lamivudine	Theoretically, based on elimination pathways, a pharmacokinetic drug-drug interaction is unlikely. However, as lamivudine is primarily renally excreted, nephrotoxic drugs could impair its elimination.			
Lopinavir/ritonavir	Theoretically, mycophenolate glucuronidation could be increased (and blood levels reduced) by RTV.	Risk of increased drug levels/toxicity of immunosuppressive drugs. Markedly lower doses of cyclosporine may be required. Some patients needed an initial dose of 25 mg b.i.d of CyA. Patients on LPV/r + TCL may need a dose reduction to 1 mg once weekly or even less. When LPV/r is initiated in a patient on TCL, the next TCL dose may need to be delayed for 3-5 weeks, depending on hepatic function. TDM of CyA, SRL and TCL is recommended.*		
Nelfinavir	Theoretically, mycophenolate glucuronidation could be increased (and blood levels reduced) by NFV.	Risk of increased drug levels/toxicity of immunosuppressive drugs. Markedly lower doses of cyclosporine, tacrolimus and sirolimus† may be required. Some patients needed an initial dose of 50-75 mg b.i.d of CyA, followed by a maintenance dose of 25 mg b.i.d. Some patients on TCL + NFV required a 40 to 70-fold dose-reduction (to 0.5 mg q.d. or even less). TDM of CyA, SRL and TCL is recommended.*		
Nevirapine	Theoretically, based on elimination pathways, a pharmacokinetic drug-drug interaction is unlikely.	Theoretically, may require increased immunosuppressive drug dosage. Minimal interactions with CyA and NNRTI are expected. Some patients needed an initial dose of 200-250 mg b.i.d of CyA, followed by a maintenance dose of 100-175 mg b.i.d. TDM of CyA, SRL and TCL is recommended.		
Ritonavir	Theoretically, mycophenolate glucuronidation could be increased (and blood levels reduced) by RTV.	Risk of increased drug levels/toxicity of immunosuppressive drugs. Markedly lower doses of cyclosporine may be required. TDM of CyA, SRL and TCL is recommended.*		
Saquinavir	Theoretically, based on elimination pathways, a pharmacokinetic drug-drug interaction is unlikely.	Risk of increased drug levels/toxicity of immunosuppressive drugs. Markedly lower doses of cyclosporine may be required. TDM of CyA, SRL and TCL is recommended.*		

Table 8. *Continued*

Drug	Mycophenolate mofetil (MFL)	Cyclosporin A (CyA)	Sirolimus (SRL)	Tacrolimus (TCL)
Stavudine	Theoretically, based on elimination pathways, a pharmacokinetic drug-drug interaction is unlikely.			
Tenofovir	Theoretically, based on elimination pathways, a pharmacokinetic drug-drug interaction is unlikely.	Increased risk of nephrotoxicity	Theoretically, based on elimination pathways, a pharmacokinetic drug-drug interaction is unlikely.	Increased risk of nephrotoxicity
Zalcitabine	Theoretically, based on elimination pathways, a pharmacokinetic drug-drug interaction is unlikely.			
Zidovudine	Both zidovudine and mycophenolate are eliminated mainly by glucuronidation. However, clinically important drug-drug interactions have not been reported.			

b.i.d: twice daily; CyA: cyclosporin A; EFV: efavirenz; LPV/r: lopinavir/ritonavir; MFL: mycophenolate mofetil; NFV: nelfinavir; q.d.: once daily; SRL: sirolimus; TCL: tacrolimus;TDM: therapeutic drug monitoring.
*The antiretroviral is an inhibitor of the P450 isoform CYP3A, which is the primary elimination pathway of CyA, SRL y TCL. Co-administration with the antiretroviral may result in increased plasma concentrations of these immunosuppressive drugs. Patients on protease inhibitors require markedly lower doses of cyclosporine, with continued lowering of the cyclosporine dose over time and ongoing cyclosporine trough monitoring because of progressively increasing cyclosporine bioavailability.
†Even with one-fifth of the recommended dose of NFV (250 mg/12 h), a nine-fold increase in sirolimus trough concentration, three-fold increase in peak concentration, and 60% increase in the area under the concentration curve 0 to 24 hours has been observed in a liver transplantation patient, compared with patients who were not on NFV.

antiretroviral and immunosuppressive drugs that should be taken into account (e.g. liver, renal and/or bone marrow toxicities, hyperlipidemia, diabetes, osteoporosis)[7,8,40,41]. As a consecuence of these important interactions between some antiretroviral families (i.e. NNRTI or PI) and immunosuppressive drugs, some researchers are using enfuvirtide (T-20) plus two nucleoside reverse transcriptase inhibitors (NRTI) in order to avoid these interactions[65].

There are also important pharmacodynamic interactions between some nucleoside reverse transcriptase inhibitors (e.g. didanosine, stavudine, zidovudine and zalcitabine) and ribavirin, a drug used in combination with pegylated interferon (PEG-IFN) to treat HCV infection recurrence in OLT recipients. These interactions have been reviewed in-depth elsewhere[66,67].

Finally, given the speed with which new antiretrovirals appear and thus generate unknown interactions, physicians are recommended to consult updated databases on drug interactions[43,44].

Course of HCV-Infection Recurrence

After OLT, HCV-infection recurrence is universal, regardless of whether the patient is infected by HIV or not. At present, it is not known whether recurrence is worse in the HIV-positive patient than in the HIV-negative patient[13]. Similarly, there is insufficient experience on the efficacy and safety of therapy with interferon (IFN) and ribavirin in HIV/HCV coinfected transplant patients. A rapid progression of HCV-related liver disease in HIV-infected recipients would represent a major drawback and lead to a shortened life expectancy of these patients.

In the experience of Samuel's group, five out of seven HIV/HCV coinfected patients survived after a median follow-up of 21 months[23]. There was an early (< 2 months) and severe relapse of HCV infection in all cases. Chronic hepatitis was developed in all but one case within the first year after transplantation. These investigators also detected a faster progression of liver fibrosis at one and two years in HIV-infected recipients in comparison with mono-infected HCV patients. Finally they observed mitochondrial toxicity in most patients studied. Liver steatosis was present in six out of seven liver biopsies and an abnormal respiratory chain (complex IV) function was detected in the five patients studied. It is important to point out that didanosine was included in the HAART regimen in four cases.

There is some preliminary data of the efficacy of the treatment of HCV reinfection in HIV-infected patients with IFN or PEG-IFN and ribavirin. In three small studies, the rates of sustained virologic response (SVR) by intention-to-treat analysis ranged from 14-18%[21,23,25].

Mortality data are controversial. In some single sites the experience is very negative[15]. Norris, et al. reported that five out of seven English HIV/HCV coinfected patients who underwent OLT died after a median follow-up of

around six months. Most died of complications due to recurrent HCV infection and sepsis, despite anti-HCV therapy in three cases[15]. Ragni, et al.[13] suggested that there was a trend of poorer outcome in HIV/HCV coinfected patients in comparison with HIV-negative recipients, but differences did not reach statistical significance. Conversely, other American[48,49], Spanish[25] and Italian[24] (G. Carosi and P. Grossi, personal communication) studies showed better results, with low mortality rates at midterm (1-3 years).

Course of HBV Infection

HBV replication is a contraindication for OLT, so only patients without plasma DNA-HBV viremia are accepted for OLT. As HBV infection recurrence can be successfully prevented using hepatitis B immunoglobulins and anti-HBV drugs (lamivudine, tenofovir, adefovir), the outcome of HBV infection after OLT is much better[5-8,14,68]. Adefovir and tenofovir have proved useful against HBV and could be used in cases of resistance to lamivudine[68]. HIV-positive patients who require antiretroviral therapy and have chronic HBV infection can use lamivudine (or emtricitabine) and tenofovir as part of triple antiretroviral therapy[45,46,68].

Conclusions

Surviral of HIV-coinfected patients with ESLD is poor and shorter than that of the non-HIV-infected population. All HIV-infected patients with ESLD should be considered as candidates for OLT if they meet the HIV inclusion criteria stated here. There is increasing experience with OLT in HIV-infected patients and current data show that short and mid-term survival is the same as that of HIV-negative patients. HIV infection can be easily controlled with antiretroviral therapy during the posttransplant period. The evaluation and the pre- and post-OLT management of this complex scenario should include an interdisciplinary team composed of members of the OLT team (hepatologists and surgeons), infectious diseases and HIV specialists, psychologists, social workers, and members of alcohol and other drug detoxification programs. Interactions between immunosuppressive agents and antiretrovirals, especially protease inhibitors, and to a lesser extent NNRTI, are important and require close monitoring of immunosuppression plasma levels. Patients do not have a greater risk of opportunistic infections or tumors, and therefore should follow the same prophylaxis protocols as the non-HIV-infected population. In patients receiving OLT for HCV cirrhosis, recurrence of the HCV infection is universal during the posttransplant period. It is unknown whether this reinfection has a worse outcome than in HIV-negative patients and there is insufficient experience with PEG-IFN and ribavirin in this population. Outcome of patients who have received a transplant due to HBV cirrhosis seems to be much better, since there is an efficacious prophylaxis against recurrence (HBV-specific immunoglobulin and anti-HBV drugs).

Future Research Needs

There are several issues that should be explored in the future:

1) Since survival of ESLD is much shorter in HIV-coinfected patients, strategies to make OLT available sooner after patient assignment to this procedure should be underlined.

2) Currently, there are many sites with active OLT programs in HIV-infected patients, but the number of cases is too small in every single institution to obtain valuable clinical information. The NIH-sponsored multicenter OLT trial (2005-7) that is being performed in the USA will be very useful. A FIPSE-founded study (2006-8) is also being performed in Spain. For these reasons, it would be important to create an international registry of cases, using standardized CRF in order to know the mid and long-term survival of OLT in HIV-infected patients and to compare it with the non-HIV-infected population.

3) Improving the management of pharmacokinetic and pharmacodynamic interactions between immunosuppressive, antiretroviral and anti-HCV drugs.

4) Knowledge of the most adequate immunosuppressive regimens for HIV-infected recipients.

5) Knowledge of the natural history of OLT HCV reinfection and improving the management of this complication in coinfected patients.

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Treatment for Hepatitis C in Jailhouses is Possible and Successful. Data from the First National French Study (POPHEC)

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Abstract

Background: A French survey in 85 prisons in 2000 yielded disappointing results regarding diagnosis and treatment of hepatitis C (HCV) in inmates: serology was available for two thirds of the patients, only 36% had undergone liver biopsies and 4% had been treated. Liver biopsy access was identified as an obstacle to therapy. This prospective study (POPHEC) was designed to increase treatment access in this population. Methods: 37 prison medical units participated. Patients were all to be treated by pegylated interferon alpha 2b and ribavirin combination. Liver biopsies were optional. When final data of the results of treatment are not available, patients have been included in nonresponders. Results: As of 1st June 2004, 200 patients were analyzed: 94% were men, with a mean age of 37 years, contamination route IVDU in 78%, transfusion in 3%. Genotype was 1a, 1b, 3a and 4 in 28, 11, 36 and 7%, respectively; 12% were coinfected with HIV; 37% were treated by methadone or buprenorphine; 33% had liver biopsy before treatment; 47.5% patients experienced complete sustained response. Conclusion: treatment for HCV in jailhouses is feasible and successful; limitation in indications for liver biopsies, specifically apply to the inmate population and facilitate access to HCV therapy. (Hepatology Reviews 2006;3:30-32)

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Key words

HCV. POPHEC. Prisons. Liver biopsy.

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In France, the medical units (UCSA), which are in the Ministry of health, were created by law for the medical care of inmates in January 1994 after an HIV epidemic in prisons during the 1980s. More than 60% of drug users are or were inmates during their lifetime. In France, two thirds of drug users are hepatitis C virus (HCV) positive. There was no national survey available for the prevalence of hepatitis C in French prisons, the only data available being from local surveys[1-6]. Prevalence was very different according to type of prison and type of inmate (range: 2-27%). Prevalence of hepatitis C in the general population in France is 0.86%. For many hepatologists, inmates had not been treated for multiple reasons: drugs users, too short a stay in prison, bad quality of follow-up. The first national French survey[7] of hepatitis C screening and therapy in 85 prisons (47% of total) in 2000 yielded disappointing results regarding diagnosis and treatment of HCV in 48,000 inmates (half of the national prison population). The results of this study showed that 97% of medical units take care of chronic viral hepatitis C, but serology was possible only for 71% of total of inmates. The rate of hepatitis C was 6.3% in inmates (range: 0-20%). Only 36% of patients had undergone liver biopsy (LB), which was necessary before treatment. A five-week mean delay was observed before LB (range: 3 days to 4 months). In the 85 jailhouses, 153 patients had been treated – only 4% of inmates with positive HCV serology.

In this first survey, LB access was identified as an obstacle to HCV antiviral therapy. We decided to organize the POPHEC STUDY (which means in French the first study of treatment of hepatitis C in prisons) with 37 medical units in French prisons in March 2001 (Table 1). This prospective study was designed to increase access to treatment amongst this population. LB was optional. Patients were all treated with pegylated interferon alpha 2b (PEG-IFNα-2b) 1.5 mg/kg/week) and ribavirin (800-1200 mg/day according to bodyweight) combination therapy. The duration of treatment was 24 weeks for HCV genotypes 2 and 3, and 48 weeks for HCV genotypes 1 and 4. Biochemical, virologic and clinical data were collected for all patients. Therapy and data collection continued for patients transferred. When the results of treatment outcome were not available, patients have been included in nonresponders. Two hundred and seventeen patients were included. As of June 1st 2004, the data from 200 patients was analyzed, six months after the end of antiviral treatment. The sample consisted 94% of men and 6% of women. The mean age was 37 years (18-51 years). The contamination route was intravenous drug users in 78% of cases and blood transfusion in 3%. The others types of contamination were rare and unknown in 11% of patients. HCV genotype was 1a, 1b, 3a, 2 and 4 in 28, 11, 36, 3 and 7%, respectively; 15% were not available. Twelve percent of patients were also infected with HIV. They have been treated with the same drugs and duration. None of the patients in the sample were coinfected with hepatitis B virus. Thirty-seven percent of patients were also receiving drug substitution with methadone (12%) or buprenorphine (25%). Before treatment, the average viral load of HCV was 1227689 IU/ml. In total, 33% had LB before treatment, with a mean histological Metavir score of A1.8 F1.7 and mean Knodell score of 8.0. For the first 100 patients included in the study, 36% had LB and for the second group (patients 101 to 200), only 30% had LB. This was probably applying the guidelines from the French conference of consensus on hepatitis C treatment of February 2002[8]. The mean antiviral treatment duration was available for two groups of patients: it ranged from seven months for patients completing therapy to four months in patients with early termination due to medical and non-medical reasons (patients transferred without hepatology care, adverse effects or voluntary end of treatment). There were no serious adverse effects from hepatitis C treatment. Virologic data is not available for 61 patients and 44 patients did not respond. The number of unknown treatment outcome is more important in medical units who included more than 20 patients in the sample than medical units who included less than 10 patients (29 *vs.* 11%, $p < 0.05$). The patients without virologic response were similar by sex, gender and HCV genotype. So, we could say that 95 patients (47.5% of included cases) experienced complete sustained virologic response. For available data, the virologic response was 68.3%. The medical factors of sustained response were similar as general studies of HCV

Table 1. *Medical units of POPHEC*

Marseille Les Baumettes	Fleury-merogis	Le Mans
Brest	Nimes	Carcassonne
Perpignan	Orleans	Toulouse
Chalons En Champagne	Cahors	Gradignan
Lyon	Saint Martin De Re	Douai
Toulon	Maubeuge	Avignon
Rennes	Rouen	Tarascon
Aix	Liancourt	Laon
Reims	Nice	Chateau-thierry
Loos Les Lille	Salon	Melun
Bethune	Longuenesse	Valenciennes
Dunkerque	Arras	Gonesse
Saint Aubin Les Elboeuf		

treatment: genotypes 2 and 3, complete treatment and no infection with HIV.

In conclusion, treatment for HCV in jailhouses is feasible and successful; limitation in indications for LBs, as recommended by the 2002 French consensus conference[8], specifically apply to the inmate population and facilitate access to HCV therapy, as well as initiatives such as POPHEC, which included hepatologists and general practitioners. A new national French survey[9] of hepatitis C diagnosis and therapy shows an increase in the number of inmates treated, from 4 to 19%!

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Clinical Implications of Hepatitis B Virus Genotype

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Abstract

Currently, hepatitis B virus (HBV) has been designated eight genotypes (A-H) based on genome sequence divergence. The epidemiology of HBV genotypes and their implications on the natural history and the response to antiviral therapy have become increasingly recognized in both Asian and Western countries. Genotypes A and D occur frequently in Africa, Europe, and India, while genotypes B and C are prevalent in Asia. Genotype E is restricted to West Africa, and genotype F is found in Central and South America. The distribution of genotypes G and H is less clear. Genotype B has been shown to be associated with a better clinical outcome than genotype C; genotype D has been shown to have a less favorable prognosis than genotype A. Nonetheless, the clinical significance of genotypes E to H remains to be examined. Regarding treatment outcome, accumulating lines of evidences indicate a better sustained response to conventional interferon in patients with genotype B than those with C, and in patients with genotype A than those with D. On the other hand, conflicting results exist regarding the response to pegylated interferon. In addition, the therapeutic responses to nucleos(t)ide analogues are comparable among patients with different HBV genotypes. In conclusion, clinical and pathogenic differences do exist among HBV genotypes, and further research is needed on the molecular and virologic mechanisms underlying the clinical phenotypes of different HBV genotypes. The impact of HBV subtypes, mixed genotype infections, and recombinants of different genotypes on the natural course of HBV infection, as well as response to antiviral treatment, awaits further examination. (Hepatology Reviews 2006;3:33-40)

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Key words

HBV. Genotypes.

Introduction

Hepatitis B virus (HBV) infection is a global health problem and has a wide spectrum of clinical manifestations[1-4]. Thus, it is important to clarify the factors affecting the natural history and treatment outcome of chronic HBV infection. Several factors including viral, host, or environmental ones have been reported as determining the progression of liver disease in patients with chronic HBV infection. Of particular note, there is increasing evidence that HBV genotype may affect the clinical outcome of HBV infection and the response to antiviral therapy[5-60]. The evidence for clinical differences is stronger between genotypes B and C, and in the response to conventional interferon (IFN), but not lamivudine, adefovir dipivoxil or entecavir[17-19,24,26,50,61-62]. This review article focuses on the recent advances in the epidemiology of HBV geno-

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types and their implications regarding natural history and treatment outcome of chronic HBV infection.

Molecular Epidemiology of HBV Genotypes and Subtypes

HBV Genotypes, Subtypes and Mixed Infections of Genotypes

Currently eight genotypes (A-H) of HBV are identified by a divergence of > 8% in the entire HBV genomic sequence[63-66]. HBV genotypes have distinct geographic and ethnic distributions[38,67,68] (Table 1). Of great interest, it is noted that genotypes B and C are prevalent in highly endemic areas, such as Asian countries, where vertical or perinatal transmission plays an important role in the spread of the virus. In contrast, genotypes A, D, E, F, and G are frequently found in areas where horizontal transmission is the main mode of transmission[69]. Whether the modes of transmission correlate with HBV genotypes awaits further studies.

Recent studies have shown that HBV genotypes can be further segregated into subtypes[70-76], which also have distinct geographic distributions (Table 1). In addition, several molecular epidemiologic studies have indicated the existence of mixed infection of different HBV genotypes in hepatitis B carriers[52,77-79].

HBV Genotypes and Clinical Outcomes

In contrast to HCV genotyping, HBV genotyping remains an investigational tool with limited clinical application. In addition, due to the unique distribution of HBV genotypes, their clinical significance could only be reliably compared between genotype B *vs.* C, and genotype A *vs.* D (Table 2).

Acute and Fulminant Hepatitis

Suzuki, et al. found that the persistence of HBV infection was higher in patients with genotype A infection (23%) than those with genotype B (11%) or C (7%) infection[80]. Their data suggested that infection with genotype A predominates in patients with acute hepatitis B in Japan where genotypes B and C prevail, is often contracted sexually, and tends to persist. In another European study of 65 patients, genotype D was more prevalent in patients with acute, self-limited hepatitis B compared with genotype A (80 *vs.* 10%; $p < 0.01$). In contrast, genotype A predominated over genotype D in patients with chronic HBV infection (80 *vs.* 11%; $p < 0.01$)[13].

The role of HBV genotype in fulminant hepatitis B remains controversial[81,82]. One Japanese study evaluated 61 patients with acute forms of liver disease (45 with acute hepatitis and 16 with fulminant hepatitis) and 531 patients with chronic liver disease. They found that HBV genotype B was found more frequently in patients with acute forms of liver disease than in those with chronic liver disease, and more frequently in patients with fulminant hepatitis than in those with acute hepatitis. These results suggested that HBV genotype B may induce more severe liver damage than other genotypes in Japan[83]. In contrast, a study from Taiwan indicated that the distribution of HBV genotype and the prevalence of precore A1896 mutation in fulminant hepatitis patients were similar to those in 18 control patients[56]. The U.S. Acute Liver Failure (ALF) Study Group compared the prevalence of HBV genotypes between 34 HBV-related ALF patients and a cohort of 530 patients with chronic HBV infection. The results showed that genotype D was more frequently found in ALF patients than in those with chronic HBV infection in the USA[84]. Based on these findings, it seems that the development of fulminant hepatitis is not clearly linked to a particular HBV genotype, and may merely reflect the predominance of certain genotypes in different populations. However, further studies are needed to examine this issue.

Seroconversion of HBeAg and HBsAg

Previous studies have shown that patients with genotype C infection are more often HBeAg positive and have higher serum HBV-DNA levels than those with genotype B infection[6,52]. Previous studies have also shown that the

Table 1. *Distribution of common HBV genotypes and known subtypes worldwide*

Genotype	Subtype	Geographic distribution
A		Northwestern Europe, Spain, Poland, Czech Rep., USA, Central Africa, India, Brazil
	Aa	Asia and Africa: India, Nepal, The Philippines, Japan, South Africa
	Ac	Cameroon
	Ae	Europe and North America: UK, Germany, France, Poland, USA
B		Southeast Asia, Taiwan, Japan, Indonesia, China, Hong Kong, Vietnam, Thailand
	Ba	Taiwan, China, Vietnam
	Bj	Japan
C		Fareast Asia, Taiwan, Japan, Korea, China, Hong Kong, Thailand, Indonesia, Polynesia, Solomon Islands, Vietnam, India, Australia, USA, Brazil
	Ce	East Asia: Taiwan, Japan, Korea, China
	Cs	Southeast Asia: China, Hong Kong, Malaysia, Thailand, Vietnam, Bangladesh
D		Mediterranean area, Albania, Middle East, Turkey, Iran, India, Spain, Czech Rep., Russia, USA, Brazil, Solomon Islands
E		West Africa
F		Central and South America, Bolivia, Venezuela, Argentina, Brazil, Polynesia, Alaska
G		France, Germany, Georgia, USA
H		Central and South America

Table 2. *Clinical and virologic differences between HBV genotype B* versus *C, and genotype A* versus *D*

Parameters	Genotype B *vs.* C		Parameters	Genotype A *vs.* D	
	B	C		A	D
HBeAg positivity	Lower	Higher	Acute hepatitis	Less	More
HBeAg seroconversion	Earlier	Later	Chronic hepatitis	More	Less
Immune clearance phase	Shorter	Longer	Histologic activity	Lower	Higher
Exacerbation after HBeAg loss	Less	More	Precore stop codon mutation	Less	More
HBsAg loss	More	Less	Basal core promoter mutation	Higher	Lower
Histologic activity	Lower	Higher	Risk of cirrhosis and HCC	Lower	Higher
Serum HBV-DNA level	Lower	Higher	HBV recurrence after liver transplant	Lower	Higher
Precore stop codon mutation	More	Less			
Basal core promoter mutation	Less	More			
Risk of cirrhosis and HCC	Lower	Higher			

persistence of HBeAg in chronic HBV infection may contribute to the progression of chronic liver disease. It is therefore reasonable to examine whether genotype C has a lower rate of spontaneous HBeAg seroconversion and therefore stays longer in the replicative phase of chronic HBV infection than genotype B. Chu, et al. first reported that genotype B was associated with spontaneous HBeAg seroconversion at a younger age and was less likely to remain in remission after this event in Chinese patients with chronic HBV infection[7]. In Taiwan, we examined 146 HBeAg-positive HBV carriers and found that patients with genotype C infection had a lower rate of spontaneous HBeAg seroconversion than those with genotype B infection at the end of follow-up (27 *vs.* 47%; $p < 0.025$). The estimated rate of HBeAg seroconversion in all HBV carriers was 12.6% per year, and the rate in genotype B and C patients was 15.5 and 7.9% per year, respectively. In addition, the mean age at HBeAg seroconversion of genotype C patients was one decade older than that of genotype B patients (41 ± 10 *vs.* 30 ± 8 years; $p < 0.001$), suggesting a delayed HBeAg seroconversion and a longer duration of active HBV replication in genotype C patients[55]. These data have been confirmed by reports from Hong Kong and Japan[25,85,86]. We further studied the clinical relevance of HBV genotype in 460 Taiwanese HBV-carrier children[46], and the data consistently indicated that the seropositive rates of HBeAg after 20 years of follow-up was 70% in genotype C, and 40% in genotype B carriers. Taken together, these facts suggest the differential phenotype regarding HBeAg seroconversion between genotypes B and C in the early phase of chronic HBV infection, and genotype C seems to stay longer in the immune clearance phase with more severe hepatitis activity. In contrast, genotype B may be associated with a faster transition through the immunoreactive stage and evolution into the residual phase when serum HBV-DNA becomes rarely detectable.

Regarding genotypes A and D, one prospective study evaluated the clinical outcomes of 258 Spanish patients with chronic HBV infection with a mean follow-up of 94 (range, 24 to 180) months[14]. The baseline HBeAg positivity was significantly lower in patients with genotype D than those with genotype A (36 *vs.* 80%; $p < 0.0001$). Although HBeAg seroconversion was unrelated to HBV genotype, the rate of sustained remission after seroconversion was higher in genotype A than in genotype D patients (55 *vs.* 32%; $p < 0.01$). Thus, it appears that genotype A patients may have a more favorable prognosis than genotype D patients.

HBV carriers developing HBsAg seroclearance usually have favorable outcomes in terms of histologic features and the development of cirrhosis as well as hepatocellular carcinoma (HCC)[87]. Yuen, et al.[88] reported that patients with HBsAg seroclearance were more likely to be of genotype B ($p = 0.014$). Comparing genotypes A and D, another study revealed that genotype D patients had a lower rate of HBsAg seroclearance than genotype A patients (8 *vs.* 16%; $p = 0.03$)[14].

Chronic Hepatitis

The frequency and severity of acute exacerbation or flare of chronic hepatitis B are associated with the development of liver cirrhosis in HBV carriers[89]. We have shown that genotype C patients were associated with persistent HBeAg-positive chronic HBV infection, despite multiple episodes of acute exacerbation[29]. Thus, compared to patients with genotype B infection, those with genotype C infection have a more aggressive clinical phenotype. In a prospective study of 146 HBeAg-positive chronic hepatitis B patients with a mean follow-up of 32 months, Chan, et al. consistently found that the disease activity in the HBeAg-positive phase was higher in genotype C patients than in genotype B patients (78 *vs.* 50%; $p = 0.032$)[90]. However, when the acute exacerbation was severe, there seemed no significant difference in the mortality rate due to hepatic decompensation between patients with genotypes B and C[91]. Recently, Chu and Liaw further demonstrated that among 202 HBeAg-positive carriers (150 genotype B, 52 genotype C) with baseline normal serum ALT levels and follow-up for three to 20 years (average 10.8 years), HBeAg seroconversion correlated with age at entry for genotype B, and with serum ALT levels for genotype C patients. Reactivation of HBV was significantly more common in genotype C patients. In addition, they found that genotype C and HBV reactivation were independent predictors of cirrhosis by using multivariate analysis[92].

Regarding fibrosis progression, a Japanese study including 258 patients with histologically verified chronic hepatitis B showed that the ratio of patients with advanced fibrosis in genotype B was significantly lower than

in genotype C (13 *vs.* 33%; p = 0.034), and the difference was more substantial in younger patients (< 45 years; 4 *vs.* 26%; p = 0.02)[25]. These data suggested that genotype B patients have a slower progression rate of liver fibrosis and less active liver disease than genotype C patients.

Cirrhosis and Hepatocellular Carcinoma

Although some studies reported that the life-long probability of progression to cirrhosis and the development of complications including HCC may not differ between genotype B and C patients[25,85,93], most retrospective and case-control studies indicated that patients with genotype C have more severe liver disease than those with genotype B[5,6,8,10,11,27,37,48,49].

In a cross-sectional study, the association between distinct genotypes and the severity of liver disease was studied in 270 Taiwanese HBV carriers[5]. The results suggested that genotype C is more prevalent in patients with cirrhosis and in HCC patients aged above 50 years compared with age-matched asymptomatic carriers (60 *vs.* 23%; p < 0.001, and 41 *vs.* 15%, p = 0.005). Our recent 14-year observational study on 4841 Taiwanese men who were HBV carriers also demonstrated that HBV genotype C was associated with an increased risk of HCC compared with other HBV genotypes (adjusted OR = 5.11; 95% CI = 3.20-8.18)[32]. In addition, the risk of HCC increased with increasing HBV viral load. Mahmood, et al. evaluated 91 cirrhotic patients over a period of seven years and similarly found that patients with genotype C and continuously high serum HBV-DNA levels were at risk for HCC development[94]. These findings indicate that both genotype C and high HBV-DNA levels are correlated with a higher risk of HCC development.

Of particular note, we also found that genotype B was significantly more common in patients with HCC aged less than 50 years compared with age-matched asymptomatic carriers in Taiwan (80 *vs.* 52%; p = 0.03). This predominance was more remarkable in younger patients with HCC (90% in those aged < 35 years) and most were noncirrhotic[5]. These data thus suggested that certain genotype B strains may be associated with the development of HCC in young, noncirrhotic, HBV carriers[5]. Similar findings were reported in Taiwanese pediatric patients with chronic HBV infection[46]. Among 26 children with HBV-related HCC, genotype B was the major genotype (74%).

Studies from Japan and China have confirmed the findings that HBV genotype C is associated with the development of HCC[27,34]. However, none of their HCC patients younger than 35 years of age had genotype B. Accordingly, the genotype B strains in Taiwan are somewhat different from those in Japan and China and need further examination[95,96].

As for other genotypes, a study from India indicated that genotype D is associated with more severe diseases and may predict the occurrence of HCC in young patients[15]. Thakur, et al. showed that genotype D was more common in incidentally detected inactive carriers with a histologic activity index score > 4 and in patients with higher Child-Pugh scores compared with genotype A. In addition, the prevalence of genotype D tended to be higher in HCC patients younger than 40 years of age than in age-matched inactive carriers. Another report from Spain indicated that liver-related death was more frequent in genotype F than in genotype A (p = 0.02) or genotype D (p = 0.002)[14].

Clinical Relevance of HBV Subtypes

Few studies have examined the clinical significance of HBV subtypes[37,43,73,97-104]. Sugauchi, et al. found that positivity of HBeAg was significantly more frequent in carriers of subtype Ba than Bj[73]. An additional study analyzed the distribution of HBV subtypes in 296 HBV-related HCC patients collected from allover Japan[102]. They found HBV subtype Ba in 4.4%, Bj in 7.4%, and genotype C in 86.5%. Interestingly, in the Tohoku district and Okinawa, subtype Ba, Bj, and genotype C were found in 6.7, 40.0, and 48.9%, respectively, compared to 4.0, 1.6, and 93.2% in the other districts in Japan. In addition, subtype Bj was more frequently found in those older than 65 years, while subtype Ba was found in all age groups. These data suggest that HBV subtype Bj may run a more indolent course than subtype Ba.

HBV in 80% of patients in Hong Kong belonged to HBV subtype Cs, and in the remaining 20% of patients to subtype Ce[103]. When subtype Cs and Ce were compared, subtype Cs was associated with a higher tendency to develop BCP mutations (80 *vs.* 50%; p = 0.14), a higher prevalence of C at nucleotide 1858 (95 *vs.* 0%; p < 0.001), and a lower prevalence of precore stop codon mutations (5 *vs.* 50%; p = 0.002). They thus suggested that subtypes Ce and Cs have different epidemiologic distributions and virologic characteristics. Since the background prevalence of BCP mutations is likely related to the distribution of HBV genotype C subtypes, they further speculated that the inconsistent relationship between BCP mutations and the development of HCC may be due to the varying distribution of HBV genotype C subtypes in different geographic areas. However, we found that subtype Cs was rare in Taiwan[104]. Thus the association between BCP mutations and the development of HCC could not be explained by the differential distribution of HBV genotype C subtypes. More large studies are needed to examine the clinical impact of HBV subtypes on the pathogenesis and progression of liver diseases.

Subtype Aa appears to be associated with low serum HBV-DNA levels as well as a low prevalence of serum HBeAg, and is implicated in the high incidence of HBV-related HCC in Africa[43,101], whereas HBV carriers infected with subtype Ae have a higher rate of sustained remission after HBeAg seroconversion and a lower rate of liver-related death than other genotypes during long-term follow-up[14]. Further studies are needed in this evolving field.

Taken together, epidemiologic and clinical data from different Asian countries have lent strong support to clinical and pathogenic differences between HBV genotype B and C. Nevertheless, additional analysis is warranted in other parts of the world, especially western countries where genotypes A and D are prevalent.

Influence of HBV Genotype on the Response to Antiviral Therapy

Currently, five drugs have been approved for the treatment of chronic hepatitis B: conventional interferon alpha (IFNα), lamivudine, adefovir dipivoxil, pegylated IFN (PEG-IFN)α-2a and entecavir[105-114]. Although pathogenic differences do exist among HBV genotypes, the association of HBV genotype and response to current antiviral treatments remains less clarified. Tables 3 and 4 show the correlation of HBV genotype to the response to antiviral therapy.

Interferon

The efficacy of IFNα in the treatment of genotype B- or C-infected chronic hepatitis B patients has been analyzed[17,18] (Table 3). The response rate, defined as normalization of serum aminotransferase level, loss of HBeAg and HBV-DNA 48 weeks posttreatment, was 41 and 15% in Taiwanese genotype B and C patients, respectively (p = 0.045). Wai, et al. similarly found the response was better in Chinese patients with genotype B than C (39 *vs.* 17%; p = 0.034)[18]. Similar situations were observed between HBV genotype A and D patients[31,115] (Table 3). Hou, et al. demonstrated that a response to IFNα treatment occurred more often in genotype A patients than in genotype D patients (33 *vs.* 11%; p = 0.03). Erhardt, et al. also revealed that of 144 subjects infected with genotype A or D, sustained response (six months after treatment) to standard IFN therapy was higher in HBV genotype A patients compared with genotype D patients (49 *vs.* 26%; p < 0.005). Subgroup analysis suggested HBeAg status had no impact on genotype-dependent IFN response. Multivariate logistic regression identified HBV genotype A and high pretreatment ALT levels (> 2 x upper limit of normal) as independent positive predictors of IFN response[113]. These studies indicate that HBV genotype may serve as an important factor affecting IFN responsiveness in HBeAg-positive chronic hepatitis B.

As for PEG-IFNα-2a, initial subgroup analysis revealed that HBV genotype B was correlated with a better response to PEG-IFN-based therapy than genotype C (33 *vs.* 21%; p = 0.102)[8]. In a multicenter study using PEG-IFNα-2b-based therapy, the overall response rate also differed according to HBV genotype: genotype A, 47%; genotype B, 44%; genotype C, 28%; and genotype D, 25%[12]. Nevertheless, conflicting data was found in another large clinical trial. Lau, et al. demonstrated that there was no statistically significant difference in the rate of posttreatment HBeAg seroconversion among HBV genotypes: genotype A was 52%; genotype B, 30%; genotype C, 31%; and genotype D, 22%[116]. To be noted, another study consistently demonstrated a higher rate of treatment response in genotype A compared to the other three genotypes in terms of HBsAg seroconversion[117]. Taken together, whether HBV genotypes correlate with the response to PEG-IFN-based therapy awaits further examinations.

Table 3. *HBV genotype and response to conventional interferon therapy for 4-6 months: Genotype B* versus *C, and genotype A* versus *D*

Genotype	Case numbers	HBeAg seroconversion at month 12 post-therapy
B*	63	25 (40%)†
C*	68	11 (16%)†
Overall	131	36 (27%)
A‡	124	64 (51%)§
D‡	101	30 (30%)§
Overall	225	94 (42%)

*Data pooled from Kao and Wai[17,18].
†p < 0.05 when compared between genotype B and C.
‡Data pooled from Hou and Erhardt[31,115].
§p < 0.05 when compared between genotype A and D.

Lamivudine

A lot of data have become available on whether HBV serotype or genotype affects the outcome of lamivudine therapy, the development of lamivudine-resistant tyrosine-methionine-aspartate-aspartate (YMDD) mutation, and the occurrence of hepatitis exacerbation accompanying the emergence of YMDD mutants[19-23,26,39,50,51,58,59,118,119].

Virologic Response

The data from our own study and another two studies in Hong Kong indicated that HBV genotype has no impact on the response to lamivudine therapy[19,26,50]. However, Chien, et al. reported that the sustained response rate to lamivudine was much higher in patients with genotype B than in those with genotype C (61 *vs.* 20%; p = 0.009)[20]. In Spain, Buti, et al. suggested that the outcome after lamivudine treatment was comparable for genotypes A and D[58]. These lines of evidence imply that HBV genotype seems to have no substantial impact on the response to lamivudine treatment.

In HBeAg-negative patients, viral factors predictive of posttreatment relapse remain largely unknown. We have studied the association between end-of-treatment virologic response and relapse after discontinuing lamivudine treatment[39]. Our results suggested that genotype C patients tended to have a lower relapse rate than genotype B patients in this special clinical setting (14.3 *vs.* 57.9%; p = 0.08). However, these preliminary findings need to be confirmed in further large-scale studies.

Lamivudine Resistance

In Germany, Zöllner et al. investigated the subgroup-dependent development of lamivudine resistance in HBV serotype *adw* (exclusively genotype A in Europe)- and *ayw* (mainly genotype D in Europe)-infected patients[22,23,51]. Their data suggested that HBV serotype *adw* is associated with a 20-fold higher risk of lamivudine resistance than *ayw*. However, a prolonged clinical observation showed that the risk of the emergence of YMDD mutation

Table 4. *Therapeutic differences for HBeAg-positive chronic hepatitis B: Comparison between genotype B and C, and between A and D*

Parameter	Genotype B *vs.* C		Genotype A *vs.* D	
	B	C	A	D
Response to conventional IFN	Better	Worse	Better	Worse
Response to PEG-IFN	Inconclusive		Better	Worse
Response to lamivudine	Comparable		Inconclusive	
Relapse after discontinuing lamivudine	Less	More	NA	
Lamivudine resistance	Comparable		Inconclusive	
Acute exacerbations after lamivudine resistance	Inconclusive		NA	
Response to adefovir	Comparable		Comparable	
Response to entecavir	Comparable		Comparable	

Ref: 8,12,17-24,24,26,30,31,39,50,51,58,116,117,120. NA, not available.

was only slightly higher in genotype A patients than in genotype D, and the difference was noted only during the first year[58]. A recent study also showed that HBV genotype did not influence the development of resistance to lamivudine during long-term lamivudine treatment of up to five years[119]. Accordingly, HBV serotype or genotype plays a minor role in the risk of lamivudine resistance.

Acute Exacerbations Accompanying the Emergence of Lamivudine Resistance

In a Japanese study, severe acute exacerbation of hepatitis occurred in four (2%) of the 185 patients with genotype C along with the emergence of YMDD mutants[21]. None of the 28 patients with other genotypes developed acute exacerbation. In contrast, the chances of YMDD mutations with virologic breakthrough and biochemical exacerbation were comparable between genotype B and C patients in a report from Hong Kong[26].

Adefovir Dipivoxil and Entecavir

Recent studies suggested that there was no statistical difference in HBeAg seroconversion rates among HBV genotypes in patients receiving adefovir dipivoxil therapy[24]. Another study also demonstrated that there was no difference between HBV genotype and the response to entecavir therapy regarding the key efficacy endpoints, including reduction of serum HBV-DNA levels and histologic improvement[120].

In summary, HBV genotype correlates well with the response to conventional IFN but not nucleos(t)ide-based therapy (Tables 3 and 4). The association between HBV genotype and the response to PEG-IFN remains inconclusive and needs more study.

Conclusions

Taking these lines of evidence together, remarkable differences exist in the clinical and virologic characteristics among patients with different genotypes. Therefore, determining HBV genotype in patients with chronic HBV infection would help gain further information for etiologic, clinical and virologic investigations. Moreover, the molecular and virologic mechanisms accounting for the clinical phenotypes of HBV genotypes need to be examined. Finally, the clinical significance of subtype, mixed genotype infections, and genotypic recombinants awaits further studies.

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