

THERAPY OF HEPATITIS C IN HIV-COINFECTION

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Abstract: One third of all European and American HIV-patients are coinfecting with hepatitis C. HIV accelerates hepatitis C virus liver disease especially when HIV-associated immune deficiency progresses. Indeed, liver cirrhosis rate is five times higher in HIV/HCV-coinfecting patients than in HCV-monoinfecting patients. With the introduction of pegylated interferon and ribavirin combination therapy sustained virological response rates of up to 40 % could be obtained in HIV/HCV-coinfecting individuals. Moreover, cohort analyses could demonstrate that with the use of highly active antiretroviral therapy (HAART) an improved course of hepatitis C and a reduction in liver disease-associated mortality can be achieved. Under consideration of the increased rate of hepatotoxicity due to the presently available antiretroviral treatment regimens in HIV/HCV coinfecting patients, however, the development of treatment strategies and guidelines for management of hepatitis coinfection in HIV remains of great clinical significance.

Key words: hepatitis C, HIV, HAART, peg-interferon, ribavirin

INTRODUCTION

Since the introduction of highly active antiviral therapy (HAART) in 1996 a dramatic decline in HIV-associated morbidity and mortality could be observed. In parallel a significant increase in mortality due to progressive liver disease in HIV-coinfecting patients was recorded [2]. The high rate of hepatitis coinfection in HIV-patients clearly underlines the clinical significance of this comorbidity. Indeed, 30 % of all European and American HIV-patients are coinfecting with hepatitis C [13].

Therefore, the development of treatment strategies for management of hepatitis coinfection in HIV-patients has become one of the most important clinical challenges. With the introduction of pharmacokinetically optimized interferon, treatment options for hepatitis C could be significantly improved also in the coinfecting patient. In the following review actual aspects in the treatment of hepatitis C in HIV-coinfecting patients will be discussed.

THERAPY OF HEPATITIS C IN HIV-COINFECTED PATIENTS

Chronic hepatitis C leads to liver cirrhosis in around 20 % of all patients after extended infection duration of 10-20 years and currently represents the most frequent indication for liver transplantation in the US.

The primary goal of hepatitis C therapy is to achieve persistent virus eradication. After limited long-term treatment success rates under interferon monotherapy the introduction of interferon/ribavirin combination therapy was able to achieve virus eradication in 40 % of all treated HCV-monoinfecting patients and became standard therapy of hepatitis C. The use of interferon/ribavirin combination treatment in HIV/HCV-coinfecting individuals, however, was rather disappointing as sustained virological response rates 24 weeks after the end of therapy did not exceed 25 % and were even lower in patients with genotype 1 [8, 14]. In parallel, an increased toxicity was observed under the combination treatment in HIV coinfecting individuals. With the introduction of pegylated interferons new hopes were generated for better treatment possibilities especially in the coinfecting patient. Binding of interferon- α to a polyethylenglykol (PEG) resulted in an optimization of the pharmacokinetic profile of interferon. The addition of polyethylenglykol protects the interferon- α protein from enzymatic degradation which leads to a significant increase in interferon half-life enabling a once weekly subcutaneous injection. Studies evaluating the use of pegylated interferon in combination with ribavirin in hepatitis C monoinfecting patients were able to demonstrate a significantly higher long-term sustained virological response versus the standard thrice weekly interferon/ribavirin combination treatment [7, 9].

In the meantime first data on the use of the combination treatment of pegylated interferon and ribavirin have been presented also in HIV/HCV-coinfecting patients (Table 1). During the recent Conference on Retroviruses and Opportunistic Infections (CROI) in San Francisco in 2004 data from the APRICOT-trial were presented for the first time. The APRICOT-trial represents the largest study for treatment of hepatitis C in HIV coinfecting individuals [17]. Within this international study three treatment arms were compared: peg-interferon- α 2a (Pegasys) \pm ribavirin versus interferon- α 2a + ribavirin for treatment of hepatitis C in HIV/HCV-coinfecting patients. Overall, 880 patients from 95 centers in 19 countries were included. Patients who were included into the study had to be naive for previous hepatitis C treatment and reveal a quantifiable HCV-RNA. In addition, liver enzymes had to be elevated and liver biopsy needed to be consistent with chronic hepatitis C. With regard to HIV-infection patients either had to have a stable CD4-count > 200/ μ l or have a CD4-count between 100 and 200/ml in the presence of low HIV-viremia < 5,000 copies/ml. Patients with stable HIV-infection

could be included with or without antiviral treatment into the trial. Overall, 80 % of the patients in all three study arms were males, the median age was 40, 15% of patients had liver cirrhosis in all three treatment arms. Hepatitis C RNA ranged between 5.2 and 6.3 IU/ml x 10⁶ at baseline. Two thirds of the patients revealed HCV-genotype 1 or 4. Over 84 % of patients already received an HIV-specific antiviral therapy with controlled HIV-infection with a median viral load of 2.3 x 1.0 log₁₀ copies/ml. 60 % of the patients had an HIV-RNA < 50 copies/ml, the median CD4-count was between 520 and 542/μl in all three study arms.

Sustained virological response 24 weeks after treatment cessation for all three treatment arms is depicted in Figure 1. In a further subanalysis patients with genotype 1 showed an end-of-treatment response of 38 % in the peg-interferon-α 2a + ribavirin arm and a sustained virological response of 29 % 24 weeks after treatment cessation. Much better response rates were

observed for genotypes 2 and 3 with an end-of-treatment response rate of 64 % and a sustained virological response rate of 62 %.

At the CROI meeting also further pegylated interferon/ribavirin treatment trials for hepatitis C in HIV-coinfected individuals were presented. Within the ACTG 5049 Study a somewhat lower overall sustained virological response rate of 27 % was reported. Sub-analysis for genotype 1 patients showed an even lower sustained virological response of only 14 % [3]. It should be noted, however, that within this trial much lower ribavirin doses were used as recommended for the treatment of hepatitis C in monoinfected patients namely starting with initial doses of only 600 mg/d which then were dose escalated up to 1000 mg/d until week 12. In the French RIBAVIC Study overall sustained virological response rates for patients receiving pegylated interferon-α 2b and ribavirin was 27 % [11]. The sustained virological response rate for genotypes

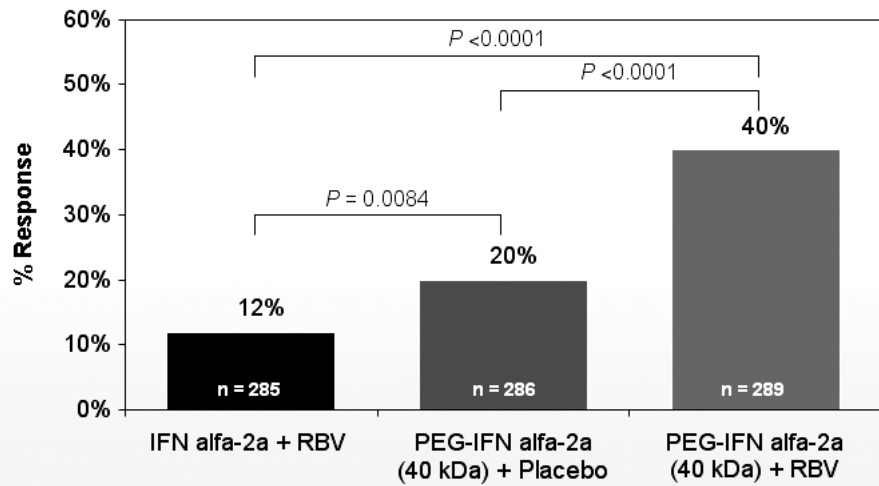


Fig. 1. Sustained virologic response (defined as <50 IU/ml HCV RNA at week 72; ITT).

Table 1. Results from therapy trials for treatment of hepatitis C in HIV-coinfected patients.

Author	Year	Treatment duration and ribavirin dose	End of treatment response	Sustained virological response (negative HCV-RNA 24 weeks after treatment cessation)	Treatment discontinuation due to adverse events
Perez-Olmeda [10]	2003	48 weeks for genotype 1, 24 weeks for genotypes 2 and 3 ribavirin dose 800 mg/d	27 of 68 (40 %)	19 of 68 (28 %)	10 of 68 (15 %)
Voigt [18]	2003	48 weeks for genotype 1, 24 weeks for genotypes 2 and 3 ribavirin dose 800 mg/d	33 of 72 (46 %)	19 of 72 (26 %)	12 of 72 (17 %)
Perronne [11]	2004	48 weeks for all geno-types ribavirin dose 800 mg/d	n.a.	55 of 205 (27 %)	77 of 205 (38 %)
Chung [3]	2004	48 weeks for all geno-types ribavirin dose starts with 600 mg/d and then: escalation to 1000 mg/d	27 of 66 (41 %)	18 of 66 (27 %)	8 of 66 (12 %)
Torriani [17]	2004	48 weeks for all genotypes ribavirin dose 800 mg/d	n.a.	115 of 289 (40 %)	12 %

1 and 4 was only 11 %. The overall poorer treatment outcome in the RIBAVIC trial can be mainly explained by the significantly higher discontinuation rate due to adverse events of almost 40 %, which was mainly related to mitochondrial toxicity from DDI containing HAART regimens.

The surprisingly low relapse rate for patients within the APRICOT trial with genotype 2 or 3 clearly suggests that longer treatment duration of 48 weeks leads to much more favorable treatment response rates over time than the shorter recommended treatment duration of only 24 weeks for genotypes 2 and 3 in monoinfected patients. Within Spanish and German pilot studies examining efficacy and safety of pegylated interferon/ribavirin combination therapy in HIV/HCV-coinfected patients with a treatment duration of only 24 weeks for genotype 2 and 3 (analogue to monoinfected patients) an almost 40 % relapse rate was observed, clearly underlining that shorter treatment durations for genotype 2 and 3 will lead to higher relapse rates [10, 18]. Therefore a treatment duration of 48 weeks has to be considered for all genotypes as the new standard within the treatment of HIV/HCV-coinfected patients. In all studies which are summarized in Table 1 the determination of HCV-RNA at week 12 was associated with a very high negative and positive predictive value with regard to subsequent virological treatment response. In patients who did not achieve a negative HCV-RNA at week 12 or at least a 2 log decline in HCV-RNA, therapy with pegylated interferon and ribavirin can be subsequently terminated as the chance of obtaining a sustained virological response becomes very low.

CONCOMITANT HAART-THERAPY IN HIV/HCV-COINFECTED PATIENTS RECEIVING RIBAVIRIN

The significantly higher discontinuation rates within the treatment of hepatitis C in HIV-coinfected patients especially in the above presented RIBAVIC

trial of almost 40 % in both study arms, underlines the complexity and difficulties within the management of treatment of HIV/HCV-coinfected patients. The choice of the respective HAART regimen appears to be of particular clinical importance. Various studies were able to demonstrate an increased rate of lactacidosis and pancreatitis under predominantly DDI-containing regimens [11, 15]. In the meantime the combination of DDI and ribavirin is regarded as contraindicated. The combination of D4T and ribavirin also should be used with great caution as several studies found an increased risk for lactacidosis with this combination. Moreover, newer data suggests an increased rate of liver steatosis under D4T-containing regimens [16]. The combination of AZT and ribavirin is possible but mandates close monitoring as the risk and the magnitude of anemia under this combination appears to be pronounced. First data looking at the supportive administration of erythropoetin for preventing hematological complications and maintaining ribavirin and pegylated interferon doses in coinfecting individuals showed significantly higher hemoglobin values under erythropoetin treatment versus those patients who just received best standard of care [4]. The use of erythropoetin and other hematologic growth factors therefore should be increasingly considered in patients with respective hematologic complications or increased risk for hematotoxicity. The observation of in vitro analysis that ribavirin interacts with various nucleoside analogues which are used for HIV-therapy by interacting with intracellular phosphorylation of AZT and D4T seems to have no clinical significance as no in vivo importance of this interaction could be observed [6].

TREATMENT GUIDELINES FOR MANAGEMENT OF HEPATITIS C IN HIV-COINFECTED PATIENTS

Table 2 summarizes the guidelines for initiation of therapy in HIV-coinfected patients.

Table 2. Guidelines for initiation of therapy in HIV-coinfected patients.

- • An indication for treatment of hepatitis C in HIV-patients is made on the basis of the presence of fibrosis (fibrosis stage F1-F4) in combination with elevated transaminases and a positive HCV-RNA.
- • Ideal candidates for hepatitis C therapy are patients with a CD4-count > 350 cells/ml and a relatively low plasma HIV-RNA level < 50.000 copies/ml with or without HAART.
- • The initiation of a treatment in patients with a CD4-count of < 350/ml is possible but should be performed with caution and under close monitoring.
- • Patients with a CD4-count < 100-200/ml should receive HAART first before initiation of HCV-specific therapy can be discussed.
- • Therapy of choice for treatment of hepatitis C in HIV-coinfected patients is a combination of pegylated interferon and ribavirin in dosages similar to monoinfected patients.
- • The treatment duration for all genotypes in HIV/HCV-coinfected patients should be 48 weeks.
- • If no 2 log drop in HCV-RNA or negative HCV-RNA can be achieved at week 12, HCV-therapy can be terminated.
- • The concomitant use of DDI and ribavirin is contraindicated.
- • In case of combining AZT or D4T with ribavirin there is an increased risk for toxicity and close monitoring is warranted.

COURSE OF HEPATITIS C UNDER ANTIRETROVIRAL THERAPY

Although HAART-therapy has no direct effect on HCV-RNA levels in HIV/HCV-coinfected patients at least case reports exist where after longer observation duration and HAART-induced immune reconstitution spontaneous hepatitis C clearance have been described [5]. Interesting data also come from a French investigation looking at the effect of highly active antiretroviral therapy on fibrosis progression in HIV/HCV-coinfected patients [1]. Within this investigation it could be demonstrated that the use of protease inhibitors was associated with a significantly lower fibrosis progression rate. The observation is further enhanced and underlined by data from the Bonn cohort analysis in HIV/HCV-coinfected patients. Within this investigation patients with HIV/HCV-coinfection who received HAART were characterized by significantly lower liver-disease related mortality versus patients with HIV/HCV-coinfection who did not receive any antiviral therapy or insufficient antiviral therapy (monotherapy or dual nucleoside therapy) during the same observation period [12]. It should, however, be highlighted that an increased risk for hepatotoxicity under HAART can be observed in HIV/HCV-coinfected patients so that close monitoring of liver values and liver function parameters (initially every 2-4 weeks) has to be recommended after initiation of HAART-therapy.

CONCLUSION AND OUTLOOK

Under consideration of the accelerated course of hepatitis C in HIV-coinfected patients and the increased risk for development of cirrhosis, therapy of hepatitis C in HIV-infected patients plays an important role. With the introduction of combination treatment with pegylated interferon and ribavirin and the clearly improved sustained virological response rates of up to 40%, hepatitis C specific therapy can be recommended especially in the presence of favorable response factors such as low hepatitis C viral load, genotype 2 or 3, and short duration of hepatitis C. Especially patients with stable immune function and a CD4-count > 350/ μ l and moderate HIV-replication < 50,000 copies/ml with or without HAART should be considered as candidates for treatment. In patients with advanced immune deficiency and CD4-counts < 100-200/ μ l HIV-therapy should be established first before hepatitis C therapy can be initiated after HAART-induced immune reconstitution has been obtained. In patients receiving HAART-therapy next to hepatitis C therapy DDI should not be administered. The use of D4T or AZT can only be provided with increased caution. Nevertheless recent data do suggest that HAART-induced immune reconstitution overall has a favorable impact on the further course of hepatitis C in HIV coinfected patients.

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