Occurrence of Hepatocellular Carcinoma and Decompensation in Western European Patients With Cirrhosis Type B

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To examine the morbidity of compensated cirrhosis type B, a cohort of 349 Western European, white patients (86% men; mean age, 44 years) with biopsy-proven cirrhosis was followed up for a mean period of 73 months and was studied for occurrence of hepatocellular carcinoma (HCC) and decompensation. At entry into the study all patients were tested for hepatitis B e antigen (HBeAg; 34% of patients were HBeAg-positive) and antibody to hepatitis delta virus (anti-HDV; 20% of patients were anti-HDV–positive); 48% of 252 patients tested were hepatitis B virus (HBV)-DNA–positive. During follow-up HCC developed in 32 (9%) of the 349 patients and decompensation was observed in 88 (28%) of 317 tumor-free patients. Five years after diagnosis, the probability of HCC appearance was 6% and the probability of decompensation was 23%. After the first episode of decompensation the probability of survival was 35% at 5 years. Cox's regression analysis identified three variables that independently correlated with HCC: age, serum levels of platelets, and liver firmness on physical examination. HBV (HBeAg or HBV-DNA) and HDV (anti-HDV) markers at presentation had no prognostic value for the development of HCC. In conclusion, a high proportion of patients with HBsAg-positive compensated cirrhosis do not experience worsening of their condition for several years, but once decompensation occurs life expectancy is poor. European, white patients with compensated cirrhosis type B are at consistent risk for HCC. Prognostic factors for HCC reflect an advanced stage of cirrhosis and support the hypothesis that development of a tumor could be the likely consequence of long-standing hepatic disease. (HEPATOLOGY 1995;21:77-82.)

Hepatocellular carcinoma (HCC) and liver failure are the leading causes of death in hepatitis B surface antigen (HBsAg)–positive cirrhosis. Indeed, cirrhosis of the liver and chronic hepatitis B virus (HBV) infection are well-recognized risk factors for HCC.[1-4] Liver cancer is one of the most common tumors in the Far East and in sub-Saharan Africa where HBV is highly endemic, whereas it is rare in most Western countries where HBV infection is also much less common.[5,6] Most studies on the risk of developing HCC in cirrhosis type B have been performed in the Far East,[7,8] and little information is available regarding the frequency, incidence, and risk factors for the development of liver cancer in HBsAg-positive compensated cirrhosis in Western countries.

Moreover, most studies on the clinical course of cirrhosis type B have been performed mainly on decompensated cirrhotic patients and, therefore, at present, it is not well-defined for how long patients who present with HBsAg-positive compensated cirrhosis will remain free from major complications.

Recently we have evaluated the survival of compensated cirrhosis type B, primarily in relation to HBV replication and hepatitis delta virus (HDV) infection.[9] The main findings of this study were that 366 HBsAg-positive patients with compensated cirrhosis had a cumulative probability of survival of 84% at 5 years, active HBV replication was a negative prognostic factor, and termination of viral replication was associated with increased survival.

In the present study our aim was to evaluate the morbidity of compensated cirrhosis type B in a cohort of Western European patients, namely, to assess the frequency and incidence of HCC and to examine the

Abbreviations: HCC, hepatocellular carcinoma; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDV, hepatitis delta virus; anti-HBs, antibody to HBsAg; HBeAg, hepatitis B e antigen; anti-HBe, antibody to HBeAg.

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rates of appearance of hepatic decompensation. We also have analyzed the data from these patients for risk factors for development of liver cancer.

PATIENTS AND METHODS

Study Population. The data were derived from a multicenter retrospective longitudinal study of HBsAg-positive compensated cirrhotic patients. The study was based on a network of nine university hospitals in Europe participating in a concerted action on viral hepatitis named EUROHEP.

The general design of this investigation has been previously described in a study evaluating the survival of compensated cirrhosis type B.[9] Briefly, data collection was performed by electronic proforma according to a protocol defining the study population, time of entry, and follow-up. The study protocol was approved by the local ethical committee. Between January 1973 and December 1991, all patients meeting the following criteria were enrolled in the study: (1) HBsAg positivity; (2) histological diagnosis of cirrhosis according to international criteria[10]; (3) no history or clinical evidence at enrollment of complications of cirrhosis, that is, ascites, variceal bleeding, encephalopathy, or jaundice (diagnosed on physical examination and confirmed by serum bilirubin > 51.7 μmol/L); (4) no clinical evidence of HCC at entry into the study; (5) information on serum HBeAg and anti-HDV at presentation; and (6) follow-up at the enrolling center for a minimum period of 6 months. Specific types of liver cirrhosis, such as hemochromatosis, Wilson's disease, or biliary cirrhosis, were excluded on the basis of serological and histological criteria.

Follow-Up of Patients. The time of entry into the study was defined as the time of diagnosis of HBsAg-positive compensated cirrhosis, provided that the patient fulfilled the inclusion criteria. The time of observation was calculated from the date of entry until death or the end of the observation period (December 31, 1991). All patients were longitudinally studied and examined at least once a year, or more frequently if indicated. The routine evaluation of the patients included clinical assessment, standard liver biochemical tests, and HBV markers. The diagnosis of HCC was based on histological findings and/or on high alpha-fetoprotein values (≥400 μg/L) and compatible ultrasonographic findings. Decompensation was defined as the appearance of at least one episode of ascites, jaundice (serum bilirubin > 51.7μmol/L), hepatic encephalopathy, or variceal bleeding (hematemesis and/or melena).

Fifteen patients (4%) were lost to follow-up and, because data regarding the appearance of HCC or decompensation were not known, they were censored at the time of drop out in the following statistics.[11] Also patients who died of conditions not related to liver disease were censored at the time of death in the following analysis.

Laboratory Tests. Data on serum HBV markers were obtained from medical records of patients or were obtained by retrospectively testing stored serum samples. All patients were tested for serum HBsAg, antibody to HBsAg (anti-HBs), hepatitis B e antigen (HBeAg), antibody to HBeAg (anti-HBe), and anti-HDV by commercially available solid-phase radioimmunoassay or enzyme-linked immunosorbent assays. Serum HBV-DNA was measured by a spot hybridization technique or by a solution hybridization assay.

Prognostic Factors. Potential prognostic factors assessed for HCC included a total of 18 clinical, biochemical, and virological variables measured at the time of diagnosis of HBsAg-positive compensated cirrhosis. The following clinical parameters were considered: sex, age, symptoms, hepatic stigmata, liver firmness on physical examination, splenomegaly, initial histology, and therapy. Symptoms were defined as the presence of dyspepsia and/or asthenia and/or right upper abdominal pain. Liver firmness was defined as an increased consistency of the liver from firm to rock-hard. Splenomegaly was documented by physical examination and/or by ultrasound (≥ 13 cm in longitudinal diameter). Biochemical and virological tests included aspartate aminotransferase, alanine aminotransferase, bilirubin, albumin, gammaglobulin, platelets, alpha-fetoprotein, HBeAg, HBV-DNA, and anti-HDV.

TABLE 1. Initial Clinical and Serological Characteristics of Patients With Compensated Cirrhosis Type B

Patients' features		
Sex (male/female)	302/47	
Age (yrs)*	44	(17-74)
Symptoms†	141/349	(40)
Hepatic stigmata†	96/346	(28)
Liver firmness†	175/219	(80)
Splenomegaly†	98/344	(28)
Esophageal varices on endoscopy†	46/132	(35)
Virological parameters†		
HBeAg-positive	118/349	(34)
Anti-HDV–positive	70/349	(20)
HBV-DNA–positive	122/252	(48)
Serum parameters*		
AST (IU/L)	112	(11-930)
ALT (IU/L)	160	(15-1,370)
Bilirubin (μmol/L)	16.1	(2.3-51)
Albumin (g/L)	40	(24-55)
Gammaglobulin (g/L)	19	(7-59)
Platelets (10^9/L)	153	(31-340)
Alpha-fetoprotein (μg/L)	24	(1-870)

* Data expressed as mean value (range).

† Data expressed as numbers positive/total numbers of patients with analyzable data (percentages).

Statistical Analysis. Descriptive statistics are provided as means ± SD. The Fisher's exact test was used for statistical comparison. The cumulative probability of developing HCC or decompensation was calculated using the method of Kaplan and Meier.[11,12] In the univariate analysis the curves of the probability of developing HCC were estimated by the Kaplan and Meier method for the various levels of each variable. For continuous variables the cutoff level chosen was its median value and in the laboratory parameters, if the median value was close to the upper normal value, the latter was used as the cutoff level. The log-rank test was used to compare the curves for different levels of the investigated variables.[13] Multivariate analysis of risk factors for HCC were also studied by stepwise forward Cox regression model.[14] In this model, the order of insertion of any variable was determined by using the maximum log-likelihood value and the statistical significance was assessed by the Wald test.[12] Because the analysis requires that all patients are represented by a complete set of variables and, in order not to reduce the number of patients, missing data were replaced by neutral estimates.[15] The univariate and multivariate analysis were performed using the BMDP statistical package.[16]

RESULTS

We studied 349 Western European, white patients with HBsAg-positive compensated cirrhosis who ful-

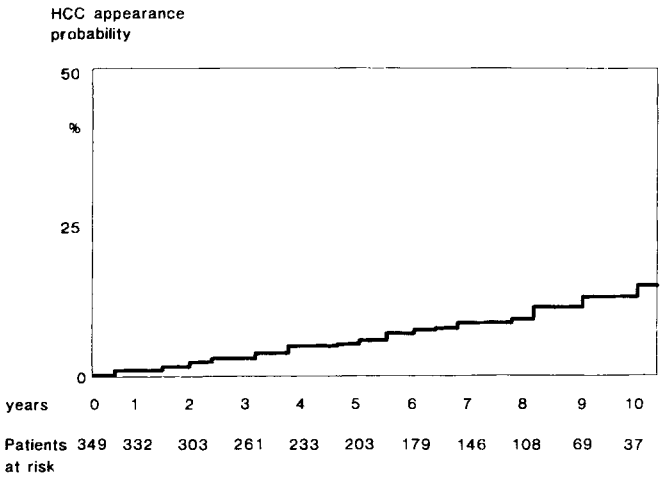

FIG. 1. Cumulative probability of HCC appearance in patients with HBsAg-positive compensated cirrhosis. The 5-year appearance rate was 6% and the 10-year appearance rate was 15%.

filled the inclusion criteria. The details of the initial clinical and serological features of the patients included in this study are shown in Table 1 and have been previously described.[9] The mean age was 44 years (range, 17 to 74 years) and there were 302 men and 47 women. Fourteen patients (4%) had a history of heavy drinking, having consumed more than 80 g of alcohol per day. Liver biopsy at entry showed active cirrhosis in 215 patients (63%), inactive cirrhosis in 46 patients (13%), early cirrhosis in 46 (13%) patients, and probable cirrhosis in 36 patients (11%).

Development of HCC. During a follow-up period of 6 to 202 months (mean ± SD, 73 ± 41 months), HCC was identified in 32 patients (9%) 7 to 178 months after entry into the study. Liver cancer was diagnosed in 19 patients on histological examination and in 13 patients on the basis of elevated alpha-fetoprotein values (≥400 μg/L) and compatible ultrasonography. The cumulative probability of developing HCC among the patients was 3% at 3 years after diagnosis of cirrhosis, 6% at 5 years when 203 patients were still in follow-up, and 15% at 10 years (Fig. 1). The overall incidence was 1%, 1.3%, and 1% during the first, second, and third year of follow-up, respectively. Twenty-eight patients (87%) were males. None of the 32 patients who developed HCC admitted alcohol abuse or homosexual activities. Four patients received immunosuppressive or antiviral therapy before the diagnosis of HCC, namely, 2 patients (6%) were treated with steroids, 1 patient (3%) was treated with interferon, and 1 patient (3%) was treated with acyclovir, usually for periods not exceeding 6 months. When the diagnosis of HCC was made, patients were between 39 and 78 years of age (59 ± 10); 3 patients (9%) were seropositive for HBeAg and 5 (15%) were anti-HDV–positive and HBeAg-negative. HBV-DNA tests were positive in 4 of 20 patients (20%) tested, including 2 HBeAg-positive (50%) and 2 HBeAg-negative (50%) cases. Twenty of the 32 patients died 1 to 28 months after the diagnosis of HCC, whereas 12 were still alive at last observation.

TABLE 2. Variables Showing Prognostic Significance by Log-Rank Test

Variables	No. of Patients	Probability of Tumor 5 yrs (SE)	Probability of Tumor 10 yrs (SE)	P
Age (n = 349)*				
≤44 yrs	174	0.02 (0.01)	0.09 (0.04)	.005
>44 yrs	175	0.09 (0.02)	0.20 (0.04)	
Liver firmness (n = 219)				
Absent	44	0 (0.00)	0.04 (0.03)	.01
Present	175	0.10 (0.02)	0.22 (0.05)	
Platelets (n = 293)				
>120 × 10^9/L	202	0.04 (0.01)	0.07 (0.02)	.008
≤120 × 10^9/L	101	0.11 (0.04)	0.29 (0.09)	
Alpha-fetoprotein (n = 148)				
≤10 μg/L	99	0.03 (0.01)	0.03 (0.01)	.0006
11-50 μg/L	37	0.19 (0.08)	0.19 (0.08)	
>50 μg/L	12	0.27 (0.17)	—	

* Numbers in parentheses represent the total number of patients on which tumor-free survival rates are based because initial data were not available from the clinical records in all patients.

TABLE 3. Significant Prognostic Variables for HCC and Their Regression Coefficients Evaluated in the Whole Population of 349 Cirrhotic Patients (Group A) and in the Subgroup of 148 Patients in Whom Alpha-Fetoprotein was Tested at Enrollment (Group B)

Group	Variables	Coefficient Regression	SE	P*
A	Age	0.080	0.0169	.0001
	Liver firmness	0.380	0.1736	.01
	Platelets	−0.007	0.0035	.02
B	Age	0.082	0.0302	.006
	Liver firmness	0.772	0.3911	.04
	Platelets	−0.010	0.0062	.10

* *P* derived from Wald test.

Factors Correlating With Development of HCC. At univariate analysis four variables studied at presentation were significantly associated with the probability of developing liver cancer (Table 2). The probability of HCC appearance was significantly higher for patients with older age, presence of liver firmness on physical examination, low levels of platelets, and higher levels of alpha-fetoprotein at entry. HCC appeared in 6 of the 37 patients with alpha-fetoprotein levels between 11 and 50 μg/L at entry and in 3 of 12 cases with alpha-fetoprotein levels > 50 μg/L at presentation. Multivariate analysis with Cox's model showed that age, serum levels of platelets, and liver firmness on physical examination were the only independent significant risk factors for development of HCC in patients with compensated cirrhosis type B (Table 3). In the subgroup of 148 patients in whom alpha-fetoprotein was tested at enrollment, Cox's model failed to demonstrate any in-

dependent prognostic significance of alpha-fetoprotein and confirmed age, serum platelet levels, and liver firmness on physical examination as independent predictors of liver cancer (Table 3). HBeAg, HBV-DNA, and anti-HDV status at the time of diagnosis of compensated cirrhosis had no prognostic value for liver cancer appearance both in the univariate and multivariate analysis.

Development of Decompensation. Of the 317 patients who remained tumor-free, 88 (28%) developed at least one episode of ascites, jaundice, hepatic encephalopathy, or variceal bleeding (hematemesis and/or melena) 2 to 144 months after entry into the study. The remaining 229 patients did not develop any of these complications during the observation period. The first episode of decompensation showed as ascites, jaundice, or variceal bleeding in 26, 15, and 7 patients, respectively, and as more than one major complication in the remaining 41 patients. The cumulative probability of developing decompensated cirrhosis is shown in Fig. 2. The third year decompensation appearance rate was 17%, the fifth-year and the tenth-year rates were 23% and 37%, respectively.

Forty-five patients died after decompensation of their chronic liver disease. After the appearance of the first major complication of cirrhosis the probability of survival was 35% at 5 years (Fig. 3).

Comparison Between Patients With HCC and Patients Developing Decompensation. When we compared the clinical, biochemical, and virological parameters measured at enrollment between the 32 patients subsequently developing HCC and the 88 patients undergoing decompensation, only mean age was significantly ($P < .01$) older at entry in patients with liver cancer (mean age ± SD; 54 ± 10 vs. 45 ± 12 years, respectively). No differences were observed between the two groups of patients in the other 17 initial clinical and serological variables considered as potential prognostic factors for HCC. The known duration of cirrhosis, calculated from the time of entry into the study to the diagnosis of HCC or decompensation, was significantly longer in the 32 patients with liver cancer compared with the 88 patients developing decompensation (mean duration of cirrhosis ± SD; 61 ± 44 vs. 39 ± 34 months, respectively; $P < .01$).

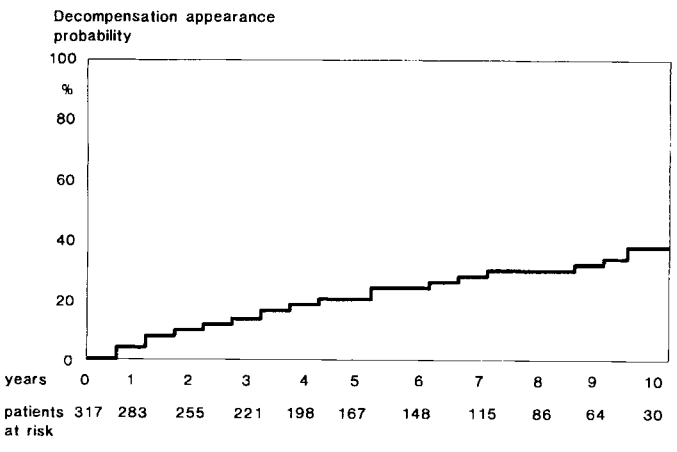

FIG. 2. Cumulative probability of developing decompensation in 317 patients with cirrhosis type B who remained tumor-free. The 5-year probability rate was 23% and the 10-year probability rate 37%.

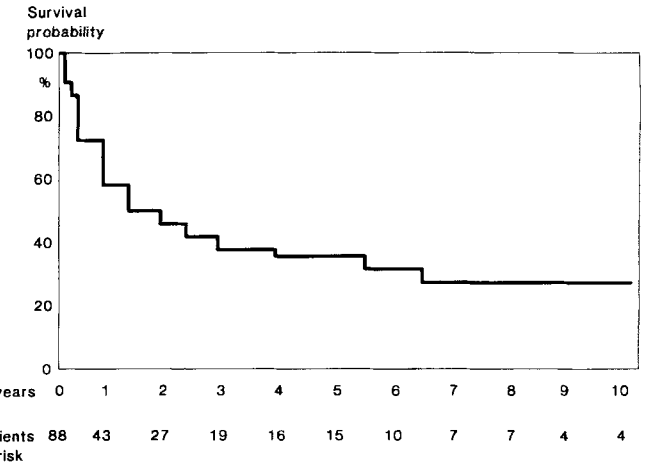

FIG. 3. Cumulative probability of survival after the appearance of the first major complication of cirrhosis in 88 HBsAg-positive cirrhotic patients undergoing decompensation during follow-up. The 5-year survival rate was 35%.

DISCUSSION

The inclusion in this study of patients with well-compensated cirrhosis provides a unique opportunity to examine the progression of HBsAg-positive cirrhosis from the very beginning. The main findings of our study regard frequency and timing of decompensation and HCC and risk factors for liver cancer. The results show that 5 and 10 years after diagnosis the probability of remaining compensated was 77% and 63%, respectively, indicating that a high proportion of patients presenting with compensated cirrhosis type B do not worsen for several years because hepatic decompensation usually occurs at a relatively late stage in the clinical course of the disease. However, once decompensation has occurred, the 5-year survival rate is only 35% compared with the 5-year survival rate of 84% previously reported in the whole population of 366 patients presenting with compensated cirrhosis type B.[9] The survival rate was calculated after the appearance of the first major complication of cirrhosis, allowing us to get an acceptable level of uniformity in the zero time point of follow-up of decompensated patients. The opportunity to evaluate the clinical course of cirrhosis from an early stage of hepatic decompensation might explain the higher survival rate of 35% at 5 years observed in our study compared with the 5-year survival rate of 14% recently reported in Western European HBsAg-positive cirrhosis patients, who were not necessarily studied from their first episode of decompensation[17]. Nevertheless, both of these studies point out the poor prognosis of HBsAg-positive decompensated cirrhosis and such information might be used to decide

the appropriate timing for therapeutic interventions, such as liver transplantation.

In the current study, including a consistent number of clinically homogeneous patients, HCC developed in 9% of 349 patients with compensated cirrhosis type B during a mean follow-up of 73 months. Indeed, previous longitudinal studies performed in Europe on the prevalence and incidence of HCC in the high-risk group of patients with cirrhosis have included small numbers of HBsAg-positive patients and/or have not specifically analyzed the group of HBsAg carriers.[18-20] In a recent study in northern Italy analyzing the prevalence of liver cancer among 417 patients with well-compensated cirrhosis of viral and nonviral origin, HCC developed in 7% of 70 HBV-related cases during follow-up periods averaging 33 months.[20] The similar prevalence of HCC observed in our Western European, white patients and in the Italian patients observed by Colombo et al[20] confirms that in Europe patients with compensated cirrhosis type B are at consistent risk for liver cancer. One might speculate that in Europe, as in the Far East and in Africa, HCC is a natural sequela of HBV-related liver cirrhosis, independently of the geographic areas or ethnic origin.

In a prospective study of compensated cirrhosis type B from Taiwan, Liaw et al[21] reported a higher yearly HCC incidence of 2.8%. This might reflect differences in the natural history of the disease in the Far East because of the fact that the oncogenic role of HBV seems to be particularly important when infection occurs early in life.

It has been recently suggested that for a better understanding of the oncogenic potential of hepatotropic viruses, such as HBV, it would be very interesting to have more information about the degree of viral replication in relation to the risk for liver cancer (Ciernik IF, N Engl J Med 1993; 329:1897, Correspondence). In our study we did explore the predictive value of markers of HBV replication and found that HBeAg and HBV-DNA status at the time of diagnosis had no prognostic value for the development of liver cancer. However, it is interesting to note that 20% of the 20 patients tested were in a replicative state according to serum HBV-DNA at the time of diagnosis of HCC. Indeed, sustained HBV replication is associated with liver cell injury, which leads to liver cell regeneration and may then promote malignancy.[22]

According to previous studies performed on European patients, HDV infection was not correlated with the development of HCC in our cirrhotic patients, thus excluding any pathogenetic role for HDV in causing liver cancer.[23-25]

In this study we have focused on a selected population of patients with compensated cirrhosis type B and we were able to evaluate the role of multiple clinical and serological cofactors for HCC, excluding the effect of the etiologic agent and the presence of cirrhosis. According to the univariate analysis, presence of liver firmness on physical examination and low platelet values, likely indicating an advanced stage of the cirrhosis at entry into the study, were indicators of a significantly higher probability of development of HCC. Also age, which may be a determinant in itself or simply a reflection of the age of infection or of the duration of the liver disease, was found to be a strong prognostic variable. Baseline serum alpha-fetoprotein above the limit of normal value was also a predictive marker for the development of HCC from cirrhosis, suggesting a close follow-up of these patients with elevated alpha-fetoprotein to improve the chance of detection of liver cancer at an early stage.

Multivariate analysis identified age, serum levels of platelets, and liver firmness at entry as independent significant predictors of liver cancer, thus confirming that only parameters reflecting a more advanced stage of cirrhosis predicted the development of HCC.

Two further observations are in keeping with age and stage of cirrhosis as important determinants of liver cancer. Indeed, our data showed that patients who developed HCC were significantly older at entry into the study compared with patients subsequently undergoing decompensation. Moreover, the known duration of cirrhosis was significantly longer in patients with liver cancer compared with patients undergoing decompensation. There is evidence that HCC shows a linear increase over a patient's lifetime and our data suggest that increasing age is an important risk factor because it likely reflects a presumably longer duration of cirrhosis. Consistent with these results is the observation that the cumulative probability of developing HCC gradually increases during follow-up of our cirrhotic patients.

In conclusion, our study of this well-defined, clinically based population indicates that progression of compensated cirrhosis type B is slow, but once decompensation occurs life expectancy is poor. Moreover, our data strengthen the epidemiological evidence of the association among chronic HBV infection, cirrhosis, and HCC also in Europe. The analysis of risk factors indicates that HCC could be the likely consequence of long-standing hepatic disease, unless the cirrhotic patient dies earlier from decompensation or other causes that are not liver related.

APPENDIX

The following institutions and investigators were members of the EUROHEP Study Group on Hepatitis B Virus and Cirrhosis: Istituto di Semeiotica e Nefrologia Medica, University of Verona, Verona, Italy (G. Fattovich); Istituto di Medicina Clinica, Clinica Medica 2a, University of Padova, Padova, Italy (A. Alberti, G. Giustina, and F. Noventa); Internal Medicine II, University Hospital Rotterdam, Rotterdam, the Netherlands (S.W. Schalm and C. Quero); Academic Department of Medicine, Hippokration General Hospital, Athens, Greece (S.J. Hadziyannis and S. Savvas); Liver Unit, Hospital Clinic, University of Barcelona, Barcelona, Spain (J.M. Sanchez-Tapias and A. Mas); Cattedra di Clinica Medica R, University of Palermo, Palermo, Italy (P. Almasio and A. Craxì); Department of Medicine B, Bispebjerg University Hospital, Copenhagen, Denmark (E. Christensen); University Hospital, Rigshospitalet, Copenhagen, Denmark (K.

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