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Original article

Clinical outcome of lamivudine-resistant chronic hepatitis B patients with compensated cirrhosis under adefovir salvage treatment. Importance of HCC surveillance

I. Elefsiniotis [a,b,*], M. Buti [b], R. Jardi [b], E. Vezali [a], R. Esteban [b]

[a] University Department of Internal Medicine, "Elena Venizelou" Hospital, Elena Venizelou Square 2, Athens, Greece
[b] Liver Unit and Biochemistry Department, Hospital Universitario Vall d' Hebron, Barcelona, Spain

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ABSTRACT

Background: Data concerning the outcome of lamivudine-resistant (LAM-R) chronic hepatitis B (CHB) patients with compensated cirrhosis under adefovir (ADV) treatment are limited. The aim of our study was to evaluate the medium term outcome of these, high-risk for fatal events, patients.
Methods: 31 LAM-R patients with compensated cirrhosis who had been treated with ADV monotherapy ($n=8$) or ADV plus LAM ($n=23$) for a mean of 27.6 months, were evaluated. Virological response (VR) was defined as HBV-DNA levels $<10^4$ copies/ml within the first year of treatment.
Results: Twenty-three patients (74.19%) achieved VR. Six patients (19.35%) developed ADV-related mutations (annual incidence 11%). Liver-related death, liver decompensation and hepatocellular carcinoma (HCC) were observed in 12.9%, 16.12% and 16.12% of patients, respectively. HCC (annual incidence 9.1%) was the main cause of liver decompensation (4/5, 80%) and of liver-related deaths (3/4, 75%). HCC development was not related to patients' age ($p=0.440$), HBeAg status ($p=0.245$), HBV genotype ($p=0.598$), baseline ALT levels ($p=0.981$), baseline viral load ($p=0.464$), VR ($p=0.504$) as well as emergence of ADV resistance ($p=0.871$).
Conclusions: ADV suppresses viral replication in more than 70% of LAM-R cirrhotic patients during the first year of treatment. Despite that, HCC is frequently observed in these high-risk patients, irrespective of virological response or emergence of ADV resistance.

1. Introduction

Chronic hepatitis B (CHB) is an important cause of morbidity and mortality worldwide [1–3]. The main goals of therapy in CHB patients are to prevent disease progression and avoid end-stage liver disease and the development of hepatocellular carcinoma (HCC) [4].

Lamivudine (LAM) was the first orally administered agent approved for the treatment of CHB and it has a well-established safety and efficacy profile [5,6]. Unfortunately the clinical benefit is rarely sustained under long-term LAM treatment due to the selection of LAM-resistant mutants [7–12].

Adefovir dipivoxil (ADV) is a nucleotide analogue with antiviral efficacy against wild type [13,14] and LAM-R [15,16] HBV. Resistance to adefovir is less common and usually occurs later in the treatment course, in comparison to lamivudine [17,18]. However, increased risk of ADV resistance is observed in LAM-R patients compared to treatment-naïve patients, especially in those treated with ADV monotherapy [19–21]. Data concerning the efficacy of ADV treatment in LAM-resistant CHB patients with compensated cirrhosis from Western Countries are limited. Data from Europe concerning the outcome of LAM-resistant CHB patients treated with ADV have been published by two groups [22,23], but both studies included only HBeAg-negative CHB patients and only a small proportion of them had cirrhosis. Moreover the clinical outcome (liver decompensation, HCC development, liver-related death) is not well documented in these high-risk patients.

The primary aim of our study was to evaluate the medium-term outcome of LAM-R CHB patients with clinical and histological proved compensated cirrhosis under ADV salvage treatment. Secondary aims were to assess the virological response and to determine the ADV resistance profile in these patients.

2. Methods

In this retrospective cohort study, data were collected from consecutive patient's files and the virological records. Both HBeAg-positive and HBeAg-negative patients with clinical, laboratory, endoscopic or radiological signs, as well as histologically confirmed compensated cirrhosis, were considered eligible if they had documented lamivudine resistance as a result of previous treatment, before the initiation of ADV therapy. Resistance to lamivudine was confirmed by detection of mutations in the YMDD motif of the RNA-dependent DNA polymerase gene of the virus in patients with elevated serum

* Corresponding author. Liver Unit and Biochemistry Department, Hospital Universitario Vall d'Hebron, Barcelona, Spain. Tel.: +30 210 9630312; fax: +30 210 7461497.
E-mail address: ielefs@nurs.uoa.gr (I. Elefsiniotis).

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Table 1
Baseline characteristics of the study population.

Gender (male/female, %)	26 (83.9%)/5 (16.1%)
Age (years, median/iqr)	59/15
LAM-Tx duration (months, median/iqr)	36/36
ALT (IU/L, median/iqr)	107/110
HBV-DNA ($-\log_{10}$ copies/ml, median/iqr)	7.0/3.0
HBeAg (+ or −, %)	9 (29%)/22 (71%)
Genotype (A/D)	13 (41.9%)/18 (58.1%)
Tx-group (ADV vs ADV/LAM)	8 (25.8%)/23 (74.2%)

HBV-DNA levels (at least 4 logs and/or more than 1 log elevation from the LAM on-treatment nadir) or elevated serum alanine aminotransferase (ALT) levels (>40 IU/L). Patients with decompensated liver cirrhosis or HCC at first visit, liver transplant patients, immunocompromised patients as well as patients with co-infections (HIV, HCV, HDV) or concomitant liver diseases were excluded from the study. Patients who exhibit liver decompensation or HCC development while they were on ADV treatment for less than 12 months as well as patients without available data at baseline and at least every 6 months during treatment were excluded from the analysis. All patients underwent abdominal ultrasound (U/S) as well as serum alpha-fetoprotein (AFP) measurement at baseline and every 6 months during the study period. Patients with pre-existing nodules at baseline U/S underwent U/S or C/T guided biopsy of the main nodule and those with histological findings of dysplastic nodule or HCC were excluded from the analysis. Moreover, patients with serum AFP levels more than 200 ng/ml at baseline control, with or without detectable nodules in the U/S were also excluded, because it was considered that hepatocarcinogenesis has been already started at that time in these patients, despite the negative radiological data.

All patients underwent a percutaneous liver biopsy within 6 months before the initiation of LAM treatment. The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Patients were treated with ADV either as monotherapy (10 mg/day) or in combination with ongoing LAM (100 mg/day). The primary outcome was either liver decompensation (defined by the development of ascites and/or jaundice and/or hepatic encephalopathy and or variceal bleeding) or the development of HCC or liver-related death. Secondary outcomes were the virological response (VR), defined as serum HBV-DNA levels less than 10^4 copies/ml, by a quantitative real time PCR assay, within the first 12 months of treatment and the emergence of ADV-related mutations. Serological markers for viral hepatitis were determined by EIA (Ortho Clinical Diagnostics, Amersham, Bucks, UK). Serum HBV-DNA was quantified using a real time PCR assay (LightCycler-FastStart DNA Master, Roche Diagnostic, Mannheim, Germany) at baseline control and every 6 months during treatment. The detection limit of this PCR technique is 10^3 copies/ml. ADV and LAM resistance-associated mutations were tested in HBV DNA positive serum samples by direct sequencing.

2.1. Statistical analysis

Three types of events were considered as endpoints: (i) virological response, (ii) emergence of ADV-related mutation and (iii) development of HCC and/or hepatic decompensation and/or liver-related death. The prognostic value of several baseline parameters was evaluated using time-to-event methods for censored observations, because of the varying length of follow-up. Time-to-event analysis was carried out using Kaplan–Meier estimates to draw the cumulative incidence curves, compared by log-rank tests, as well as by univariate and multivariate Cox's proportional hazards models of relevant prognostic variables. The hazards ratio or relative hazards (HR) are presented with 95% confidence intervals (CI) and p-values. p-values of <0.05 were considered to be statistically significant. Stata™ 9.0 statistical software was used for the statistical analyses (STATA Corp. College Station, Texas, USA).

3. Results

Thirty-one patients with compensated HBV cirrhosis who had been treated previously with LAM monotherapy for a mean of 41.7 ± 21.9 months fulfilled the study criteria. The baseline characteristics of the study population are presented in Table 1. The rtM204V-I mutation was present in all cases, 25 of them (80.64%) also exhibited compensatory mutations (20 the double rtL180M/M204V-I mutation and 5 the triple rtV173L/L180M/M204V-I mutation). Eight patients (25.8%) received ADV monotherapy and 23 (74.2%) a combination of ADV plus LAM, both for a mean period of 27.6 ± 16.2 months.

3.1. Clinical outcome

Six patients (19.4%) died during the study period. Four of them (12.9% of the whole group studied) died due to their liver disease. Five patients (16.12%) developed hepatic decompensation and four of them died from their liver disease. The main cause of functional decompensation was HCC development (four patients exhibited liver decompensation after the development of HCC and only one due to the progression of his liver disease). Five patients (16.12%) developed HCC during the study period.

It is important to note that among patients without VR or emergence of ADV-related mutations only one patient developed

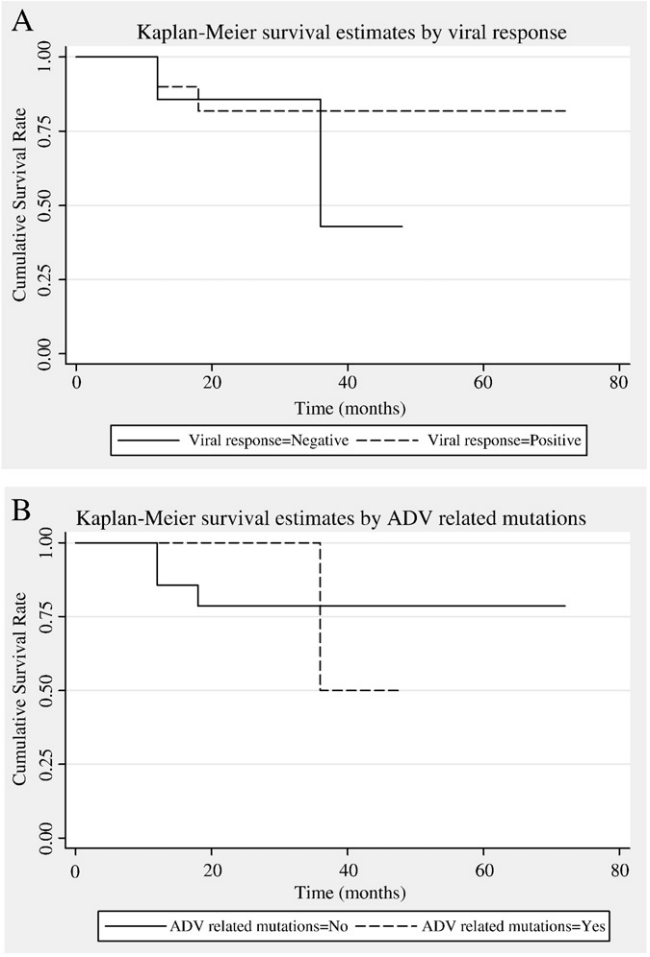

Fig. 1. A. Cumulative probability of HCC among patients with or without virological response ($p = 0.488$). B. Cumulative probability of HCC among patients with or without ADV-related mutations ($p = 0.869$).