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Cost-effectiveness of Lamivudine, Telbivudine, Adefovir Dipivoxil and Entecavir on decompensated hepatitis B virus-related cirrhosis

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Abstract. – OBJECTIVE: To evaluate the cost-effectiveness of lamivudine (LMV), telbivudine (LdT), adefovir dipivoxil (ADV) and entecavir (ETV) on decompensated hepatitis B virus-related cirrhosis.

PATIENTS AND METHODS: 1332 patients with decompensated hepatitis B virus-related cirrhosis were randomly assigned into 5 groups with different clinical treatment including LMV treatment, LdT treatment, ADV treatment, LMV+ADV treatment and ETV treatment. And then the liver function, Child-Pugh scores, sero-conversion of HBeAg/HBeAb, polymerase gene mutations, cost-effectiveness, incremental cost-effectiveness and side effects were investigated and further analyzed.

RESULTS: LMV, ADV, LdT, LMV+ADV and ETV were all effective on decreasing Child-Pugh scores and conversing negatively hepatitis B virus (HBV) DNA and HBeAg, whereas LMV+ADV and ETV more effective than LMV, ADV and LdT. HBV DNA polymerase genotypic mutations were rare in the 5 groups. The less mutation rate was found in the LMV+ADV and ETV group than in the LMV, ADV and LdT group. Compared to the cost-effectiveness and incremental cost-effectiveness ratio, ETV was the optimal selection, LMV+ADV was the alternative selection and LMV was the cheapest option. The side effects of the 5 plans were all rare and could be controlled.

CONCLUSIONS: LMV, ADV, LdT, LMV+ADV and ETV were all effective on treatment of decompensated hepatitis B virus-related cirrhosis whereas ETV and LMV+ADV were recommended.

Key Words:
Hepatitis B virus, Lamivudine, Telbivudine, Adefovir Dipivoxil, Entecavir, Cirrhosis.

Introduction

Hepatitis B virus (HBV) is the most common hepatitis virus that causes chronic liver infection in human, affecting more than 400 million individuals, among whom 10-20% of individuals progress to liver cirrhosis, resulting in 600,000 deaths each year from cirrhosis and hepatocellular carcinoma (HCC)[1]. The natural history of HBV infection varies widely from the immune tolerance characterized by high viral load but little inflammation to the clearance of virus which is marked by a loss of HBsAg, though HBV may remain integrated in the host genome as covalently closed circular DNA. Antiviral agents have been proved to be able to control viral replication, improve liver function, reduce the HCC development[2]. Nucleoside (LMV, LdT and ETV) and nucleotide analogues (ADV) and Tenofovir Disoproxil have all been approved for hepatitis B virus-related cirrhosis therapy worldwide[3]. Though ETV and Tenofovir Disoproxil have been recommended as the first-line options for treatment of naive CHB patients, they are not used widespread in the countries with limited health resources due to the high daily cost or less available, and therefore LMV, LdT and ADV are still widely used especially in the economically less developed regions due to their low cost and easy availability. Based on the paradigm that drug combination therapy is more effective than monotherapy for the treatment of human immunodeficiency virus, combination therapy of LAM and ADV is also a good plan for the patients with

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decompensated liver cirrhosis. In the present study, we aimed to evaluate the cost-effectiveness of treatment of LMV, LdT, ADV, LMV+ADV and ETV on patients with decompensated hepatitis B virus-related cirrhosis.

Patients and Methods

Patients

Adult patients who had decompensated hepatitis B virus-related cirrhosis were enrolled in the study over 8-year period (January 1, 2006 to November 30, 2014) in our hospital. The diagnosis of decompensated cirrhosis was based on clinical, laboratory, previous histological and CT examinations of cirrhosis with at least 1 sign of liver decompensation (ascites, variceal bleeding, hepatic encephalopathy, non-obstructive jaundice)[4]. A total of 1332 patients including 748 males and 584 females with a median age of 42 years (40-59 years) were enrolled and analyzed by prospective double-blind study. Child-Pugh score was used to assess the clinical status of each patient[5]. Exclusion criteria: Patients were excluded for resistance to LMV, ADV, LdT or ETV, co-infection with hepatitis C virus, hepatitis D virus, hepatitis E virus or human immunodeficiency virus, and autoimmune hepatitis, alcoholic cirrhosis, hepatorenal syndrome, grade 3 or 4 hepatic encephalopathy, or spontaneous bacterial peritonitis, and severe heart, renal, brain diseases.

Treatment of Patients

The patients were randomly divided into five groups: LMV (n=256), LdT (n=260), ADV (n=276), LMV+ADV (n=276) and ETV (n=264). Drug usage: LMV (GlaxoSmithKline Pharmaceutical Company Limited, Shanghai, China) 100 mg oral administration once a day; LdT (Beijing Novartis Pharma Ltd, Beijing, China) 600 mg oral administration once a day; ADV (GlaxoSmithKline Pharmaceutical Company Limited, Shanghai, China) 10 mg oral administration once a day; ETV (Bristol-Myers Squibb Pharmaceutical Company Ltd., Shanghai, China) 0.5 mg oral administration once a day.

Biochemical and Virological Analysis

Peripheral blood was taken from all of the patients in the morning after fasting for at least 8 h. The complete blood count was determined by using an automated cell counter (Beckman Coulter LH750, Brea, CA, USA). Liver alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were measured by using standard commercial kits (Boehringer, Mannheim, Germany). The Child-Pugh scores were counted. All samples were screened to detect HBsAg, anti-HBs, HBeAg, anti-HBe, anti-HBc (total) and anti-HBc IgM by using third-generation microparticle enzyme immunoassays (Abbott Laboratories, Chicago, IL, USA).

HBV DNA was investigated by real-time polymerase chain reaction (PCR) (COBAS TaqMan 48 analyzer, Roche Diagnostics, Indianapolis, IN, USA) according to the manufacturer's instructions.

Genotypic Analysis

HBV mutations were analyzed by direct sequencing. Extracted from serum samples, HBV DNA polymerase gene region was amplified by nested-PCR using specific primers. We employed the primers and PCR program of Osiowy[6]. Briefly, forward primer spr1F (5'-GTT CAG GAA CAG TAA GCC C-3') and the reverse primer spr1R (5'-GAA AGG CCT TGT AAG TTG GCG-3') were used in the first round PCR. The inner primers spr2F (5'-GGT GGA CTT CTC TCA ATT TTC TAG G-3') and antisense primer spr2R (5'-ACT TTC CAA TCA ATA GGC C-3') were used for the second round of nested PCR. The following PCR thermal-cycling program was performed: 35 cycles consisting of 94°C for 30s, 56°C for 30s (first round) or 50°C for 30s (second round), and 72°C for 40s. The intended fragment were amplified using 2×PCR master mix solution (Tiangen Biotech Company Limited, Beijing, China) with 5 μl of DNA extract and 2 μl of the first round PCR product. After the amplification of polymerase gene, the amplicons (730bp) were visible after agarose gel electrophoresis and gel purified using High Pure PCR Product Purification Kit (Roche Diagnostic Gmbh, Mannheim, Germany). The purified PCR products were bi-directionally sequenced commercially using inner primers.

Cost Calculation

A cost calculation was performed by means of identification and subsequent quantification of resources used, and assigning unitary cost to each. The costs are presented in dollars of the year 2013. Unitary cost of LMV, LdT, ADV and ETV was 1.8, 2.2, 2.7 and 4.9 dollars respectively.

Cost-effectiveness Ratios (CER) and Incremental Cost-Effectiveness ratio (ICER)

Standing for the cost for each unit of effectiveness produced by each therapeutic plan, cost-effectiveness ratio is computed by dividing the difference in the mean costs of the two therapies (referred to as costs) by the difference in the mean effects of the therapies (referred to as effects) and is assessed by the following formulas:

$$CER_{LMV} = \frac{Cost_{LMV}}{Effectiveness_{LMV}}$$

$$CER_{LdT} = \frac{Cost_{LdT}}{Effectiveness_{LdT}}$$

$$CER_{ADV} = \frac{Cost_{ADV}}{Effectiveness_{ADV}}$$

$$CER_{LMV+ADV} = \frac{Cost_{LMV+ADV}}{Effectiveness_{LMV+ADV}}$$

$$CER_{ETV} = \frac{Cost_{ETV}}{Effectiveness_{ETV}}$$

The incremental cost-effectiveness ratio (ICER), defined as the additional cost incurred to achieve an extra unit of effectiveness was calculated applying the following formula in reference to LMV:

$$ICER_{ADV\ vs.\ LMV} = \frac{Cost_{ADV} - Cost_{LMV}}{Effectiveness_{ADV} - Effectiveness_{LMV}}$$

$$ICER_{LdT\ vs.\ LMV} = \frac{Cost_{LdT} - Cost_{LMV}}{Effectiveness_{LdT} - Effectiveness_{LMV}}$$

$$ICER_{LMV+ADV\ vs.\ LMV} = \frac{Cost_{LMV+ADV} - Cost_{LMV}}{Effectiveness_{LMV+ADV} - Effectiveness_{LMV}}$$

$$ICER_{ETV\ vs.\ LMV} = \frac{Cost_{ETV} - Cost_{LMV}}{Effectiveness_{ETV} - Effectiveness_{LMV}}$$

Statistical Analysis

Statistical testing was performed by using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA). Data are expressed as means±standard error of the mean (SEM) of the indicated number of separate experiments. Statistical comparison between experimental group and control was performed by using one-way ANOVA analysis and unpaired two-tailed Student's *t*-tests (for measurement data) or chi-square test (for percentage). $p < 0.05$ was considered significant.

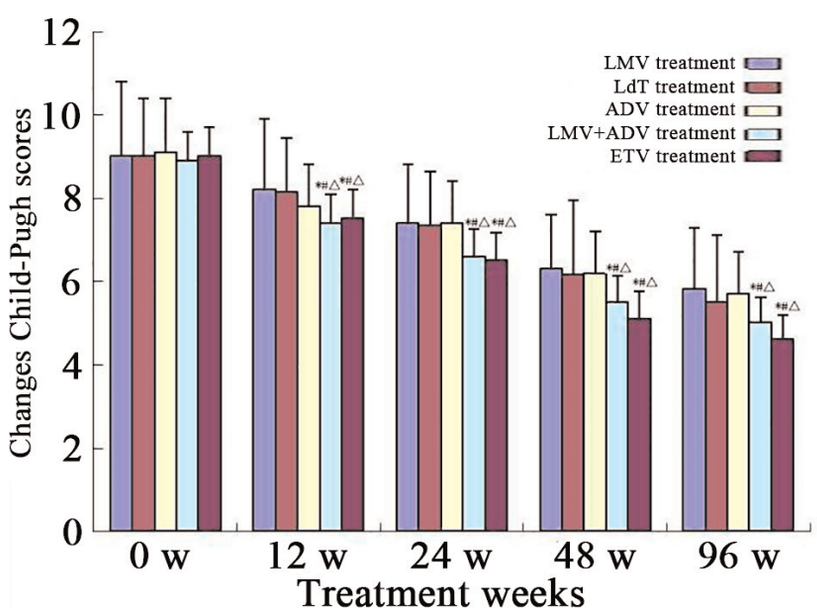

Figure 1. Changes Child-Pugh scores of the 5 groups during 96 weeks therapy. *: vs LMV group, $p < 0.05$; #: vs LdT group, $p<0.05$; §: vs LdT+ADV group, $p < 0.05$.

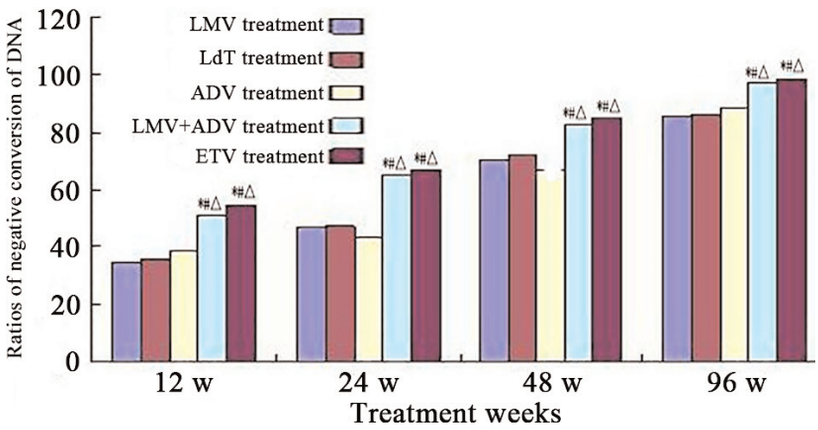

Figure 2. DNA negative conversion ratio of the 5 groups during 96 weeks therapy. *: vs LMV group, $p < 0.05$; #: vs LdT group, $p < 0.05$; §: vs LdT+ADV group, $p < 0.05$.

Results

Changes Child-Pugh Scores

As shown in Figure 1, after treatment for 12 weeks, Child-Pugh scores were decreased in LMV, LdT, ADV, LMV+ADV and ETV groups, and further decreased LMV+ADV or ETV groups.

Virological Response

As shown in Figure 2, at week 12, 24, 48, and 96, the ratio of patients with biochemical response was 34.3%, 46.8%, 72.3%, and 85.9% in LMV group respectively; 35.6%, 47.2%, 72.0% and 86.6% in the LdT group respectively; 38.5%, 43.3%, 66.7%, and 88.8% in ADV group respectively; 50.7%, 65.2%, 82.6%, and 97.0% in LMV+ADV group respectively; 54.5%, 66.7%, 84.8%, and 98.5% in ETV group respectively. Ratios of negative conversion of DNA of ETV group and LMV+ADV group are significantly higher than that of LMV group, LdT group and ADV group.

Ratio of Sero-Conversion of HBeAg/HBeAb

As shown in Figure 3, at week 12, 24, 48, and 96 of treatment, ratio of sero-conversion of HBeAg/HBeAb was 15.6%, 20.3%, 26.6%, and 28.1% in the LMV group respectively; 16.3%, 21.3%, 23.6% and 29.3% in the LdT group respectively; 18.3%, 20.0%, 31.7%, and 33.3% in the ADV group respectively; 23.2%, 30.4%, 43.5% and 55.1% in LMV+ADV group respectively; 27.3%, 34.8%, 48.5% and 59.1% in the ETV group respectively. Ratios of sero-conversion of HBeAg/HBeAb of the ETV group and the LMV+ADV group are significantly higher than that of LMV group, LdT group and ADV group.

Genotypic Mutation of DNA Polymerase

As shown in Table I, at week 96 of treatment, 40 patients (15.6%) developed viral breakthrough and genotypic mutation including 28

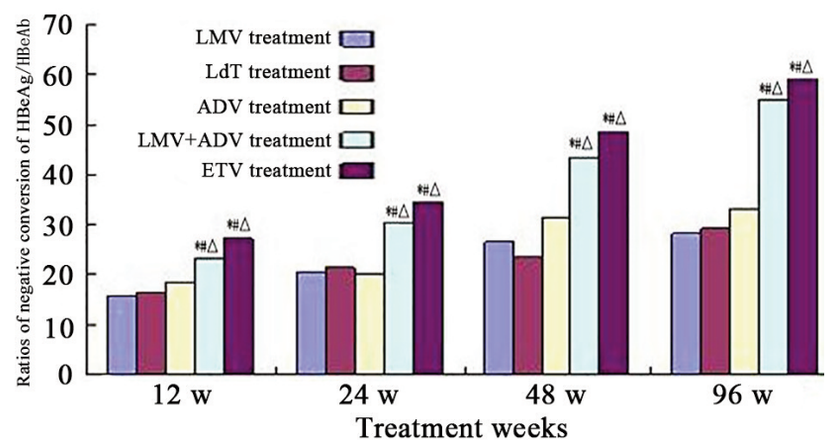

Figure 3. HBeAg/HBeAb seroconversion ratio of the 5 groups during 96 weeks therapy.
*: vs LMV group, $p < 0.05$; #: vs LdT group, $p < 0.05$; §: vs LdT+ADV group, $p < 0.05$.

Table I. Genotypic mutation of DNA polymerase of the 5 groups.

Group	n	Genotypic mutation (n, %)	Non-Genotypic mutation (n, %)	Mutation Genotype (n)
LMV	256	40 (15.6)	216 (84.6)	RtM204V (28); RtM204I (12)
LdT	260	44 (16.9)	216 (83.1)	RtM204V (28); RtL180M (16)
ADV	276	14 (5.1)*	262 (94.9)	RtA181V (8); RtN236T (4)
LMV+ADV	276	8 (2.9)*#	268 (97.1)	RtN236T (3); RtM204V (5)
ETV	264	0 (0)*#§	264 (100)	0

*, vs LMV group, $p < 0.05$; #, vs ADV group, $p < 0.05$; §, vs LMV+ADV group, $p < 0.05$.

RtM204V and 12 RtM204I in the LAM group, 44 (16.9%) including 28 RtM204V and 16 RtL180M in the LdT group, 12 (5.1%) including 8 RtA181V and 4 RtN236T in the ADV group, 8 (2.9%) including 3 RtN236T and 5 RtM204V in the LMV+ADV group, 0% in ETV group. Ratio of genotypic mutation in the ETV group is the least, in the LMV+ADV group the second least, and in the LMV group the most.

Cost-effectiveness Analysis and Incremental Cost-Effectiveness Ratio of the Five Groups

At week 96 of treatment, in the LMV, LdT, ADV, LMV+ADV and ETV group, the cost was 1142.4, 1478.4, 1818.4, 3024.0 and 3292.8 dollars, respectively; ratio of negative conversion of HBV DNA was 85.9, 86.3, 88.3, 95.6 and 97.0, respectively; cost-effectiveness ratio of negative conversion of HBV DNA was 13.3, 17.1, 20.6, 31.6 and 33.9, respectively; ratio of sero-conversion of HBeAg/HBeAb was 28.1, 29.3, 33.3, 55.1 and 59.1, respectively; cost-effectiveness ratio of sero-conversion of HBeAg/HBeAb was 40.7, 50.5, 54.6, 54.9 and 55.7, respectively; ratio of non-genotypic mutation ratio was 84.6, 83.1, 95, 97.1 and 100 respectively; cost-effectiveness ratio of non-genotypic mutation was 13.5, 29.3, 19.1, 31.1 and 32.9, respectively. In reference to LMV, for LdT, ADV, LMV+ADV and ETV group, incremental cost-effectiveness ratio of negative conversion of HBV DNA was 840.5, 281.8, 193.9, and 193.7, respectively, incremental cost-effectiveness ratio of sero-conversion of HBeAg/HBeAb was 280.2, 127.6, 69.7 and 69.4, respectively, incremental cost-effectiveness ratio of non-genotypic mutation was 224.1, 65, 175.9 and 139.6, respectively. Cost-effectiveness ratio of negative conversion of HBV DNA, sero-conversion of HBeAg/HBeAb and non-genotypic mutation of LMV group was the least, and of the ETV group was the most. Incremental cost-effectiveness ratio of negative conversion of HBV DNA, sero-conversion of HBeAg/HBeAb and non-genotypic mutation of LMV+ADV group was the most (Table II).

Table II. Cost-effectiveness and incremental cost-effectiveness analysis of the 5 groups.

Group	LMV	LdT	AdV	LMV+ADV	ETV
Cost	1142.4	1478.4	1818.4	3024.0	3292.8
Ratio of negative conversion of HBV DNA	85.9	86.3	88.3	95.6*#§	97.0*#§
Cost-effectiveness ratio of negative conversion of HBV DNA	13.3	17.1	20.6	31.6	33.9
Incremental cost-effectiveness ratio of negative conversion of HBV DNA	–	840.5	281.8	193.9	193.7
Ratio of sero-conversion of HBeAg/HBeAb	28.1	29.3	33.3	55.1*#§	59.1*#§
Cost-effectiveness ratio of sero-conversion of HBeAg/HBeAb	40.7	50.5	54.6	54.9	55.7
Incremental cost-effectiveness ratio of sero-conversion of HBeAg/HBeAb	–	280.2	127.6	69.7	69.4
Ratio of non-genotypic mutation	84.6	83.1	95	97.1*#	100*#
Cost-effectiveness ratio of non-genotypic mutation	13.5	29.3	19.1	31.1	32.9
Incremental cost-effectiveness ratio of non-genotypic mutation	–	224.1	65	175.9	139.6

*, vs LMV group, $p < 0.05$; #, vs ADV group, $p < 0.05$; §, vs LMV+ADV group, $p < 0.05$.

Side Effects

All the patients tolerated well and there was no patient discontinued the therapy. At week 96 of treatment, ratio of side was 7.8% including 12 patients with diarrhea and 8 patient with nausea effects in the LMV group, 5.4% including 14 patients with creatine kinase elevation (132.8 μmol/L) in the LdT group, 6.9% including creatine Kinase 19 patients with blood urea nitrogen elevation (mean 15.4 mmol/L) in the ADV group, 15.2% including 10 patients with BUN elevation (mean 14.2 mmol/L) and 5 patients with diarrhea and 6 patients with nausea in the LMV+ADV group, 6.8% including 11 patients with headache and 7 patients with dizziness in the ETV group (Table III). Acute renal or myopathy was not observed in any patient during the rescue therapy. The patients suffering side effects recovered after accepting symptomatic treatments.

Table III. Side effects of the 5 groups.

Group	Number	Side effects (Number, %)
LMV	256	20 (7.8)
LdT	260	14 (5.4)
ADV	276	19 (6.9)
LMV+ADV	276	21 (15.2)*
ETV	264	18 (6.8)

*, vs LMV group, $p < 0.05$.

Discussion

HBV persistent infection is an important risk factor for the development of liver cirrhosis or for the occurrence of HCC. For HBV-related cirrhotic patients, long-term HBV suppression may prove to be necessary even with a low ALT level and HBV replication. Nucleoside/nucleotide analogues are the only antiviral agents recommended for patients with hepatitis B decompensated cirrhosis. In the last few years, antiviral therapy has altered the natural course of HBV patients with decompensated cirrhosis and allowed us to stabilize most patients for liver transplantation and to improve significantly the prophylaxis of HBV recurrence on the graft[7]. Current guidelines have provided physicians with clear recommendations on how to select the most effective treatments for each patient[8]. In order to assist and streamline the management of HBV infection, the European Association for the Study of the Liver (EASL) published specific clinical practice guidelines in 2012 and stated that no matter how much the virus reproduction level is, the patients should accept anti-virus therapy, because severe exacerbation of hepatitis may result in hepatic failure for patients with decompensated hepatitis B virus-related cirrhosis[9].

LMV is the first available antiviral agents in the treatment of chronic hepatitis B, but long-term therapy is associated with mutations in the polymerase gene with a ratio of 14%-30% annually, particularly in rtM204I/V known as tryosine-methionine -aspartic acid-aspartic acid (YMDD) mutant. The emergence of rtM204I/V YMDD mutation of HBV polymerase gene is associated with rebounds in serum HBV DNA and flares of transaminase level[10]. LdT is an L-nucleoside that is structurally related to lamivudine and highly selective for hepatitis B virus DNA and inhibits viral DNA synthesis with no effect on human DNA or other viruses[11]. ADV is an effective rescue therapy for LMV-resistant HBV[12], but it may be associated with a proximal renal tubular toxicity as reflected by hypophosphatemia and elevated creatinine levels[13,14]. ETV can suppress both wild-type HBV and LMV-resistant HBV replication more rapidly and effectively than LMV or ADV[15,16].

In the present study, in the LMV, ADV, LMV+ADV and ETV groups, a sustainable increasing proportion of patients achieved undetectable HBV DNA levels and a sustainably increasing proportion of patients achieved sero-conversion of HBeAg/HBeAb from 12 weeks to 96 weeks, which indicates that all the 5 plans have good prognosis because the negative conversion of HBV is a predictor for the decreasing impairment of liver function and hepatitis B e antigen seroconversion is a predictor for lower ratios of cirrhosis and slower disease progression. At week 96 of treatment, 15.6% developed viral breakthrough and genotypic mutation in the LAM group, 16.9% in the LdT group, 5.1% in the ADV group, 2.9% in the LMV+ADV group and 0% in the ETV group. The lowest cost-effectiveness ratio of negative conversion of HBV DNA, sero-conversion of HBeAg/HBeAb and non-genotypic mutation was found in LMV group and the highest was in ETV group. Comparatively, LMV+ADV group obtained the highest incremental cost-effectiveness ratios. Ratio of side effects in the LMV, LdT, LMV+ADV and ETV group was 7.8%, 5.4%, 6.9%, 15.2% and 6.8% respectively, which are rare and can be controlled.

LMV, ADV and ETV are still used widely in the economically less developed regions since they are of low cost, relatively rare side effects and relatively high effects in inhibiting HBV replication and promoting HBeAg seroconversion. As was proved to be able to significantly further decrease the rates of decompensated cirrhosis and hepatocellular carcinoma events with the least drug resistance among these 4 pharmacons, ETV has become the best selection if the cost can be accepted by the patients. If ETV is unavailable, LMV+ADV is an alternative selection because it is nearly as effective as ETV. However, there are still many problems needed to be studied such as: How about the side effects and how to deal with them after a longer time? How to deal with the viral breakthrough and multidrug-resistance? We will carry out further randomized, larger sample size and longer term investigations to solve these questions.

Conclusions

LMV, ADV, LdT, LMV+ADV and ETV are all effective on treatment of decompensated hepatitis B virus-related cirrhosis, with ETV as the optimal selection, LMV+ADV as the alternatively good selection and LMV as the cheapest selection.

Acknowledgements

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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