

Prolonged Combination Therapy is More Effective than Monotherapy in Management of Chronic Hepatitis B Patients With Sustained Virological Response: An Experience From a 'Real-World' Clinical Setting

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Background: Little is known about the duration of combination therapy for patients with chronic hepatitis B (CHB) and suboptimal response to nucleos(t)ide analogues (NAs) monotherapy.

Objectives: This study aimed to assess whether monotherapy could be used for treatment of CHB patients, who poorly responded to Adefovir Dipivoxil (ADV) but obtained good responses after at least 12-month lamivudine (LAM) or telbivudine (LdT) add-on therapy.

Patients and Methods: Forty-five patients were enrolled, and the baseline time-point was determined according to enrollment data. Twenty-six patients chose to continue combination therapy (LAM+ADV or LdT+ADV, Group A) and 19 patients switched to single-drug maintenance therapy (LAM or LdT or ADV, Group B).

Results: There were no significant differences between two groups in baseline characteristics ($P > 0.05$). At 12th month, sustained virological response rate was greater in group A compared to group B (96.2% vs. 47.4%, $P < 0.001$), and the rates of NAs-associated resistance were 0% in group A and 15.8% in group B. Alanine aminotransferase normalization rate was also significantly higher in group A compared with group B (92.3% vs. 36.8%, $P < 0.001$). Among hepatitis positive patients with Be antigen (HBeAg), 40% (4/10) in group A and 9.1% (1/11) in group B achieved HBeAg seroconversion at the 12th month. Of patients in group B with positive-HBeAg before the previous combination therapy and detectable HBV DNA at 6 months of previous combination therapy were associated with high risks of viral relapse after switching to single-drug maintenance therapy.

Conclusions: Prematurely switching to single-drug maintenance therapy would be resulted in viral relapse, and prolonged combination therapy was effective to maintain sustained responses for patients with initial suboptimal response to ADV.

Keywords: Hepatitis B, Chronic; Combined Modality Therapy; Hepatitis Be Antigens

1. Background

About a quarter of the world population, more than 2 billion people, have been infected with hepatitis B virus (HBV), including 350 million people with chronic hepatitis B (CHB) (1, 2). According to the report from World Health Organization, HBV infection is highly endemic in the Asia pacific regions (3-6), and 15 to 25% of CHB patients would progress to life-threatening liver diseases including cirrhosis and hepatocellular carcinoma (3, 5).

Although completely eradication of HBV is seldom achieved by current antiviral treatments, but long-term suppression of HBV DNA to undetectable levels with antiviral therapy has been shown to significantly reduce liver disease progression (6, 7). At present, several nucleos(t)ide analogues (NAs) are available for the treatment of

CHB (8, 9), and the treatment usually requires a long time to get the responses. Recently, high rates of suboptimal viral response and resistance have diminished the long-term clinical benefits of antiviral therapy (8, 10). Because of limited choice of antiviral agents, more attention has gradually been drawn to the strategy of combination therapy (11). In recent years, increasing evidence suggests that combination therapy could effectively suppress viral replication and significantly delay or prevent the emergence of drug resistance (11-13), and combination therapy has become a potentially attractive therapeutic option in clinical practices (14, 15). Compared to other antiretroviral therapies, the experience of combination antiviral therapy in CHB patients is relatively limited, and both the duration and long-term effectiveness of combination therapy remain to be confirmed (16). Though some

Implication for health policy/practice/research/medical education:

To verify whether monotherapy could be used for treatment of CHB patients, who poorly responded to immunotherapy but obtained good responses after receiving combined treatment.

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evidence suggested that the rates of viral rebound and/or recurrence were high with the cessation of antiviral therapy (17-19), it is still unclear whether switching from combination therapy to single-drug maintenance therapy would lead to high viral rebound and/or accelerated disease progression for patients who already had achieved sustained virological response. In addition to long-term sustained suppression of viral replication of CHB, how to limit the medication regimen complexity and decrease the cost of drugs also have been widely concerned (16, 20, 21), because it is mainly associated with CHB patients' compliance of antiviral therapy.

In recent years, a strong doubt has been raised about the necessity of long-term combination therapy on CHB patient, which just poorly responded to single NAs but already showed good responses after receiving a certain dose of combination therapy; and this doubt also plagued our clinicians and patients in 'real-world' clinical practices.

2. Objectives

The aim of this study was to assess whether switching to monotherapy could be used for the treatment of CHB patients, who poorly responded to Adefovir Dipivoxil (ADV) but had good responses after receiving at least a 12-month lamivudine (LAM) or telbivudine (LdT) add-on therapy.

3. Patients and Methods

3.1. Study Design

In our previous study (22), the efficacy of LAM + ADV or LdT + ADV combination therapy on 72 CHB patients with suboptimal response to ADV (serum HBV DNA levels $> 3 \log_{10}$ copies/mL by PCR assays after ≥ 12 months of initial ADV monotherapy) were assessed; and after 1-year combination therapy, a total of 61 patients had a normal level of alanine aminotransferase (ALT) and sustained virological response.

This is a prospective, non-randomized cohort study from February 2011 to April 2012, to assess whether switching to single-drug maintenance therapy could be used as a treatment of CHB patients, who poorly responded to ADV but obtained good responses after receiving at least 12 months of LAM + ADV or LdT + ADV combination therapies. This study was conducted in Chengdu, in west China; and all the 61 candidates were recruited in present 'real-world' study (ChiCTR.org identifier: ChiCTR-ON-RC-12001921). Of 61 candidates, 16 patients withdrew from this study for various reasons, and 45 patients successfully were enrolled: 26 patients involved in continuous combination treatment (LAM + ADV or LdT + ADV, Group A) and 19 patients in single-drug maintenance treatment (LAM or LdT or ADV, Group B) according to their personal

choices.

All included patients were prospectively followed-up every 3 months, and baseline time-point of those patients was determined according to their enrollment date.

The inclusion criteria in this study were as follows: 1) lack of co-infection with hepatitis C virus or human immunodeficiency virus; 2) lack of other causes of liver disease, such as autoimmune hepatitis, and primary biliary cirrhosis; 3) no evidence of advanced liver diseases, such as decompensated cirrhosis, severe hepatitis, and hepatic carcinoma. Patients were excluded if they had poor compliance or no availability of detailed laboratory test results.

The study was conformed to the ethical guidelines of the 1975 Declaration of Helsinki. The approval of this study was obtained from the Ethics Committee of West China Hospital of Sichuan University, and written informed consent was obtained from participants.

3.2. Laboratory Tests

In present study, biochemical tests were performed using standard procedures (Olympus AU5400, Olympus Corporation, Tokyo, Japan), the upper limit of normal ALT was defined as 55 IU/L for men and 38 IU/L for women. Serological markers, including hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg) and anti hepatitis B e antibody (Anti-HBe) were evaluated by electrochemiluminescence immunoassay (Elecsys; Roche Diagnostics, China). Serum HBV DNA extraction and real-time PCR quantification were performed by fully automatic COBAS AmpliPrep/COBAS TaqMan 48 system (CAP-CTM; Roche, Branchburg, NJ), with a lower detection limit of 70 copies/mL. HBV genotype and drug-resistance mutations to NAs were detected by pyrosequencing.

3.3. Definition

In present study, treatment positive responses were calculated 12 months after study enrollment. Viral relapse was defined as HBV DNA detected by PCR after achieving undetectability of HBV DNA (< 70 copies/mL), and confirmed in two consecutive times at least one month apart. Sustained viral response (SVR) was defined as a persistent of undetectable serum HBV DNA at month 12. HBeAg serological response was defined as a confirmed seroconversion of HBeAg to Anti-HBe in HBeAg-positive patients at baseline. Combined response (CR) was defined as a combination of normal serum ALT level and undetectable serum HBV DNA at month 12, regardless of HBeAg status at baseline in present study.

3.4. Statistical Analysis

Quantitative variables were expressed as mean, 95% confidence interval (95% CI), median and interquartile range (IQR). Categorical variables were presented as number

and percentages. By considering the lower sample size, the comparisons between quantitative variables were performed using T-test or Mann-Whitney U test with bootstrap resampling; and the evaluation of qualitative variables were performed using Chi-square test or Fisher's exact test. The statistical analysis was carried using the SPSS 19.0 (SPSS Inc., Chicago, IL, USA). P-value less than 0.05 (two-tailed) indicating significant difference. The values of PPV and NPV were also calculated to determine the reliability of predictors of SVR in single-drug maintenance therapy.

4. Result

4.1. Patient Characteristics

A total number of 45 patients were finally included in the study (Figure 1), including 10 HBeAg-positive patients in group A and 11 HBeAg-positive patients in group B. The baseline characteristics of CHB patients between two groups were summarized in Table 1, and the standard demographic and laboratory characteristics were similar in two groups ($P > 0.05$).

Table 1. Baseline Clinical Features of the Patients in two Groups

Characteristic	Continue Combination Therapy (Group A)	Single-Drug Maintenance Therapy (Group B)	P-value
Sample size, No.	26	19	
Male, No. (%)	16 (61.54)	11 (57.9)	0.805
Age, (y)			
Mean (95%CI)	34.4 (31.6-36.8)	35.3 (31.8-38.4)	0.674
Median (IQR)	35.0 (9.25)	35.0 (12)	
Weight			
Mean (95%CI)	59.3 (57.0-63.2)	55.8 (51.5-58.2)	0.109
Median (IQR)	60.0 (11.25)	55.0 (8.0)	
Family history of HBV infection, No. (%)	14 (53.8)	8 (42.1)	0.436
Positive HBeAg, No.(%)	10 (38.5)	11 (57.9)	0.197
Duration of past combination therapy, mo			
Mean (95%CI)	15.4 (14.2-17.2)	13.5 (12.8-14.0)	0.717
Median (IQR)	14.0 (3.0)	13.0 (3.0)	
Duration of past ADV monotherapy, - mo			
Mean (95%CI)	13.6 (12.9-14.0)	17.7 (15.8-21.0)	0.109
Median (IQR)	15.0 (4.5)	16.0 (11.0)	
Past treatment with LAM+ADV/LdT+ADV, No. (%)	16(61.5)/10(38.5)	8(42.1)/11(57.9)	0.197

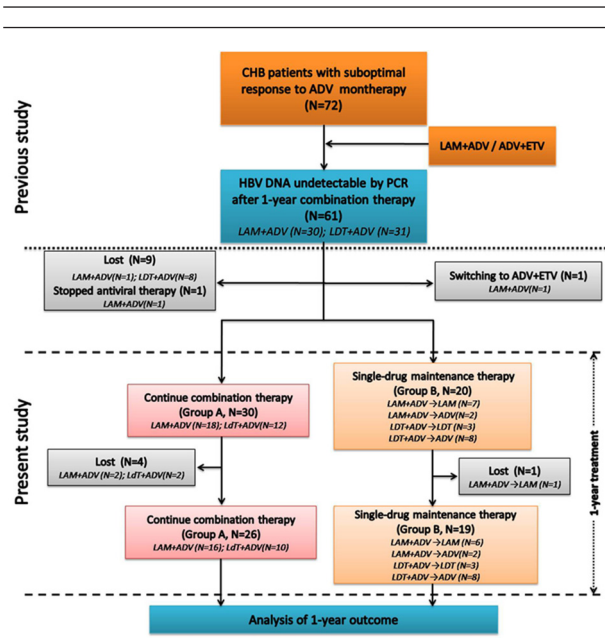


Figure 1. Screening and Follow-up Flow Chart

4.2. Treatment Response

The treatment outcomes of two groups are summarized in Table 2. At the beginning, all patients had normal ALT and undetectable HBV DNA. After 12 months of therapy, 92.3% (24/26) patients showed normal persistent ALT level and 96.2% (25/26) had SVR in group A, while only 36.8%

(7/19) patients had normal persistent ALT level and 47.4% (9/19) had SVR in group B; and the difference in either persistent ALT normalization or SVR between two groups were statistically significant (both $P < 0.001$). With respect to the combined response (CR), the rate of CR in group A was also significantly greater than group B (92.3% (24/26) vs. 36.8% (7/19), $P < 0.001$).

Among patients who were HBeAg-positive at baseline, 40% (4/10) of patients in group A and 9.1% (1/11) of patients in group B were HBeAg seroconversion at month 12, respectively; and the rate of HBeAg seroconversion between two groups was similar ($P = 0.149$).

4.3. Viral Relapse and Resistance

In total, 11 patients experienced VB during 12 months of observation, including 1 patient (1/26, 3.8%) in group A and 10 patients (10/19, 52.6%) in group B. Of the 10 patients in group B, 4 patients had HBV DNA level between 1000 and 100,000 copies/mL, which did not meet the minimum viral load required for analytical detecting of NAS-resistant strains.

Among 7 patients, by using genotypic drug-resistant analysis at month 12, 1 patient in group A and 3 patients in group B did not have any mutation conferring resistance to LAM, ADV, or LdT. While the other 3 patients (15.8%, 3/19) in group B showed NAS-associated resistance (Table 2), including 1 patient with rtM204V+rtL180M combined mutation (LAM-resistance), and 2 patients with rtA181T+rtN236T combined mutations (ADV-resistance).

Table 2. Virological, Biochemical and Serological Responses at Month 12

Responses	Continue Combination Therapy (Group A)	Single-drug Maintenance Therapy (Group B)	P-value
Sample Size, No.	26	19	
Sustained viral response			
Patients, No. (%)	25 (96.2)	9 (47.4)	< 0.001
Persistent ALT normalization			
Patients, No. (%)	24 (92.3)	7 (36.8%)	< 0.001
HBeAg seroconversion^a			
Patients, No. (%)	4/10 (40)	1/11 (9.1)	0.149
Combined response			
Patients, No. (%)	24/26 (92.3)	7/19 (36.8)	< 0.001
NAs-associated resistance			
Patients, No. (%) ^b	0 (0%)	3 (15.8%)	

^a for HBeAg positive patients enrolled in this study.

^b because of small sample size, the difference between two groups was not analyzed statistically.

4.4. Safety

The majority of patients were well tolerated in two groups. The increase in serum creatinine level was not observed in both groups. Among patients in group A, 1

patient with LDT+ADV showed a serum creatine kinase slightly increase (260 U/L, normal range: 38 - 174 U/L) but had normalized serum creatine kinase MB, and 1 patient with LAM+ADV showed a decline in the quality and duration of sex life; and there was no discontinuation due

to these adverse events. Among patients in group B, 1 patient with ADV reported hair loss, and 2 patients with ADV reported liver cirrhosis by abdominal ultrasonography. In both groups, no decompensated cirrhosis and hepatocellular carcinoma were reported.

4.5. Associated Factors to SVR in Patients Switching to Monotherapy

The clinical features of SVR and non-SVR patients at month 12 in group B were studied. As shown in Table 3, HBeAg positivity prior the past combination therapy ($P = 0.02$) and undetectable serum HBV DNA at month 6 ($P = 0.033$) were associated with probability of achieving SVR

in patients in group B. While the baseline of HBeAg in this study ($P = 0.141$), before ADV monotherapy ($P = 0.682$), and the type of past combination therapy ($P = 0.628$) were not related to SVR for patients in group B who switched to single-drug maintenance therapy in this study.

As showed in Figure 2, the serum HBV DNA level at week 24 of past combination therapy prior to enrollment, had a positive predictive value (PPV) of 64.3% and a negative predictive value (NPV) of 100% for SVR at month 12 in group B patients, and these findings indicated that detectable serum HBV DNA level at week 24 of past combination therapy was associated with an extremely lower probability of maintaining SVR after switching to single-drug maintenance therapy.

Table 3. Comparison of Clinical Features in SVR and non-SVR Patients at Month 12 in Group B

Characteristic	SVR	Non-SVR	P-value
Sample size, No.	9	10	
Male sex, No. (%)	6 (66.7)	5 (50.0)	0.650
Age, y			
Mean (95%CI)	35.6 (31.4-39.8)	35.0 (29.2-37.9)	0.804
Median (IQR)	35.0 (14.0)	32.0 (11.8)	
Weight, kg			
Mean (95%CI)	55.7 (51.2-60.3)	55.9 (51.4-59.8)	0.935
Median (IQR)	53.0 (9.0)	55.5 (8.0)	
Family history of HBV infection, No. (%)	3 (33.3)	5 (50)	0.650
Positive-HBeAg at baseline of this study, No. (%)	5 (55.6)	9 (90)	0.141
Positive-HBeAg prior to past combination therapy, No. (%)*	3 (33.3)	9 (90)	0.02
Duration of past ADV monotherapy, mo			
Mean (95%CI)	18.2 (15.5-22.4)	17.2 (13.7-20.9)	0.674
Median (IQR)	16.0 (9.0)	14.5 (12.3)	
Past combination therapy prior to enrollment			
LAM+ADV/LdT+ADV	2/7	4/6	0.628
Undetectable HBV DNA at month 3, No. (%)	5 (55.6)	4 (40)	0.656
Undetectable HBV DNA at month 6, No. (%)	9 (100)	5 (50)	0.033

5. Discussion

This prospective, cohort study is the first 'real-world' assessment of different post-processing strategies of combination therapy in patients with CHB up to date. The results demonstrated that prematurely switching to single-drug maintenance therapy would be resulted

in high risk viral relapses, but prolonged combination therapy was effective to maintain sustained response in CHB patients in a clinical setting. To some extent, our results presented a controversy regarding whether it is able to reduce or withdraw drug from combination therapy. Which were also consistent with previously published clinical trial reports on combination therapy (15, 16).

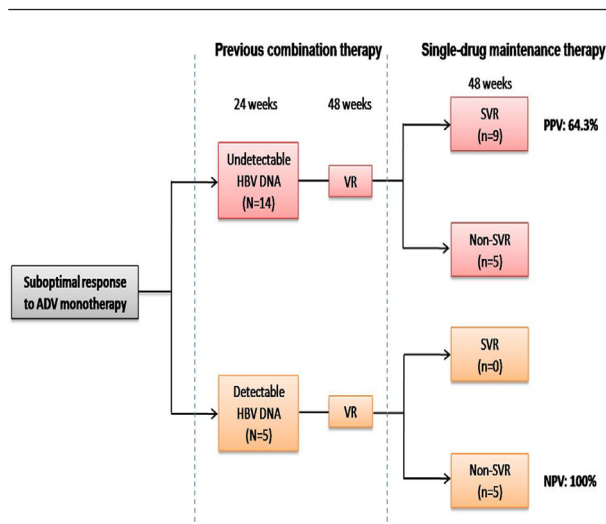


Figure 2. Sustained Viral Response (SVR) Distributions at week 48 in Group B According to Serum Viral Level at Week 24 of Previous Combination Therapy

According to new AASLD and EASL guidelines for management of CHB (23, 24), less potent antiviral agents such as LAM and ADV have not recommended for monotherapy of patients with CHB in many countries. However, because of limitations on health insurance systems, costs, or availability of drugs, LAM and ADV are still widely used in developing countries (25, 26). In China, it is estimated that more than 50% of patients with CHB are receiving LAM or ADV monotherapy. Thus combination therapy in optimized suboptimal responses to ADV monotherapy or rescuing treatment failure to LAM monotherapy would be common for a long period of time in future. Due to the lack of data on combination therapy, the time and procedure in which the physician have to stop combination therapy is widely concerned (27). Theatrically, switching to single drug therapy is possible, because viral titer has already been suppressed in very low levels, and this potential therapeutic strategy is supported by previous studies, showing that less potent antiviral agents also could effectively control virus replication in patients with low viral loads (28-30). However, in present study, sustained response rates (including viral and biochemical response rates) in patients who switched to single-drug maintenance therapy were significantly lower than patients who continued combination therapy. These findings suggest that only long-term combination therapy could ensure sustained efficacy in patients with CHB; in contrast, switching to single-drug maintenance therapy would result to high risk of viral relapse.

In this 'real-world' cohort, genotypic resistance mutations were not detected immediately after the emergence of viral rebound, hence all patients chose to continued current treatment during 3-month careful observation. After retrospective analysis of frozen serum samples that had been previously collected, we found that 3 patients in

group B with single-drug maintenance therapy had NAS-resistance, and resistance rate was 15.8% at month 12 after changing to single-drug maintenance therapy. Thus, prematurely switching to single-drug maintenance therapy would not only result to viral relapse and resistance, but also can lead to the loss of achieved clinical benefits and risk of disease progressions.

Some studies reported the efficacy of antiviral therapy was different in patients with positive HBeAg and negative HBeAg (31, 32). Due to the small sample size, subgroup analysis of sustained efficacy based on HBeAg statue was not carried out in both groups. However, univariate analysis in present study showed that HBeAg positivity prior to combination therapy (LAM+ADV or LDT+ADV in optimizing ADV suboptimal response) was a significantly high risk factor of viral relapse in patients, who switched to single-drug maintenance therapy in this study.

In previous studies, lower baseline viral load and early viral response had been shown to be a good predictor of long-term sustained viral response and drug resistance (29, 33). In this study, we found that serum HBV DNA level at month 6 of past combination therapy were associated with probability of SVR in patients who switched to monotherapy. Of patients switched to single-drug maintenance therapy, detectable serum viral level at month 6 of past combination therapy before this study had a negative predictive value of 100% for SVR at month 12. This finding suggested that detectable serum viral level at month 6 after starting combination therapy was associated with an extremely lower probability of SVR after switching to single-drug maintenance therapy.

In this study, the majority of patients were well tolerated, and discontinuation due to adverse events was not observed. The overall safety profile of either combination therapy or single-drug maintenance therapy in CHB patients was similar to those reported in other studies (4, 32, 34).

Limitations of this prospective study are the small sample size and a potential bias in treatment assignment due to the study design, and clinical trials with large sample size and low risk of bias are needed to confirm our findings. However, statistical analysis showed that demographical and laboratory characteristics between two groups were comparable, which reduced the bias of treatment assignment in a certain extent.

In conclusion, prolonged combination therapy was effective to maintain sustained viral responses in a 'real-world' setting.

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Authors' Contribution

All the authors contributed to all parts of the research process; including the conduction and collection of clini-

cal and laboratory data. En-Qiang Chen and Hong Tang wrote the final version of the manuscript. All authors have seen and approved the final draft of the paper.

Financial Disclosure

There is no conflict of interest.

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References

- Williams R. Global challenges in liver disease. *Hepatology*. 2006;**44**(3):521-6.
- André F. Hepatitis B epidemiology in Asia, the Middle East and Africa. *Vaccine*. 2000;**18**, Supplement 1():S20-S22.
- Zidan A, Scheuerlein H, Schüle S, Settmacher U, Rauchfuss F. Epidemiological Pattern of Hepatitis B and Hepatitis C as Etiological Agents for Hepatocellular Carcinoma in Iran and Worldwide. *Hepat Mon*. 2012;**12**(10 HCC).
- Mahabadi M, Norouzi M, Alavian SM, Samimirad K, Azad TM, Saberfar E, et al. Drug-Related Mutational Patterns in Hepatitis B Virus (HBV) Reverse Transcriptase Proteins From Iranian Treatment-Naïve Chronic HBV Patients. *Hepat Mon*. 2013;**13**(1).
- Liang X, Bi S, Yang W, Wang L, Cui G, Cui F, et al. Epidemiological serosurvey of hepatitis B in China—declining HBV prevalence due to hepatitis B vaccination. *Vaccine*. 2009;**27**(47):6550-7.
- Zhou JY, Zhang L, Li L, Gu GY, Zhou YH, Chen JH. High hepatitis B virus load is associated with hepatocellular carcinomas development in Chinese chronic hepatitis B patients: a case control study. *Viral J*. 2012;**9**:16.
- Yuen MF, Seto WK, Chow DH, Tsui K, Wong DK, Ngai VW, et al. Long-term lamivudine therapy reduces the risk of long-term complications of chronic hepatitis B infection even in patients without advanced disease. *Antivir Ther*. 2007;**12**(8):1295-303.
- Paik YH, Han KH, Hong SP, Lee HW, Lee KS, Kim SO, et al. The clinical impact of early detection of the YMDD mutant on the outcomes of long-term lamivudine therapy in patients with chronic hepatitis B. *Antivir Ther*. 2006;**11**(4):447-55.
- Vigano M, Lampertico P. Antiviral drugs for HBV liver disease. *Expert Opin Biol Ther*. 2011;**11**(3):285-300.
- Kim SR, Yang J, Kudo M, Hino O. Recent advances in the management of chronic hepatitis B. *Hepat Mon*. 2011;**11**(8):601-11.
- Chen EQ, Wang LC, Lei J, Xu L, Tang H. Meta-analysis: adefovir dipivoxil in combination with lamivudine in patients with lamivudine-resistant hepatitis B virus. *Viral J*. 2009;**6**:163.
- Wang LC, Chen EQ, Cao J, Liu L, Wang JR, Lei BJ, et al. Combination of Lamivudine and adefovir therapy in HBeAg-positive chronic hepatitis B patients with poor response to adefovir monotherapy. *J Viral Hepat*. 2010;**17**(3):178-84.
- Vassiliadis TG, Giouleme O, Koumerkeridis G, Koumaras H, Tziomalos K, Patsiaoura K, et al. Adefovir plus lamivudine are more effective than adefovir alone in lamivudine-resistant HBeAg-chronic hepatitis B patients: a 4-year study. *J Gastroenterol Hepatol*. 2010;**25**(1):54-60.
- Rapti I, Dimou E, Mitsoula P, Hadziyannis SJ. Adding-on versus switching-to adefovir therapy in lamivudine-resistant HBeAg-negative chronic hepatitis B. *Hepatology*. 2007;**45**(2):307-13.
- Terrault NA. Benefits and risks of combination therapy for hepatitis B. *Hepatology*. 2009;**49**(5 Suppl):S122-8.
- Liu F, Wang L, Li XY, Liu YD, Wang JB, Zhang ZH, et al. Poor durability of lamivudine effectiveness despite stringent cessation criteria: a prospective clinical study in hepatitis B e antigen-negative chronic hepatitis B patients. *J Gastroenterol Hepatol*. 2011;**26**(3):456-60.
- Liang Y, Jiang J, Su M, Liu Z, Guo W, Huang X, et al. Predictors of relapse in chronic hepatitis B after discontinuation of anti-viral therapy. *Aliment Pharmacol Ther*. 2011;**34**(3):344-52.
- Reijnders JG, Perquin MJ, Zhang N, Hansen BE, Janssen HL. Nucleos(t)ide analogues only induce temporary hepatitis B e antigen seroconversion in most patients with chronic hepatitis B. *Gastroenterology*. 2010;**139**(2):491-8.
- Lacey LF, Gane E. The cost-effectiveness of long-term antiviral therapy in the management of HBeAg-positive and HBeAg-negative chronic hepatitis B in Singapore. *J Viral Hepat*. 2007;**14**(11):751-66.
- Lacey L, Chien RN, Chuang WL, Pwu RF. Economic evaluation of chronic hepatitis B treatments in Taiwan. *J Gastroenterol Hepatol*. 2008;**23**(4):571-9.
- Chen EQ, Zhou TY, Bai L, Wang JR, Yan LB, Liang LB, et al. Lamivudine plus adefovir or telbivudine plus adefovir for chronic hepatitis B patients with suboptimal response to adefovir. *Antivir Ther*. 2012;**17**(6):973-9.
- European Association For The Study Of The Liver. EASL Clinical Practice Guidelines: management of chronic hepatitis B. *J Hepatol*. 2009;**50**(2):227-42.
- Nwokediuko SC. Chronic hepatitis B: management challenges in resource-poor countries. *Hepat Mon*. 2011;**11**(10):786-93.
- Abbas Z, Siddiqui AR. Management of hepatitis B in developing countries. *World J Hepatol*. 2011;**3**(12):292-9.
- Segovia MC, Chacra W, Gordon SC. Adefovir dipivoxil in chronic hepatitis B: history and current uses. *Expert Opin Pharmacother*. 2012;**13**(2):245-54.
- Chen EQ, Zhou TY, Liu L, Liu C, Lei M, Tang H. A comparison of treatment with adefovir and entecavir for chronic hepatitis B in China: The 2-year results of a prospective study: Adefovir versus Entecavir for Chronic Hepatitis B. *Hepat Mon*. 2011;**11**(1):27-31.
- Shin SR, Koh KC, Gwak GY, Choi MS, Lee JH, Paik SW, et al. A low viral load predicts a higher initial virologic response to adefovir in patients with Lamivudine-resistant chronic hepatitis B. *Gut Liver*. 2010;**4**(4):530-6.
- Lee JM, Park JY, Kim do Y, Nguyen T, Hong SP, Kim SO, et al. Long-term adefovir dipivoxil monotherapy for up to 5 years in lamivudine-resistant chronic hepatitis B. *Antivir Ther*. 2010;**15**(2):235-41.
- Marcellin P, Heathcote EJ, Buti M, Gane E, de Man RA, Krastev Z, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. *N Engl J Med*. 2008;**359**(23):2442-55.
- Hou J, Yin YK, Xu D, Tan D, Niu J, Zhou X, et al. Telbivudine versus lamivudine in Chinese patients with chronic hepatitis B: Results at 1 year of a randomized, double-blind trial. *Hepatology*. 2008;**47**(2):447-54.
- Manolakopoulos S, Striki A, Deutsch M, Mela M, Ketikoglou I, Tzourmakliotis D, et al. Long-term adefovir plus lamivudine therapy does not decrease creatinine clearance in HBeAg-negative chronic hepatitis B patients. *Liver Int*. 2011;**31**(10):1525-32.
- Lam YF, Yuen MF, Seto WK, Lai CL. Current Antiviral Therapy of Chronic Hepatitis B: Efficacy and Safety. *Curr Hepat Rep*. 2011;**10**(4):235-243.
- Nguyen MH, Keeffe EB. Chronic hepatitis B: early viral suppression and long-term outcomes of therapy with oral nucleos(t)ides. *J Viral Hepat*. 2009;**16**(3):149-55.
- Sacchetto MSLds, Barros SSLV, Araripe Tda, Silva AM, Faustino SKM, Silva JMNd. Hepatitis B: Knowledge, Vaccine Situation and Seroconversion of Dentistry Students of a Public University. *Hepat Mon*. 2013;**13**(10).