ORIGINAL RESEARCH PAPER
Volume - 12 | Issue - 11 | November - 2023 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

MORE POTENT HBV DNA SUPPRESSION DOES NOT RESULT IN A HIGHER SUPPRESSION OF HEPATITIS B e ANTIGEN LEVEL

Gastroenterology

Chee K HUI* MD, Peter MacCallum Cancer Centre, Melbourne, Australia., Royal Melbourne Hospital, Melbourne, Australia., Department of Gastroenterology, Center for Digestive Diseases, Kuala Lumpur, Wilayah Persekutuan, Malaysia. *Corresponding Author

Sophie CL HUI Department of Gastroenterology, Center for Digestive Diseases, Kuala Lumpur, Wilayah Persekutuan, Malaysia.

Kit HUI Department of Gastroenterology, Center for Digestive Diseases, Kuala Lumpur, Wilayah Persekutuan, Malaysia.

ABSTRACT

Background: Despite more potent anti-hepatitis B virus (HBV) activity of newer agents, there appears to be a "ceiling" effect with regards to hepatitis B e antigen (HBeAg) seroconversion in HBeAg-positive chronic HBV patients after 48-weeks of therapy. ***Aim:*** This study aims to determine the effect of viral suppression on HBeAg suppression. ***Methods:*** One-hundred-and-seventy-one consecutive HBeAg-positive patients treated with adefovir (n=59), entecavir (n=58) or lamivudine (n=54) for 48 weeks (end-of-follow-up) without drug resistance were included into this study. HBeAg was retrospectively quantified with a microparticle enzyme-immunoassay. ***Results:*** The entecavir group had the lowest HBV DNA at end-of-follow-up [mean±standard error of mean (SEM) 2.18±0.16 log IU/ml] followed by the lamivudine group (mean±SEM 3.74±0.22 log IU/ml) and the adefovir group (mean±SEM 5.16±0.25 log IU/ml, p<0.001). However, there was no significant difference in the end-of-follow-up HBeAg level in the entecavir group (mean±SEM 2.13±1.31 log PEIU/ml) when compared with the lamivudine (mean±SEM 2.40±1.76 log PEIU/ml) and the adefovir groups (mean±SEM 2.17±1.63 log PEIU/ml), (p=0.10). HBeAg level below the lower-limit-of-detection at end-of-follow-up was not higher in the entecavir group when compared with the adefovir group [26/58 (44.8%) vs. 25/59 (42.4%), p=0.79] ***Conclusion:*** Potent HBV DNA suppression during therapy does not result in higher HBeAg suppression.

KEYWORDS

HBeAg quantification; entecavir, adefovir, lamivudine, HBeAg seroconversion; potent HBV DNA suppression.

INTRODUCTION

An estimated 350 million people worldwide are chronically infected with the hepatitis B virus (HBV).[1] Chronic HBV infected people are at an increased risk of developing cirrhosis, hepatic decompensation and hepatocellular carcinoma (HCC) with 500,000 people dying annually from HBV related complications.[2] The goal of therapy in patients with chronic HBV is the prevention of liver cirrhosis and its complications.

However, unlike the therapy of chronic hepatitis C virus (HCV), total eradication of chronic HBV remains elusive.[3,4,5] The aims of therapy in hepatitis B e antigen (HBeAg) positive chronic HBV patients are to achieve sustained suppression of HBV replication and remission of liver disease.[6] The parameters used to assess treatment response in HBeAg positive chronic HBV include normalization of serum alanine aminotransaminase (ALT), decrease in serum HBV DNA level, HBeAg with or without detection of hepatitis B e antibody (HBeAb) and improvement in liver histology.[6]

HBeAg seroconversion and suppression of HBV DNA has been associated with reduction in HBV viremia, improving long-term clinical outcome of chronic HBV patients who are HBeAg positive.[6,7] This is because the disappearance of HBeAg from serum is associated with the disappearance of replicative viral intermediates in liver tissues.[8,9] Furthermore, seroconversion from HBeAg to HBeAb usually occurs after suppression of HBV DNA. Therefore, HBeAg seroconversion is considered to be one of the most important surrogate markers for assessing the durability and efficacy of antiviral therapy in chronic hepatitis B patients with HBeAg positive disease.

Currently, there are 2 major types of antiviral drugs that are being used for the treatment of chronic HBV: drugs that directly interfere with HBV replication and drugs that modulate HBV specific immune response.[6] Since the advent of newer more potent anti-viral drugs, many studies have been performed to determine whether these more potent anti-virals can improve treatment response in HBeAg positive chronic hepatitis B.

The potential advantages of potent viral suppression, in addition to virologic response are delayed or decreased anti-viral resistance, increased HBeAg seroconversion and sustained off therapy response. However, although the newer anti-viral drugs have more potent anti-viral effects, they have consistently failed to demonstrate consistent benefit in HBeAg seroconversion or sustained off therapy response.[10-14] The reason for this is uncertain.

Although, several small studies on conventional interferon have demonstrated that dynamic monitoring of quantitative HBeAg may predict the likelihood of subsequent HBeAg seroconversion and virologic response.[15-17] the effect of potent suppression of HBV replication by anti-viral therapy on HBeAg is uncertain. The aim of this study is to determine whether more potent HBV DNA suppression with anti-HBV therapy can result in more potent HBeAg suppression.

METHODS

Study Population

One hundred and seventy-one consecutive HBeAg positive patients without drug resistance at 48 weeks of antiviral treatment from the Centre for Digestive Diseases were included into this study. They were treated with either adefovir daily (n=59), entecavir daily (n=58) or lamivudine daily (n=54) for 48 weeks (end of follow-up) from January 2005 to August 2015.

All subjects included into this study fulfilled the following criteria: 1) HBsAg positive for at least 6 months before commencement of therapy; 2) HBeAg positive for at least 6 months before commencement of therapy; 3) treatment naïve; 4) serum ALT levels above the upper limit of normal (normal range of serum ALT was 7-53 U/L for males and 7-33 U/L for females, respectively) for the preceding 12 months before commencement of therapy; 5) more than 18 years of age; 6) alcohol intensity of less than 10 gm/day as defined previously;[18] and 7) no evidence of lamivudine, entecavir or adefovir resistance at end of follow-up. Subjects were excluded from the study if they had: 1) previous therapy with nucleoside/nucleotide analogue or immunomodulators; 2) co-infection with hepatitis C virus (HCV), human immunodeficiency virus (HIV) or hepatitis D virus; or 3) hepatocellular carcinoma.

Quantification of HBeAg

Quantification of HBeAg was performed retrospectively on frozen sera by using ARCHITECT i2000SR analyser (Abbott Laboratories, North Chicago, IL, USA) as previously described.[19] The assay was validated in-house with the use of reference standards obtained from the Paul Ehrlich Institute (PEIU/ml). The dynamic range of the assay was 0.11-200 PEIU/ml, with samples of concentrations beyond this range being diluted with fetal calf serum to ensure linearity. A linear correlation was observed with the reference standards.

Virological Studies

HBsAg, HBeAg, HBeAb [Abbott Laboratories, North Chicago, Ill,

USA] and anti-HCV (Ortho Diagnostics System, Raritan, New Jersey, USA) were assayed with the second-generation enzyme-linked immunosorbent assay. HBV genotype was retrospectively determined using the INNO-LiPA HBV genotyping assay (Fujirebio, Gent, Belgium). Lamivudine, adefovir and entecavir resistance was retrospectively tested according with the INNO-LiPA HBV Multi-DR kit (Fujirebio, Gent, Belgium).[20,21]

Follow-Up Visits

All patients underwent a physical examination and blood testing for liver biochemistry [ALT, aspartate aminotransaminase, alkaline phosphatase, gamma-glutamyl transpeptidase, albumin and bilirubin], complete blood count, prothrombin time, activated partial thromboplastin time and renal biochemistry before commencement of therapy. All patients were followed-up every 4-8 weekly until week 48 (end of follow-up). Liver biochemistry, complete blood count, thyroid function test, HBsAg, HBeAg and HBeAb were checked at each follow-up. Serum HBV DNA was quantified with the Abbott real time HBV assay (Abbott Laboratories, North Chicago, Ill, USA) with a linear range of 10-10^{9} IU/ml.

Definition Of Endpoint

HBeAg seroconversion was defined as loss of HBeAg accompanied by the development of HBeAb for 2 consecutive readings three months apart.

This retrospective study was approved by the local Institutional Review Board.

Statistical Analysis

All statistical analyses were performed using the SPSS software (IBM SPSS Statistics for Windows, Version 20.0, IBM Corp, Armonk, New York, USA). The chi-square test was used to analyse relationships between categorical variables. The ANOVA test was used to compare values between different groups, and the Student's *t* test was used to analyze single specific differences of biological interest. Continuous variables were expressed in mean standard error of mean (SEM). The primary endpoint of this study was to determine suppression of HBeAg. All statistical analyses were performed on an intention-to-treat basis. Statistical significance was defined as p<0.05 (2 tailed).

RESULTS

The baseline demographic data for the 3 groups of patients are shown in Table 1.

Table 1. Baseline Characteristics Of Patients.

	ADV (n=59)	ETV (n=58)	LAM (n=54)	P-value
Age, years	443	426	432	0.75
Sex, M:F	42:17	50:8	41:13	0.14
Serum alanine aminotransaminase, U/L	140±11	141±13	139±9	0.60
HBV DNA, log IU/ml	8.10±0.35	8.18±0.91	7.85±0.42	0.23
HBeAg, log PEIU/ml	3.05±2.23	3.00±2.23	3.04±2.35	0.88
Genotype:				0.12
B	29	19	18	
C	30	39	36	
HBeAg:				-
Positive	59	58	54	
Negative	0	0	0	
HBeAb:				-
Positive	0	0	0	
Negative	59	58	54	

ADV- adefovir, ETV- entecavir, LAM- lamivudine, HBeAg- hepatitis B e antigen, HBeAb- hepatitis B e antibody.
P-value by ANOVA.

Entecavir Therapy Resulted In Highest On-therapy Reduction In Serum HBV DNA

Serum HBV DNA in all 3 groups fell throughout the 48 weeks of therapy [Figure 1A]. A significant drop in serum HBV DNA among the 3 groups could be detected at week 4 of therapy (P<0.001 by ANOVA) [Figure 1A]. This significant drop in serum HBV DNA in the three groups persisted until week 48 of therapy or the end of follow-up. The entecavir group had the lowest serum HBV DNA at the end of follow-up (mean ± SEM 2.18 ± 0.16 log IU/ml) followed by the lamivudine group (mean ± SEM 3.74 ± 0.22 log IU/ml) and the adefovir group (mean ± SEM 5.16 ± 0.25 log IU/ml, p<0.001 by ANOVA) [Figure 1A].

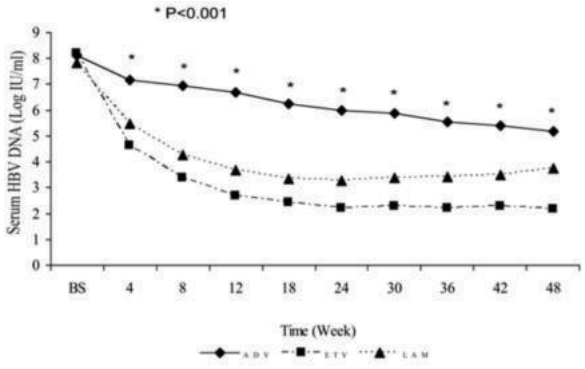

Figure 1A

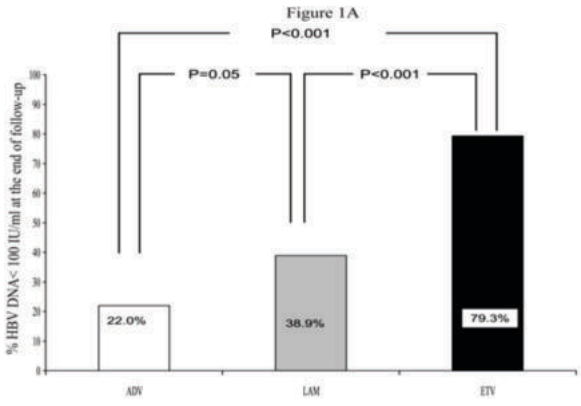

Figure 1B

Figure 1. Graph showing (A) reduction of serum HBV DNA during therapy and at the end of follow-up and (B) HBV DNA below 100 IU/ml at the end of follow-up.

At the end of follow-up, serum HBV DNA was also lower in the lamivudine group when compared with patients in adefovir group at the end of follow-up (mean ± SEM 3.42 ± 0.22 vs. 5.16 ± 0.25 log IU/ml, p=0.02 by Student's *t* test)

At the end of follow-up, 80 of the 171 patients (46.8%) had serum HBV DNA less than 100 IU/ml. The entecavir group [46/58 (79.3%)] had the highest number of patients with serum HBV DNA less than 100 IU/ml at the end of follow-up when compared with the lamivudine group [21/54 (38.9%), p<0.001] or the adefovir group [13/59 (22.0%), p<0.001] [Figure 1B]. There was a trend that the lamivudine group also had a higher number of patients with serum HBV DNA less than 100 IU/ml at the end of follow-up when compared with the adefovir group (p=0.05) [Figure 1B].

Highest On-Therapy Reduction in Serum HBV DNA with Entecavir Therapy Did Not Result in Higher Suppression of HBeAg Level

Serum HBeAg level in all three groups also decreased during the 48 weeks of therapy [Figure 2A]. However, unlike serum HBV DNA level, there was no significant decrease in serum HBeAg level among the three groups at each time point of follow-up (all p>0.05 by ANOVA) [Figure 2A].

At the end of follow-up, the serum HBeAg level was lowest in the entecavir group (mean ± SEM 2.13 ± 1.31 log PEIU/ml) followed by the adefovir group (mean ± SEM 2.17 ± 1.63 log PEIU/ml) and the lamivudine group (mean ± SEM 2.40 ± 1.76 log PEIU/ml). However, there was no significant difference in the serum HBeAg level among the three groups at week 48 of therapy or end of follow-up (p=0.10 by ANOVA).

The serum HBeAg level was lower in the entecavir group at the end of follow-up when compared with the lamivudine group (p=0.02 by Student's *t* test). The serum HBeAg level was also lower in the adefovir

group when compared with the lamivudine group (p=0.03 by Student's *t* test) at the end of follow-up. However, there was no difference in the serum HBeAg level in the adefovir group when compared with the entecavir group (p=0.83 by Student's *t* test).

Sixty-four of the 171 patients had serum HBeAg level below the lower limit of detection (<0.11 PEIU/ml) at the end of follow-up. The entecavir group had a higher number of patients with serum HBeAg level below the lower limit of detection at the end of follow-up when compared with the lamivudine group [26 of the 58 patients (44.8%) vs. 13 of the 54 patients (24.1%) respectively, p=0.02] [Figure 2B]. The adefovir group also had a higher number of patients with serum HBeAg level below the lower limit of detection at the end of follow-up when compared with the lamivudine group [25 of the 59 patients (42.4%) vs. 13 of the 54 patients (24.1%) respectively, p=0.04] [Figure 2B].

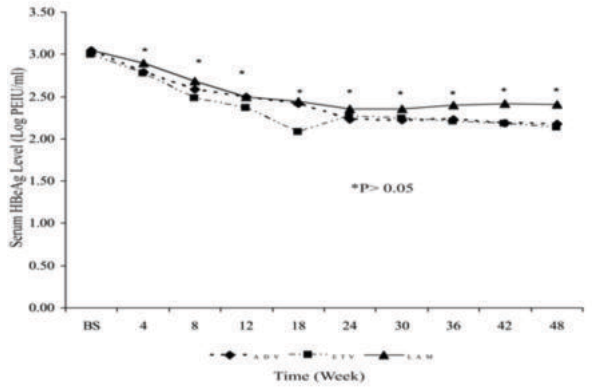

Figure 2A

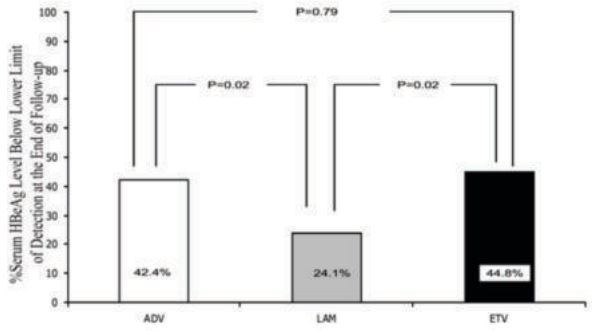

Figure 2B

Figure 2. Graph showing (A) reduction of serum HBeAg during therapy and at the end of follow-up and (B) HBeAg below the lower limit of detection at the end of follow-up.

However, the suppression of serum HBeAg level below the lower limit of detection was not higher in the entecavir group when compared with the adefovir group [26/58 (44.8%) vs. 25/59 (42.4%), p=0.79] [Figure 2B].

DISCUSSION

Indications for treatment HBeAg positive chronic hepatitis B are well established and rely on a combination of raised ALT or raised HBV DNA.[2,6,22] Six nucleoside/nucleotide analogues; lamivudine, adefovir dipivoxil, tenofovir disproxil, tenofovir alafenamide, entecavir and telbivudine; has been approved for the treatment of chronic HBV infection.

The differences among nucleoside/nucleotide analogues are mostly in terms of potency in viral suppression and development of resistance. However, in general, there appears to be a "ceiling" effect in the 48 week efficacy of nucleoside/nucleotide analogues with regards to the rate of HBeAg seroconversion. Despite more potent antiviral suppression with the newer agents like entecavir or tenofovir, 48 weeks of therapy with these more potent nucleoside/nucleotide analogues have shown no differences in the rate of HBeAg seroconversion rates when compared with lamivudine.[23] Similarly, more potent viral suppression demonstrated by pegylated interferon alfa-2a plus lamivudine combination therapy also did result in higher HBeAg seroconversion rate when compared with pegylated interferon alfa-2a monotherapy.[12]

In this study, we explored the effect of viral suppression on serum HBeAg level. Here, we demonstrated that despite a more profound viral suppression by both entecavir and lamivudine therapy over adefovir therapy, this more potent viral suppression did not result in a higher suppression of HBeAg level. In fact, despite a more potent on-therapy viral suppression in lamivudine group when compared with the adefovir group, adefovir therapy had a lower serum HBeAg level at 48 weeks of therapy or at the end of follow-up. Furthermore, adefovir also resulted in more patients with serum HBeAg level below the lower limit of detection when compared with those on lamivudine therapy.

Similarly, the more potent antiviral effect by entecavir also did not increase the suppression of HBeAg level when compared with adefovir therapy. This may mean that in order to increase the efficacy of HBeAg seroconversion or sustained virological response, one may need to combine drugs that can result in a synergistic suppression of serum HBeAg level. This is because Perrillo et. al. showed that the serum HBeAg level at the end of follow-up is more strongly correlated with resultant sustained virological response when compared with serum HBV DNA level at either the end of therapy or end of follow-up.[17]

Therefore, more potent antiviral suppression with the newer generation nucleoside/nucleotide analogues does not increase the rate of HBeAg seroconversion because simply enhancing viral suppression alone is inadequate in increasing the level of serum HBeAg suppression. We, hypothesise that the way by which viral suppression is achieved, in addition to potent viral suppression, is also an important factor required to achieve a higher reduction of serum HBeAg level. This hypothesis is given further credence by the observation that adefovir therapy resulted in a higher reduction in serum HBeAg level when compared with those on lamivudine therapy despite its weakest effect on viral suppression.

The limited effect of lamivudine monotherapy on reduction in serum HBeAg level may help to explain why current 48 weeks therapy with nucleoside/nucleotide analogues rarely results in seroconversion of HBsAg and the observation that following treatment with lamivudine, HBV-specific T cells responses increase significantly only in a subset of patients and may be transient.[12,13,24,25] It is unclear how lamivudine induces HBV-specific T cell activity. One possibility is that the reduction in HBV viral antigen reduces HBV-induced "anergy". However, it has been previously shown that sustained permanent HBeAg clearance does not occur despite the rapid reduction to undetectable serum HBV DNA during the combination conventional interferon-alfa and lamivudine treatment.[26] This is probably explained by the relative lack of impact of lamivudine on suppressing serum HBeAg level as shown here. And HBeAg is considered a rather "crude" immune marker of chronic hepatitis B infection as HBeAg (which is not required for viral infection, replication and assembly) is rapidly secreted into the blood and has been shown to tolerize T cells in transgenic mice.[27]

The durability of response also differs between those treated with nucleoside/nucleotide analogues and interferon-alfa based therapy, with the latter being more durable.[12,13,28] Furthermore, for those who had achieved HBeAg seroconversion to HBeAb with the lamivudine, the response is durable in only 30~80% of cases as lamivudine results in a higher rebound of serum HBeAg level at the end of follow-up.[29,30] This lack of durability of response may be related to a higher rebound in serum HBeAg level at the end of follow-up with the use of nucleoside/nucleotide analogue therapy alone.

In conclusion, potent viral suppression alone does not increase the level of HBeAg suppression. This may be the reason why treatment with more potent viral agents failed to increase the rate of HBeAg seroconversion at 48 weeks of therapy. The method by which viral suppression is achieved may also an important factor in achieving a better HBeAg suppression, and, a higher rate of HBeAg seroconversion. Development of future monotherapy or combination anti-HBV therapy should also take into consideration the effect of the agent or agents on suppression of serum HBeAg level, in addition to HBV DNA suppression.

Abbreviations:

HBeAg- hepatitis B e antigen; HBeAb- hepatitis B e antibody; HBsAg- hepatitis B surface antigen; HBV- hepatitis B virus; ALT- alanine aminotransaminase; HCC- hepatocellular carcinoma.

Authors Contributions:
Chee K Hui and Kit Hui designed the study, interpreted the data, wrote the manuscript and guarantee the accuracy of data. Sophie CL Hui collected and analysed the data. All authors have approved the final version of the manuscript and the paper has not been published elsewhere.

Conflicts Of Interest: Nil.

Funding: Nil.

REFERENCES

1. Lee WM. Hepatitis B infection. N Eng J Med 1997; 337: 1733-1745.
2. EASL Clinical Practice Guidelines: Management of chronic hepatitis B. J Hepatol 2009; 50: 227-242.
3. Hui CK, Monto A, Belaye T, Lau E, Wright TL. Outcomes of interferon-α and ribavirin treatment for chronic hepatitis C patients with normal serum aminotransaminases. Gut 2003; 52: 1644-1648.
4. Falade-Nwulia O, Suarez-Cuervo C, Nelson DR, Fried MW, Segal JB, Sulkowski MS. Oral Direct-Acting Agent Therapy for Hepatitis C Virus Infection: A Systematic Review. Ann Intern Med. 2017; 166: 637-648.
5. Simmons B, Saleem J, Hill A, Riley RD, Cooke GS. Risk of late relapse or reinfection with hepatitis C virus after achieving a sustained virological response: a systematic review and meta-analysis. Clin Infect Dis 2016; 62: 683-694.
6. Tang LSY, Covert E, Wilson E, Kottilil S. Chronic Hepatitis B Infection: A Review. JAMA 2018; 319: 1802-1813.
7. Yang HI, Lu SN, Liaw YF, You SL, Sun CA, Wang LY, et. al. Hepatitis B e antigen and the risk of hepatocellular carcinoma. N Eng J Med 2002; 347: 168-174.
8. Liu LZ, Sun J, Hou J, Chan HLY. Improvements in the management of chronic hepatitis B virus infection. Expert Rev Gastroenterol Hepatol 2018; 12: 1153-1166.
9. Di Bisceglie AM, Waggoner JG, Hoofnagle JH. Hepatitis B virus deoxyribonucleic acid in liver of chronic carriers. Correlation with serum markers and changes associated with loss of hepatitis B e antigen after antiviral therapy. Gastroenterology 1987; 93: 1236-1241.
10. Lau GK, Cooksley H, Ribeiro RM, Powers KA, Shudo M, Bowden S, et. al. Impact of early viral kinetics on T-cell reactivity during antiviral therapy in chronic hepatitis B. Antivir Ther 2007; 12: 705-718.
11. Lau GK, Piratvisuth T, Luo KX, Marcellin P, Thongsawat S, Cooksley G, et al. Peginterferon Alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. N Engl J Med 2005; 352:2682-95.
12. Marcellin P, Lau GK, Bonino F, Farci P, Hadziyannis S, Jin R, et al. Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. N Engl J Med 2004: 351:1206-17.
13. Janssen HL, van Zonneveld M, Senturk H, Zeuzem S, Akarca US, Cakaloglu Y, et. al. Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomized trial. Lancet 2005; 365: 123-129.
14. Lai CL, Gane E, Liaw YF, Hsu CW, Thongsawat S, Wang Y, et. al. Telbivudine versus lamivudine in patients with chronic hepatitis B. N Eng J Med 2007; 357: 2576-2588.
15. Hayashi PH, Beames MP, Kuhns MC, Hoofnagle JH, Di Bisceglie AM. Use of quantitative assays for hepatitis B e antigen and IgM antibody to hepatitis B core antigen to monitor therapy in chronic hepatitis B. Am J Gastroenterol 1996; 91: 2323-2328.
16. Heijtink RA, Janssen HL, Hop WC, Osterhaus AD, Schalm SW. Interferon-alpha therapy in chronic hepatitis B: early monitoring of hepatitis B e antigen may help to decide whether to stop or prolong therapy. J Viral Hepat 2000; 7: 382-386.
17. Perrillo R, Mimms L, Schechtman K, Robbins D, Campbell C. Monitoring of antiviral therapy with quantitative evaluation of HBeAg: a comparison with HBV DNA testing. Hepatology 1993; 18: 1306-1312.
18. Monto A, Alonzo J, Watson JJ, Grunfeld C, Wright TL. Steatosis in chronic hepatitis C: relative contributions of obesity, diabetes mellitus, and alcohol. Hepatology 2002 Sep;36(3):729-36.
19. Zhou B, Liu M, Lv G, Zheng H, Wang Y, Hou J. Quantification of hepatitis B surface antigen and E antigen: correlation between Elecsys and Architect assays. J Viral Hepat 2013; 20: 422-429.
20. Chantratita W, Song KS, Pongthanapisith V, Thongbaiphet N, Angkanavin K, Nimse SB, et. al. HBV/4DR 9G test and its comparison with INNO-LiPA HBV multi-DR test for detection of drug-resistant Hepatitis B virus. J Virol Methods 2016; 237: 58-63.
21. Hui CK, Hui K. Switchover to tenofovir disoproxil in chronic HBV patients with primary treatment failure to entecavir. Gastroint Hepatol Dig Dis 2023; 6: 1-4.
22. Furquim d'Almeida A, Ho E, Van Hees S, Vanwolleghem T. Clinical management of chronic hepatitis B: A concise overview. United European Gastroenterol J 2022; 10: 115-123.
23. Chang TT, Gish RG, de Man R, Gadano A, Sollano J, Chao YC, et. al. A comparison of entecavir and lamivudine for HBeAg positive chronic hepatitis B. N Eng J Med 2006; 354: 1001-1010.
24. Boni C, Bertoletti A, Penna A, et. al. Lamivudine treatment can restore T cell responsiveness in chronic hepatitis B. J Clin Invest 1998; 102: 968-975.
25. Boni C, Penna A, Bertoletti A, Lamonaca V, Rapti I, Missale G, et. al. Transient restoration of anti-viral T cell responses induced by lamivudine therapy in chronic hepatitis B. J Hepatol 2003; 39: 595-605.
26. Marinos G, Naoumov NV, Williams R. Impact of complete inhibition of viral replication on the cellular immune response in chronic hepatitis B virus infection. Hepatology 1996; 24: 991-995.
27. Chen MT, Billaud JN, Sällberg M, Guidotti LG, Chisari FV, Jones J, et. al. A function of the hepatitis B virus precore protein is to regulate the immune response to the core antigen. Proc Natl Acad Sci 2004 101: 14913-14918.
28. van Nunen AB, Hansen BE, Suh DJ, Lohr HF, Chemello L, Fontaine H, et. al. Durability of HBeAg seroconversion following antiviral therapy for chronic hepatitis B: relation to type of therapy and pretreatment serum hepatitis B virus DNA and alanine aminotransferase. Gut 2003; 52: 420-424.
29. Song BC, Suh DJ, Lee HC, Chung YH, Lee YS. Hepatitis B e antigen seroconversion after lamivudine therapy is not durable in patients with chronic hepatitis B in Korea. Hepatology 2000; 32: 803-6.
30. Dienstag JL, Cianciara J, Karayalcin S, Kowdley KV, Willems B, Plisek S, et. al. Durability of serologic response after lamivudine treatment of chronic hepatitis B. Hepatology 2003; 37: 748-755.