Oral Antiviral Therapy for Chronic Hepatitis B Virus Infection: Is Continuous Treatment Needed?

Abstract

Potent nucleos(t)ide analogues (NAs) have improved patient prognosis via suppression of viral load, HBeAg seroconversion and in some cases, HBsAg seroconversion. However, the duration and end point of NA treatment are still debatable. Current international guidelines recommend that discontinuation of NA treatment can be considered when HBeAg seroconversion and undetectable HBV DNA status is maintained for at least 6-12 months for HBeAg-positive patients and undetectable HBV DNA status on 3 separate occasions 6 months apart for HBeAg-negative patients if they have been treated for at least 2 years. Durability of NA, particularly after off-treatment, remains uncertain. A proportion of patients who discontinue NA therapy after HBeAg seroconversion may require retreatment if sustained serological and/or virological response fails and high off-treatment virological relapse can develop in HBeAg-negative patients. Therefore, NA treatment may be continued until HBsAg clearance with or without antibodies to HBsAg, particularly in patients with severe fibrosis or cirrhosis.

Keywords

Seroconversion; Durability; Relapse

Abbreviations

NA: Nucleos(t)ide Analogue; HBV: Hepatitis B Virus; cccDNA: covalently closed circular DNA

Introduction

Long-term usage of oral antiviral is highly effective in treating chronic hepatitis B virus (HBV) infection and can effectively suppress HBV proliferation which may prevent the progression of liver fibrosis and the development of HCC after long term use of NAs but cannot completely eradicate the virus. Furthermore, the safety of long-term usage of antivirals is still a concern that needs to be assessed and the increasing cost of antiviral treatments can be a serious financial burden. It is still unclear how long antiviral treatment needs to be continued and how to determine when discontinuation of the treatment is appropriate. The presence of covalently closed circular DNA (cccDNA) in hepatocytes correlates to immune activity and is used as a predictive factor to evaluate sustained viral suppression after termination of antiviral treatment [1]. Unlike pegylated interferon, oral antivirals do not have direct immunomodulatory effects and only temporarily induce a modest increase in immune function. Therefore, oral antiviral treatments are unlikely to provide continued viral suppression after termination.

Discussion

HBeAg-positive chronic HBV infection

Patients that reach sustained viral suppression (HBV DNA negativity and HBeAg loss or seroconversion) with lamivudine usage show a virologic relapse rate of 15.9-48%, 29-50%, 54-55.7%, and 44-64.8% 1, 2, 3, and 4 years after discontinuation of lamivudine respectively [2-8]. A considerable number of patients that undergo HBeAg seroconversion upon oral antiviral treatment cannot maintain sustained viral suppression after stopping treatment [9]. However, when consolidation treatment [2,4,5,8] was performed before termination of lamivudine treatment or when patients were young [4-8], the rate of virologic relapse was dramatically reduced. In 178 patients with HBeAg-positive chronic HBV infection that showed HBV DNA loss as well as HBeAg loss with lamivudine treatment, virologic relapse rates of 15.9% and 30.2% 1 and 5 years after stopping treatment, respectively were seen. It has also been reported that when patients were younger than 40 or underwent 1 or more year(s) of consolidation treatment the durability of sustained viral suppression was increased [8]. Patients who used clevudine or entecavir (n=48) to maintain HBV DNA levels at less than 300 copies/mL and HBeAg seroconversion for 6 months or more, experienced an accumulated virologic relapse of 41% and 60% after 12 and 24 months off therapy respectively [10]. In this study, when patients were younger than 40 years or when consolidation treatment was carried out for 15 months or more the rate of relapse was particularly low. According to guidelines for patients with HBeAg-positive chronic HBV infection from various countries, one may consider termination of treatment after HBeAg seroconversion followed by 6-12 months or more of consolidation treatment [11-14]. However, if treatment is stopped after HBeAg seroconversion, as suggested by the guidelines, the rate of sustained viral suppression maintenance is low. Therefore, HBeAg seroconversion alone is insufficient as a determining factor for discontinuing antiviral treatments [9].

In a small-scale study, a patient on the 104th week of telbivudine treatment with less than 100 IU/mL serum HBsAg and those on the 24th and 52nd week of treatment that experienced rapid reduction in HBeAg levels had highly sustained viral suppression (HBV DNA <300 copies/mL, HBeAg seroconversion)
Oral Antiviral Therapy for Chronic Hepatitis B Virus Infection: Is Continuous Treatment Needed?

2 years after stopping telbivudine treatment [15]. This study suggests that the level of HBsAg may be an effective marker in determining when to terminate antiviral treatment.

HBeAg-negative chronic HBV infection

Patients with HBeAg-negative chronic HBV infection are required to undergo long-term treatment with oral antivirals. Few studies have looked at the suitable length of treatment and the results have largely been disappointing. With lamivudine treatment for 2 years and more strict criteria for termination of treatment, the virologic relapse rate was still higher than 50% after 12 months of termination [16-18]. Out of 145 patients taking adefovir who were HBV DNA-negative for more than 18 months by PCR, 95 patients (61.4%) underwent virologic relapse as observed by serum HBV DNA $>$2000 IU/mL. Ninety-three percent of all virologic relapse cases occur within 1 year of stopping treatment [19]. However, young patients (20-25 years old) showed a dramatically reduced rate of post-treatment virologic relapse [18,19]. When entecavir was administered to patients for 52 weeks and then stopped, sustained viral suppression was only observed in 48% of patients after 24 weeks [20]. Patients that were given various antivirals (25 patients given entecavir, 14 patients given lamivudine and 6 patients given adefovir) with 3 consecutive HBV DNA negative by PCR 6 months apart showed virologic relapse rates of 48.9% and 73.3% 6 months and 1 year after termination of treatment, respectively. Furthermore, the clinical relapse rate (HBV DNA $>$2000 IU/mL and ALT more than double the normal level) is reported to be 35.6% and 53.3% respectively [21]. Entecavir and tenofovir are known to have stronger effects on viral suppression with a relatively lower likelihood of developing drug resistance than lamivudine. However, it is believed that these drugs cannot increase sustained viral suppression upon discontinuation of treatment. Therefore, various countries state in their guidelines to continue administration of oral antivirals until HBsAg loss or HBsAg seroconversion is observed [11,12,14].

Since HBsAg loss occurs very rarely, patients with HBeAg-negative chronic HBV may need to take oral antivirals indefinitely. However, the Asian Pacific Association of the Study of Liver (APASL) suggests that if serum HBV DNA is not detected in patients for 3 or more times when tested at least every 6 months by PCR, the patients may stop taking oral antivirals [13]. However, a recent study followed 95 patients with HBeAg-negative chronic HBV infection who took entecavir with at least 3 consecutive HBV DNA negative 6 months apart by PCR, who terminated treatment as suggested by APASL guidelines. Within 12 months of stopping treatment, 55 patients (58%) showed virological relapse and 45% showed clinical relapse [22]. This suggests that the virological relapse rate is still high even when following APASL guidelines. In 53 HBeAg-negative chronic HBV patients who were treated with lamivudine for 12-76 months (average of 34 months) discontinued treatment and were followed for an average of 47 months (1-116 months) and 12 months after termination of treatment, 9 patients (17%) showed sustained viral suppression (HBV DNA $<$200 IU/mL). All 5 patients with HBsAg levels of less than 100 IU/mL or at least 1 log reduced from baseline upon stopping treatment showed sustained viral suppression 12 months after termination. However, sustained viral suppression could not be observed in any of the 40 patients who had HBsAg levels higher than 100 IU/mL and less than 1 log reduction from baseline [23]. Another study showed that higher sustained viral suppression was observed with HBsAg reduction during treatment and the level of HBsAg upon termination of treatment decreased [24]. Therefore, monitoring HBsAg levels may be effective for determining the appropriate time of antiviral treatment termination.

As the above studies show, the post-treatment relapse rate appears to be approximately 50%, regardless of the suppressive ability of antiviral treatment or the likelihood of drug resistance [16,18-20,22,24-26]. Therefore, it may be important to apply APASL guidelines for stopping antiviral treatments to patients who find long-term treatment financially burdensome or who are experiencing side effects associated with long-term usage of drugs or treatments.

Conclusion

HBeAg seroconversion is not typically maintained in patients with HBeAg-positive chronic HBV infection after discontinuation of treatment. Therefore, it cannot be applied to all patients uniformly as a standard for stopping treatment while excluding young patients that underwent more than 1 year of consolidation treatment and thus have a lower likelihood of relapse. Furthermore, many studies have shown that even with strong oral antiviral treatment followed by long-term consolidation treatment, a finite period of antiviral treatment is not suitable for most HBeAg-negative chronic HBV patients. Regardless of HBeAg loss, long-term antiviral treatment is needed for most patients with chronic HBV infection [27]. In particular, patients whose infection has progressed to cirrhosis are recommended to undergo long-term treatment as they can experience relapse of hepatitis and withdrawal hepatitis after stopping treatment which may lead to hepatic insufficiency or even death. The exact markers or criteria to determine when to effectively stop antiviral treatments are currently unknown. HBsAg levels show great potential as a biomarker for determining the timing of antiviral treatment termination.

References

1. Sung JJ, Wong ML, Bowden S, Liew CT, Hui AY, et al. (2005) Intrahepatic hepatitis B virus covalently closed circular DNA can be a predictor of sustained response to therapy. Gastroenterology 128(7): 1890-1897.
2. Song BC, Suh DJ, Lee HC, Chung YH, Lee YS (2000) Hepatitis B e antigen seroconversion after lamivudine therapy is not durable in patients with chronic hepatitis B in Korea. Hepatology 32(4 Pt 1): 803-806.
3. van Nunen AB, Hansen BE, Suh DJ, Lohr HF, Chemello L, et al. (2003) 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 52(3): 420-424.
4. Yoon SK, Jang JW, Kim CW, Bae SH, Choi JY, et al. (2005) Long-term results of lamivudine monotherapy in Korean patients with HBeAg-positive chronic hepatitis B: response and relapse rates, and factors
related to durability of HBeAg seroconversion. Intervirology 48(6): 341-349.

5. Chien RN, Yeh CT, Tsai SL, Chu CM, Liaw YF (2003) Determinants for sustained HBeAg response to lamivudine therapy. Hepatology 38(5): 1267-1273.

6. Lee HC, Suh DJ, Ryu SH, Kim H, Shin JW, et al. (2003) Quantitative polymerase chain reaction assay for serum hepatitis B virus DNA as a predictive factor for post-treatment relapse after lamivudine induced hepatitis B e antigen loss or seroconversion. Gut 52(12): 1779-1783.

7. Kim JH, Lee SJ, Joo MK, Kim CH, Choi JH, et al. (2009) Durability of antiviral response in HBeAg-positive chronic hepatitis B patients who maintained virologic response for one year after lamivudine discontinuation. Dig Dis Sci 54(7): 1572-1577.

8. Lee HW, Lee HJ, Hwang JS, Sohn JH, Jang JY, et al. (2010) Lamivudine maintenance beyond one year after HBeAg seroconversion is a major factor for sustained virologic response in HBeAg-positive chronic hepatitis B. Hepatology 51(2): 415-421.

9. Reijnders JG, Perquin MJ, Zhang N, Hansen BE, Janssen HL (2010) Nucleos(t)ide analogues only induce temporary hepatitis B e antigen seroconversion in most patients with chronic hepatitis B. Gastroenterology 139(2): 491-498.

10. Song MJ, Song do S, Kim HY, Yoo SH, Bae SH, et al. (2012) Durability of viral response after off-treatment in HBeAg positive chronic hepatitis B. World J Gastroenterol 18(43): 6277-6283.

11. European Association for the Study of the Liver (2012) EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. J Hepatol 57(1): 167-185.

12. Lok AS, McMahon BJ (2009) Chronic hepatitis B: update 2009. Hepatology 50(3): 661-662.

13. Liaw YF, Leung N, Kao JH, Piratvisuth T, Gane E, et al. (2008) Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2008 update. Hepatol Int 2(3): 263-283.

14. The Korean Association for the Study of the Liver (2012) KASL Clinical Practice Guidelines: Management of chronic hepatitis B. Clin Mol Hepatol 18(2): 109-162.

15. Cai W, Xie Q, An B, Wang H, Zhou X, et al. (2010) On-treatment serum HBsAg level is predictive of sustained off-treatment virologic response to telbivudine in HBeAg-positive chronic hepatitis B patients. J Clin Virol 48(1): 22-26.

16. Fung SK, Wong F, Hussain M, Lok AS (2004) Sustained response after a 2-year course of lamivudine treatment of hepatitis B e antigen-negative chronic hepatitis B. J Viral Hepat 11(5): 432-438.

17. Chan HL, Wong VW, Tse AM, Tse CH, Chim AM, et al. (2007) Serum hepatitis B surface antigen quantitation can reflect hepatitis B virus in the liver and predict treatment response. Clin Gastroenterol Hepatol 5: 1462-1468.

18. Liu F, Wang L, Li XY, Liu YD, Wang JR, et al. (2011) 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 26(3): 56-60.

19. Ha M, Zhang G, Diao S, Lin M, Sun L, et al. (2012) A prospective clinical study in hepatitis B e antigen-negative chronic hepatitis B patients with stringent cessation criteria for adefovir. Arch Virol 157(2): 285-290.

20. Lai CL, Shouval D, Lok AS, Chang TT, Cheinquer H, et al. (2006) Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. N Engl J Med 354(10): 1011-1020.

21. Kim YJ, Kim K, Hwang SH, Kim SS, Lee D, et al. (2013) Durability after discontinuation of nucleos(t)ide therapy in chronic HBeAg negative hepatitis patients. Clin Mol Hepatol 19(3): 300-304.

22. Jeng WJ, Sheen IS, Chen YC, Hsu CW, Chien RN, et al. (2013) Off-therapy durability of response to entecavir therapy in hepatitis B e antigen-negative chronic hepatitis B patients. Hepatology 58(6): 1886-1896.

23. Chan HL, Wong GL, Chim AM, Han HY, Chu SH, et al (2011) Prediction of off-treatment response to lamivudine by serum hepatitis B surface antigen quantification in hepatitis B e antigen-negative patients. Antivir Ther 16(8): 1249-1257.

24. Hadziyannis SJ, Sebastianos V, Rapti I, Vassiliopoulos D, Hadziyannis E (2012) Sustained responses and loss of HBsAg in HBeAg-negative patients with chronic hepatitis B who stop long-term treatment with adefovir. Gastroenterology 143(3): 629-636.e1.

25. Chan HL, Wang H, Niu J, Chim AM, Sung JJ (2007) Two-year lamivudine treatment for hepatitis B e antigen-negative chronic hepatitis B: a double-blind, placebo-controlled trial. Antivir Ther 12(3): 345-353.

26. Chien RN, Liaw YF (2006) Short-term lamivudine therapy in HBeAg-negative chronic active hepatitis B in Taiwan. Antivir Ther 11(7): 947-952.

27. Reijnders JG, Janssen HL (2013) Relapse of chronic hepatitis B after discontinuation of nucleos(t)ide analogs: is the glass half full or half empty? Hepatology 58(6): 1885-1887.