Editorial

Hepatitis B Management: It Is Time to Change the Strategy

Chronic hepatitis B (CHB) infection is a major global public health concern. The World Health Organization estimates that approximately 2 billion people worldwide have been infected with hepatitis B virus (HBV) and that approximately 350 million live with chronic infection.[1] CHB infection is a dynamic process that is influenced by immune, host, and virological factors. The aims of treating CHB with antiviral agents are to achieve sustained suppression of HBV replication and remission of the ongoing liver inflammation, with the ultimate goal of improving quality of life and survival by preventing cirrhosis and hepatocellular carcinoma (HCC). However, the current treatment options are far from ideal. The unique abilities of HBV to chronically persist in host hepatocytes due to the existence of covalently closed circular DNA (cccDNA) in the nucleus of infected hepatocytes makes eradication very difficult. Furthermore, treatment of CHB became more complex with the long-term use of oral nucleos(t)ide analogs. Conventional interferon alpha (IFN-α), the only agent licensed in 1991, has been superseded by pegylated IFN-α. Five nucleos(t)ide analogs have been licensed since 1998.[2] The long-term use of oral nucleos(t)ide analogs has resulted in the selection of antiviral-resistant mutations. First-generation nucleos(t)ide analogs, including lamivudine, telbivudine, and adefovir, were associated with the highest drug resistance rate. Therefore, these agents are no longer considered as firstline treatment options for HBV infection in several of the recently published HBV management guidelines. Newer antiviral agents (entecavir and tenofovir) took over as firstline agents due to their superior potency and low drug resistance rate.[3,4]

In this issue of the Journal, Yu *et al* report the antiviral efficacy of lamivudine, entecavir, telbivudine, and a combination of lamivudine and adefovir dipivoxil in previously untreated hepatitis B patients at different time points during a 52-week treatment period. The study reported no statistically significant differences in the effectiveness between the various nucleos(t)ide analogs when treating treatment-naive patients.[5] The researchers also confirmed the importance of early HBV suppression in achieving a better response after 52 weeks of treatment. This finding is in agreement with previously published reports.

Although there were no differences between the four groups in term of achieving a positive response at week 52 in treatment-naive patients, entecavir should be the firstline agent when choosing to treat treatment-naive patients. The other firstline agent that has gained popularity over the last few years is tenofovir, which was not included in this study. One of the important goals of treatment is to achieve prolonged suppression of the virus to decrease the negative viral effect on liver tissue. Entecavir and tenofovir are potent agents with no (tenofovir) or very low (entecavir)resistance rates. The major disadvantage of lamivudine is the high risk of developing antiviral resistance, approaching 70% at four years of treatment. This feature also limits the use of other antiviral agents due to cross-resistance, so lamivudine should not be used as a firstline agent anymore.[6] Similarly, relatively high resistance rates were reported with the use of telbivudine, and therefore, it is not considered as a firstline agent in recently published guidelines.[7] Adefovir is the least potent agent among all nucleos(t)ide analogs and does not achieve complete viral suppression in the first six months in the majority of patients. Additionally, this drug's resistance rate reaches 29% at 5 years, and the potential side effects, including nephrotoxicity, limit its use as a firstline agent, especially in patients with high viral loads.[8]

Therefore, tenofovir or entecavir is more likely to achieve the long-term goal of sustained viral suppression and should be considered as a firstline therapy for treatment-naive HBV patients. Additionally, multiple randomized controlled trials comparing the effects of newer antiviral agents with those of older agents showed a superior response to the second-generation agents. Lai *et al*. compared entecavir with lamivudine in CHB infection, and their study revealed that the rate of histological improvement, the virological response, and the normalization of liver enzymes were significantly greater with entecavir at 48 weeks.[9] Two other randomized trials conducted by Marcellin *et al*. and Hou *et al*. showed a superior antiviral effect with tenofovir compared with adefovir at 48 weeks.[10,11]

In their study, Yu *et al*. showed excellent virological, biochemical, and HBeAg-loss rates at 52 weeks, although this study did not answer a more important question, which is what the post-treatment durability is. The authors, however, mentioned that a follow-up study assessing post-treatment durability will be conducted.

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The authors also revealed that early viral suppression was linked to better clinical and virological responses at 52 weeks of treatment. However, the small number of patients enrolled in this study and the short follow-up period limit any solid conclusions. The authors did not classify the treatment response based on the stage of fibrosis, which would have added an important aspect to this study.

Despite the prospective nature of this study, its limitations are of major concern, limiting its clinical value. Furthermore, the epidemiology of HBV infection in China, including the mode of transmission, the age of infection, and the impact of genotypic differences, compared with other parts of the world makes generalization of the treatment response and outcome questionable.

In conclusion, the development of potent HBV drugs with high genetic barriers to resistance has resulted in significant suppression of viral replication over a longer period of time. As a result, overall patient survival has improved due to the prevention of disease progression to cirrhosis. Recent data showed regression of cirrhosis in 71 of 96 (74%) cirrhotic patients treated with tenofovir, which was confirmed by paired biopsies at baseline and after five years.[12] However, the preventive effect of these agents against HCC development is less clear. Therefore, the use of older-generation drugs, such as lamivudine, adefovir, and telbivudine, should be avoided when treating HBV in treatment-naive patients. For the time being, more potent drugs with high genetic barriers to resistance should be used as firstline agents until better treatment becomes available.

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REFERENCES

1. Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. J Viral Hepat 2004;11:97-107.
2. Yuen MF, Lai CL. Treatment of chronic hepatitis B: Evolution over two decades. J Gastroenterol Hepatol 2011;26 Suppl 1:138-43.
3. Coffin CS, Fung SK, Ma MM, Canadian Association for the Study of the Liver. Management of chronic hepatitis B: Canadian Association for the Study of the Liver Consensus Guidelines. Can J Gastroenterol 2012;26:917-38.
4. Abaalkhail F, Elsiesy H, AlOmair A, Alghamdi MY, Alalwan A, AlMasri N, *et al*. SASLT practice guidelines for the management of hepatitis B virus. *Saudi J Gastroenterol* 2014;20:350-5.
5. Yu S, Zhou Q, Zhao X, Yaun M, Wang C, Cheng X, *et al*. Comparison of the antiviral effects of different nucleos(t)ide analogues in Chinese patients with chronic hepatitis B: A head-to-head study. Saudi J Gastroenterol [In Press].
6. Lai CL, Dienstag J, Schiff E, Leung NW, Atkins M, Hunt C, *et al*. Prevalence and clinical correlates of YMDD variants during lamivudine therapy for patients with chronic hepatitis B. *Clin Infect Dis* 2003;*36*:687-96.
7. Liaw YF, Gane E, Leung N, Zeuzem S, Wang Y, Lai CL, *et al*. 2-Year GLOBE trial results: Telbivudine is superior to lamivudine in patients with chronic hepatitis B. *Gastroenterology* 2009;136:486-95.
8. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, *et al*. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B for up to 5 years. Gastroenterology 2006;131:1743-51.
9. Lai CL, Shouval D, Lok AS, Chang TT, Cheinquer H, Goodman Z, *et al*. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. N Engl J Med 2006;354:1011-20.
10. 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;359:2442-55.
11. Hou JL, Gao ZL, Xie Q, Zhang JM, Sheng JF, Cheng J, *et al*. Tenofovir disoproxil fumarate versus adefovir dipivoxil in Chinese patients with chronic hepatitis B after 48 weeks: A randomized controlled trial. *J Viral Hepat* 2014 doi: 10.1111/jvh.12313. [Epub ahead of print]
12. Marcellin P, Gane E, Buti M, Afdhal N, Sievert W, Jacobson IM, *et al*. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: A 5-year open-label follow-up study. *Lancet*. 2013;381:468-75.