Response-guided antiviral therapy in chronic hepatitis B: nucleot(s)ide analogues vs. pegylated interferon

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Preface

Since interferon-alpha, an immunomodulatory drug was authorized for treatment of chronic hepatitis B (CHB) in the early 90s, it has been used as a primary treatment. In addition, with the introduction of oral antiviral agents (nucleoside/-tide analogues, called NA hereafter) and pegylated interferon during the last 10 years, there have been great advances in treatment of chronic hepatitis B. As we can see in the major large-scale studies including REVEAL study, complications such as liver cirrhosis and hepatocellular carcinoma (HCC) occurring during the natural course of chronic hepatitis B will be greatly affected by serum HBV DNA levels.1,2 Thus, it became apparent that how effectively we can suppresses the proliferation of HBV through antiviral therapy is the key factor to the success of CHB treatment. However, since therapeutic efficacy of the current antiviral agents is not perfect with some degree of the emergence of resistant viruses during treatment, there are still many limitations to achieve these goals. Thus, in order to suppress fully HBV replication through antiviral therapy, it is necessary to modify the treatment for each individual according to on-treatment response, discarding the uniform treatment. Several international guidelines published so far advice to select the agents by considering predictors before treatment (e.g., pretreatment ALT level, serum HBV DNA levels, HBV genotype, etc.). In recent years, the method is on the rise to vary with the individual treatment duration, or to switch early to other drugs, or to consider add-on therapy by assessing on-treatment response as well as pretreatment predictors.3 Here, the individualized treatment strategy based on on-treatment responses will be described with the focus on serum HBV DNA and quantitative HBsAg level (called gHBsAg hereafter) in using NA and pegylated interferon.

Main discourse

In recent years, it has been tried to modify treatment strategy on the drugs and duration of treatment appropriately by monitoring the on-treatment responses as well as the baseline predictors before treatment. It has an important meaning in terms of social and economic costs due to the unnecessary prescription of drugs, the emergence of resistant viruses and the drug-related side effects.4
**Oral antiviral agents**

According to the literature analyzing a total of 3,400 patients registered for 26 prospective clinical trials, the reduction in serum HBV DNA levels during antiviral therapy showed significant correlation with the histological, biochemical and serological response to treatment. It suggests that the decline of serum HBV DNA level can be used as a surrogate marker to evaluate the treatment outcomes in the middle of the treatment. Moreover, through GLOBE trial, a large-scale prospective study that compared telbivudine and lamivudine, whether the serum HBV DNA level became undetectable at Week 24 of telbivudine treatment was found to be the most powerful factor for prediction of virologic response at Year 2. It was better than the other predictors such as pretreatment serum HBV DNA levels, ALT levels, and the treatment response at Week 4 and 12 after treatment in maintaining the remission stage for a long time (ALT normalization, serum HBV DNA suppression, HBeAg seroconversion in HBeAg-positive patients, prevention of emergence of resistant mutations), which was a phenomenon commonly applied to telbivudine and lamivudine. In the studies using entecavir, another antiviral drug, the similar phenomenon was observed. Roadmap concept recently presented, similarly, recommends to measure serum HBV DNA level at Week 12, 24 and 48 after treatment and to modify treatment plan based on the on-treatment response (Fig. 1).

![Figure 1. HBV treatment Roadmap concept: on-treatment virologic response and corresponding management plans in patients receiving NA for chronic hepatitis B (modified from Keeffe et al.).](image)
is verified at Week 12. A primary non-response is rare, but since there are many cases due to the decreased compliance of patients, it needs to be checked. If the drug has been taken regularly, it should be seriously considered to take other drugs. The most important thing is the result of serum HBV DNA level at Week 24, and it is classified into three kinds of virologic response groups according to serum HBV DNA levels: complete response group, partial response group, and suboptimal response group. Complete response group (complete virologic response) is defined as the cases where serum HBV DNA is not detected in the real-time PCR assay (less than 60 IU/mL), and the same drug continues to be used for treatment in this case. If the condition is stable, the interval of follow-up can be extended by six months at the discretion of the physician in charge. In most cases of the complete response group, the probability that serum HBV DNA is undetected using real-time PCR method after 2 years exceeds 90%. The ALT level is maintained within the normal range over 80%, and viral breakthrough is within 5%. In cases of the partial response group (partial virologic response), serum HBV DNA is detectable at Week 24, but as the cases less than 2,000 IU/mL, there are differences in changing the drug treatment strategy according to the type of drugs. In cases of high genetic barriers such as entecavir or tenofovir, the treatment can be continued until Week 48. If a complete response is shown at Week 48, the treatment continues without changing the drug, but the drugs should be changed if serum HBV DNA levels still fall short of complete response and stay in the levels of partial response, or rise above it. However, if being treated for drugs with low genetic barrier (e.g. lamivudine) or with medium-level genetic barrier (e.g. telbivudine, emtricitabine), it is recommended to add the second-line drugs without cross-resistance rather from the 24th week. The cases of inappropriate treatment group (suboptimal response) implies that serum HBV DNA decreased compared to that before the start of treatment but it is maintained still above 2,000 IU/mL. In this case, resistant strains occur after 2 years for approximately 30-60%, and further treatment outcomes are not good. The HBV DNA threshold of 2,000 IU/mL is the value presented by a vast literature review, since the risk of developing cirrhosis and HCC can grow even in this level of proliferation of viruses, and resistant strains can emerge or it can cause acute exacerbations. For these patients, more powerful drugs with out cross-resistance should be added, and their states should be checked through continuous monitoring every 3 months. Also in this case, if the measurement of serum HBV DNA levels at Week 48 shows the decrease less than 60 IU/mL, the treatment continues with follow-up at the interval of 6 months afterwards. The interval of follow-up during antiviral therapy is about 3-6 months depending on the situation described above, but in case the progression of liver disease such as cirrhosis is severe, regardless of good or bad response, the interval of follow-up should be kept in every 3 months.

Since this roadmap concept was proposed to identify the patients with high probability of emerging resistant strains and to strengthen the treatment for them in advance, it is most appropriate to apply to the cases where drugs with low genetic barrier are used for the primary drug, and more research is needed for the drugs with high genetic barrier in the future. In addition, because the roadmap concept was established basically in the situation where NA was used for initial treatment, it cannot be applied uniformly to the cases treated with other immune modulating drugs including interferon other than NA, to the cases where NA is used after a failure of interferon treatment, to the cases administered with more than two kinds of NA simultaneously, or to the cases where resistant viruses are already identified before the treatment. In addition, since the baseline serum HBV DNA level and the timing of judgment are somewhat different for the roadmap concept according to the studies, it should be revised in the future to obtain a consistent conclusion. For example, adefovir, with which the rate of serum HBV DNA suppression is slower compared with lamivudine or telbivudine, requires the timing at Week 48 rather than Week 24 for serum HBV DNA testing to predict the further sustained response. Similarly, in entecavir, undetectable HBV DNA
DNA at Week 48 was suggested as a more important prognostic factor. In contrast, in other studies with Telbivudine, serum HBV DNA negative at Week 12 of treatment appeared to be more significant indicator for the prediction of maintaining the remission stage for a long time (state of serum HBV DNA maintaining negative for 3 years) than serum HBV DNA negative at Week 24 after treatment. Even in defining primary non-response, the European Association for the Study of the Liver (EASL) applies the same criteria with the roadmap concept described above, while the American Association for the Study of the Liver Diseases (AASLD) defines it as the case if the decrease is not more than 2 log at Week 24, hence further studies on this are also needed.

In addition, the evaluation of on-treatment responses can be conducted based on the trends in qHBsAg. However, in the cases treated with NA (particularly lamivudine and adefovir), since the decreasing rate of qHBsAg is slow unlike pegylated interferon, its usefulness is limited yet. In recent GLOBE study, in the cases where qHBsAg decreased rapidly more than 1 log IU/mL at the first year of treatment with telbivudine, the probability of HBsAg loss was high, and in the cases where more than 2 log IU/mL was decreased, the sustained treatment responses were found in most cases. Also in a study for patients treated with entecavir for 2 years, continuous decreases in qHBsAg during the treatment were observed, but the decreased qHBsAg was not identified as a crucial variable to predict further treatment responses. Therefore, since the studies on the decrease of qHBsAg and treatment response have not been conducted sufficiently, the further complementary studies will be required in the future.

Peg-Interferon Therapy

Even in the treatment of interferon, an immunotherapy drugs, it is possible to assess the on-treatment response by using serum HBV DNA levels like NA, but it has a very different interpretation criteria from NA which directly inhibits the virus. In cases treated only with pegylated interferon or combination drug therapy with Lamivudine, we were able to predict the loss of HBeAg if serum HBV DNA levels decreased more than 1 log at Week 32. In HBeAg-negative CHB, 64% of patients in whom serum HBV DNA levels were decreased to 400 copies/mL at Week 12, ALT levels were normalized at Week 24 after treatment and serum HBV DNA levels were maintained below 20,000 copies/mL. In another study, sustained treatment responses were observed in 64% of patients in whom serum HBV DNA levels were decreased to 1000 copies/mL at Week 24. Thus, in the treatment of pegylated interferon, the reduction of serum HBV DNA occurs relatively late, and even in the cases where serum HBV DNA became negative at Week 12 or 24, sustained treatment responses after treatment remained less than approximately 70%. Hence, there are many limitations to predict the future treatment responses with serum HBV DNA in the early stage of treatment as in NA. In addition, since there is no difference in the changing pattern of serum HBV DNA levels between sustained virologic responders and the relapers after treatment, it is far from applying the roadmap concept that could be applied in NA. Rather, because most of the treatment responses were poor in cases where serum HBV DNA levels were not decreased to less than $10^4$ copies/mL at Week 8 from the beginning of treatment, early termination of pegylated interferon treatment and switching to NA is recommended, and the so-called "early stopping rule" can be applied.

In the pegylated interferon treatment, due to many limitations on the methods using serum HBV DNA levels as above, the quantitative HBsAg method (qHBsAg) can be rather more useful. In HBeAg-positive CHB, approximately 50% of the
Table 1. Recent clinical studies with qHBsAg in interferon therapy for HBV infection (modified from Lee et al.).

<table>
<thead>
<tr>
<th>Author (ref.)</th>
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<td>Chan et al. 22</td>
<td>Peg-IFN+LAM</td>
<td>cccDNA</td>
<td>Low baseline qHBsAg can predict SVR.</td>
<td>Peg-IFN+LAM decreases cccDNA and HBsAg, which are well correlated.</td>
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<tr>
<td>Manesis et al. 23</td>
<td>IFN vs. LAM</td>
<td>HBV DNA</td>
<td>Low baseline qHBsAg can predict SVR.</td>
<td>IFN induces sharper decrease in qHBsAg than LAM.</td>
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<td>Wiegand et al. 24</td>
<td>FAM±LAM</td>
<td>HBV DNA (not correlated)</td>
<td>Decline of qHBsAg can predict HBsAg loss</td>
<td>2 log drop to below 100 IU/ml is associated with HBsAg clearance.</td>
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<td>Moucari et al. 19</td>
<td>Peg-IFN</td>
<td>HBV DNA</td>
<td>Early qHBsAg drop can predict SVR.</td>
<td>qHBsAg may be useful to optimize PEG-IFN therapy.</td>
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<td>Brunetto et al. 25</td>
<td>Peg-IFN±LAM vs. LAM</td>
<td>HBV DNA</td>
<td>On-treatment qHBsAg decline can predict sustained HBsAg loss</td>
<td>qHBsAg&lt;10 IU/ml at week 48 and 1 log decline predict sustained HBsAg clearance to optimize treatment strategy.</td>
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<td>Lau et al. 17</td>
<td>Peg-IFN±LAM</td>
<td>-</td>
<td>On-treatment qHBsAg can be used as an early predictor of SVR</td>
<td>In HBeAg(+) patients, qHBsAg reduction through weeks 12, 24 and 48 were higher in patients with HBeAg seroconversion.</td>
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<td>Marcellin et al. 18</td>
<td>Peg-IFN±LAM</td>
<td>-</td>
<td>qHBsAg at week 12 can predict long-term HBsAg clearance</td>
<td>35% of patients who had qHBsAg &lt;1,500 IU/mL at week 12 cleared up HBsAg by 4 years post-treatment.</td>
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<tr>
<td>Lu et al. 26</td>
<td>Peg-IFN±LAM</td>
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<td>qHBsAg was superior to cccDNA and serum HBV DNA in predicting SVR</td>
<td>Area under ROC curve with qHBsAg, cccDNA and HBV DNA was 0.769, 0.734, and 0.714, respectively, for predicting SVR.</td>
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<tr>
<td>Brunetto et al. 27</td>
<td>Peg-IFN±LAM</td>
<td>-</td>
<td>On-treatment qHBsAg can be used as an early predictor of SVR</td>
<td>On-treatment decline in HBsAg appears to be genotype dependent. Genotype B patients showed the most rapid and pronounced decline.</td>
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Patient in whom qHBsAg level reached 1500 IU/mL or less at Week 12 or 24 after treatment were successful in HBeAg seroconversion for cessation of treatment. In a study conducted by Marcellin et al. for HBeAg-negative CHB, about 35% of patients in whom qHBsAg level were less than 1500 IU/mL at Week 12 maintained HBsAg loss status up to 4 years after stopping treatment. In addition, according to the study conducted by Moucari et al, the probability of sustained responses after treatment termination was identified as 97% in cases qHBsAg level decreased more than 1 log IU/mL at Week 24 of treatment. Table 1 below shows the summary of a study on the usefulness of qHBsAg level for the prediction of response to interferon. Like serum HBV DNA level, the early stopping rule can be applied using qHBsAg. In HBeAg-positive CHB in whom qHBsAg level did not decrease at Week 12 of treatment, the probability that treatment response may not be maintained stands at 97%, and also in HBeAg-negative CHB, almost 100% failed to obtain treatment responses if both qHBsAg and HBV DNA level did not decrease more than 2 log IU/mL at Week 12. Therefore, also in this case, pegylated interferon therapy should be terminated early and switched to other treatments.
Conclusion

For treatment of CHB, it enables optimal individualized treatment to evaluate the on-treatment responses by measuring serum HBV DNA or qHBsAg level in addition to the traditional pretreatment predictors, predicting more accurately the future treatment outcomes. In addition, on-treatment monitoring can further enhance the current treatment, or adjust the duration of treatment, or terminate unnecessary treatment in early stage, and switching to another drug for individuals. However, so far, there appear to be some controversial to determine the criteria and timing for assessing on-treatment responses. Further research is needed based on clinical trials.

참고문헌

2. Iloeje UH, Yang HI, Su J, Jen CL, You SL, Chen CJ. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. Gastroenterology 2006;130:678-86.