Chronic hepatitis B virus (HBV) infection is the major cause of chronic liver disease worldwide. After the introduction of a universal vaccination program in neonates, the positive rate for hepatitis B surface antigen (HBsAg) in infants and children has been dramatically decreased in Korea, but HBsAg is still estimated to be positive in 5-7% of the general population. Accordingly, about 70% of liver cirrhosis and hepatocellular carcinoma are related to chronic HBV infection in Korea.

Until quite recently, interferon (IFN) alfa-2b and lamivudine were the only available drugs for the treatment of chronic hepatitis B. However, persistent viral suppression was not feasible owing to the limited efficacy, adverse effects (IFN) or rapid development of antiviral resistance (lamivudine). With the recent advances in drug development, several treatment options are now available, but all of these agents still have limited long-term efficacy and are not free of adverse effects or development of antiviral resistance. In this session, I will briefly review four different existing guidelines (KASL, AASLD, APASL, guideline by Keeffe et al.), especially about conflicting points in the treatment of HBeAg positive chronic hepatitis B.

### Candidates for Therapy

#### 1. Upper limits of normal (ULN) for serum alanine aminotransferase (ALT) level

The guideline by Keeffe et al. recommended that an ULN of 30 IU/L for men and 19 IU/L for women be used for serum ALT levels when making decisions on the initiation of therapy. This opinion mainly based on two studies. One retrospective study involving a cohort of first-time blood donors suggested that ULNs for serum ALT levels are 30 IU/L for men and 19 IU/L for women, which were determined by excluding the persons with high risk factors for liver diseases including nonalcoholic fatty liver disease. The most important factor affecting the ULN was body mass index (BMI). They calculated the normal ranges of ALT values in subjects with BMI <25 kg/m², but did not analyze whether the ALT levels still change with BMI even in those with normal BMI. Our recent analysis showed the increase of ULNs with older age, but this effect predominantly resulted from increase in BMI with age even in subjects with BMI <25 kg/m². The mean age of the subjects in the study of Prati et al. was 29.8 ± 9.5 years suggesting that these populations were relatively young and thereby had low BMI. However, serum ALT levels increase with BMI even in non-obese subjects and there is no cut-off level of...
BMI that results in an abrupt increase of the ULN for ALT levels.\(^6,7\) Therefore, the results of Prati et al. might be partly influenced by predominant inclusion of subjects with relatively low BMI. Given that some patients with chronic HBV infection may be obese or have combined fatty liver disease, there are not still sufficient evidences that these new criteria for ULN of serum ALT levels should be used for the initiating antiviral therapy in chronic hepatitis B patients.

Kim et al. showed that the relative risk of mortality from liver disease increased with the increase of ALT levels even in individuals with normal ALT levels defined by conventional criteria.\(^8\) However, this study tested only serum AST, ALT, glucose, cholesterol and relied on self reported questionnaire for excluding preexisting diseases. Serum HBsAg and anti-HCV were not tested routinely in this study. The number of deaths from liver disease was 690 during the eight years’ follow up of 94,533 men and 47,522 women. More deaths were related to hepatocellular carcinoma than other non-cancer liver diseases suggesting that many HBsAg-positive individuals might be included in this study. Therefore, these data suggested that current ULN for ALT levels is not optimal in identifying the subjects with underlying liver diseases, especially cirrhosis, if only based on questionnaire and ALT levels without serum HBsAg status. However, this finding does not necessarily suggest that the ULN of ALT levels should be adjusted in determining the initiation of therapy. In clinical practice, advanced liver diseases can be detected by several other diagnostic modalities. In addition, hepatocellular carcinoma can develop in HBsAg positive subjects with inactive or mild disease activity. There are still no data whether antiviral therapy can prevent the development of hepatocellular carcinoma in HBsAg positive subjects with inactive disease activity.

In conclusion, although the current ULN for ALT levels is not adequate and should be adjusted for the screening of liver diseases, there is not still enough evidence that the newly proposed ULN of ALT levels should be used in determining the initiation of antiviral therapy.

2. ALT levels for initiation of antiviral therapy in HBeAg positive patients

Guidelines by KASL, AASLD, and APASL recommended that treatment can be initiated in patients with ALT levels \(\geq 2 \times \text{ULN}\) in HBeAg positive patients. In patients with borderline ALT elevations, liver biopsy can be considered in determining antiviral therapy. The guideline by Keeffe et al. recommended active antiviral therapy in patients with elevated ALT levels based on the newly proposed ULN. However, there are still no enough data regarding this issue. The rationale for ALT levels \(\geq 2 \times \text{ULN}\) is mainly based on previous IFN or lamivudine trials. Patients with low ALT levels usually cannot achieve HBeAg seroconversion with IFN or lamivudine therapy. Therefore, patients who had a high probability for treatment-induced HBeAg seroconversion in short-term period were regarded as best candidates for treatment. However, recent development of antiviral agents with low rates of antiviral resistance enables long-term antiviral therapy and HBeAg seroconversion rate increases with longer duration of antiviral therapy. From a different point of view, mild ALT elevation can mean mild disease activity or concomitant fatty liver disease. Considering the high rate of antiviral resistance during long-term lamivudine therapy and side-effects of IFN, the clinical benefits were doubtful in these patients. However, low ALT levels does not necessarily reflect disease activities in chronic hepatitis B. HBeAg positive patients even with normal ALT levels, especially those above age 40, may have advanced liver disease.\(^9,10\) Therefore, more active application of liver biopsy should be considered on a case-by-case basis in patients with
normal or mildly elevated ALT levels.

3. HBV DNA levels

Current guidelines recommended that treatment be initiated in HBeAg positive patients with elevated ALT levels (or ≥2×ULN) and HBV DNA ≥10⁵ copies/mL. This cut-off level for HBV DNA is somewhat arbitrary and based on previous clinical trials which used hybridization assays for the detection of serum HBV DNA. Some previous studies suggested that low HBV DNA level may reflect that patients are undergoing spontaneous HBeAg seroconversion. However, there have been no data regarding the true threshold HBV DNA level associated with necroinflammatory activity. In addition, some patients may have fluctuating HBV DNA levels during their course of disease. Therefore, serum HBV DNA levels <10⁵ copies/mL do not exclude the contribution of HBV to ALT elevation. However, other contributing factors should be ruled out carefully and an observation period is needed before initiation of treatment.

4. Acute exacerbation of hepatitis B

Acute exacerbation of hepatitis B is defined as elevations of aminotransferase activity to more than 10 times the ULN and more than twice the baseline value. In a prospective randomized trial for clevudine conducted in Korea, the annual incidence of acute exacerbation in control group was 14.8%, which was defined as ALT or AST elevations >20 × ULN or >10 × ULN and a 10-fold change from the lowest on-study value. Acute exacerbation of hepatitis B sometimes leads to hepatic decompensation, although ALT normalization and/or HBeAg seroconversion can occur during or after the course of flare-up. In a small prospective study conducted in Korean patients, ALT normalization and loss of HBV DNA, measured by the Digene hybrid capture II assay, were observed in 71% and 57%, respectively, even without antiviral therapy. HBeAg seroconversion rate was 28.6%. However, 1 of 7 untreated patients showed persistent ALT elevation >800 IU/L and 3 patients experienced secondary episodes of acute exacerbation with jaundice within 1 year. In contrast, serum ALT normalization and loss of HBV DNA were achieved in 100% of patients treated with lamivudine and the HBeAg seroconversion rate was 50%. This study was terminated early because of the ethical problem. In summary, despite the high rate of ALT normalization and spontaneous HBeAg seroconversion, antiviral therapy should be initiated immediately because of the possible progression to hepatic failure and a high rate of secondary episodes. IFN treatment is contraindicated during episodes of acute exacerbation because of the possible hepatic decompensation. The guideline by APASL recommended an immediate antiviral treatment in patients with acute exacerbation if there are signs of hepatic decompensation, while delaying treatment for an observation period of 3 months if there is no concern about hepatic decompensation. However, there are no clinical trials supporting this approach. Immediate initiation of therapy seems to be safer because of lack of serious side-effects or harmful effects on HBeAg seroconversion with antiviral therapy and possible rapid deterioration of hepatic function during the course of illness without treatment.
When to Stop Therapy?

HBeAg loss or seroconversion is generally regarded as end-points of therapy. Many prospective randomized trials have shown the durable viral suppression after cessation of antiviral therapy in patients who achieved HBeAg loss/seroconversion.\textsuperscript{15,16} In contrast, all the studies conducted in Korea and Taiwan reported frequent post-treatment relapse.\textsuperscript{17-20} The reason is still unknown, but two contributing factors can be considered. In most of the phase II or phase III trials, patients with acute exacerbation were excluded from the trials. In contrast, most studies reporting high rates of post-treatment relapse included patients with acute exacerbation. High rates of HBeAg seroconversion in these studies suggested the possible contribution of acute exacerbation in HBeAg seroconverted patients. Therefore, the frequent post-treatment relapse may reflect the fluctuating course of disease activity, thereby worse prognosis in patients with acute exacerbation. Another possible factor is the contribution of HBV genotype. One study from Taiwan suggested that genotype C is associated with frequent post-treatment relapse after lamivudine induced HBeAg seroconversion.\textsuperscript{21} Anyway, to reduce post-treatment relapse, most guidelines recommended additional therapy for at least 6 months after HBeAg loss/seroconversion. The guideline by KASL recommended 1-year extension of antiviral therapy. Some retrospective studies suggested 6-month extension of lamivudine therapy reduces post-treatment relapse.\textsuperscript{17,22} However, the exact duration of extended therapy cannot be determined accurately because the time intervals for testing serum HBeAg and anti-HBe could not be uniform in retrospective analyses. Patients lost to follow-up also can make the analysis inaccurate. Our prospective study showed that the relapse rates are still high even in patients who received either 6-month (59%) or 1-year additional therapy (50%). In addition, the incidence of virological breakthrough during extended lamivudine therapy was 8.1% at 1 year. Therefore, the relapse and treatment failure rates were essentially the same in both groups.\textsuperscript{20} A similar finding could be observed in another prospective study. Although extended lamivudine therapy for 2 years or more reduced post-treatment relapse rate to 31%, the virological breakthrough rates during lamivudine extension therapy were 12% and 20% at 2 and 3 years.\textsuperscript{23} Therefore, there is not still enough evidence that more prolonged therapy can reduce the overall treatment failure plus post-treatment relapse in patients who achieved HBeAg loss/seroconversion. Older age was the most consistent predictive factor for post-treatment relapse in many studies, which might explain the different post-treatment relapse rates.\textsuperscript{17,19,20,23} Serum HBV DNA levels by PCR-based assay at the time of cessation of therapy was also a predictive factor,\textsuperscript{20} but it is not certain whether this observation is a co-incidental finding suggesting more vigorous immune clearance or prolonged therapy up to undetectable serum HBV DNA by PCR-based assay can really reduce the post-treatment relapse.

Treatment of HBeAg Positive Chronic Hepatitis B

Nowadays, many treatment options are available due to the recent advances in antiviral drug development. However, all of these drugs have some limitations such as adverse effects, limited efficacy, safety issues, and development of antiviral resistance. Treatment should be determined considering these problems, and thereby there is still no recommended standard therapy. Cost is another important determining factor for selecting antiviral agent in Korea. Therefore, daily clinical practice can be different from the recommended treatment in
1. Interferon-alfa (IFN-α) and pegylated interferon alfa (pegIFN-α)

IFN-α is the first drug proven to be effective in suppressing HBV replication and hepatic necroinflammation. The reported HBeAg loss and seroconversion rates are 33% and 18%, respectively. The response in Asian patients with normal ALT is very poor, thereby not indicated. The recommended dosing regimen is 5 MU daily or 10 MU 3 times weekly for at least 16 weeks. Therapy is associated with many adverse effects such as flu-like symptoms, fatigue, depression, cytopenia, and thyroid disease. Therefore, IFN therapy is not recommended in patients with acute exacerbation or decompensated liver cirrhosis.

PegIFN-α has improved pharmacokinetic profile and the advantages of more convenience in administration and more sustained viral suppression. A 24-week course of PegIFN-α-2a achieved more HBeAg loss than conventional IFN-α-2a (37% with 90 μg, 35% with 180 μg vs. 25%). However, the dosing regimen of conventional IFN-α-2a was 4.5 MU 3 times weekly for 6 months in this study, which was lower than that of standard recommended dosing schedule. The frequency and severity of adverse events were comparable. In a study in comparison with lamivudine, a 48-week course of PegIFN-α-2a achieved greater rates of HBeAg seroconversion (32% vs. 19%), suppression of HBV DNA and ALT normalization than lamivudine. Combination therapy with lamivudine conferred no advantages. HBV genotype A showed more favorable response than genotype C in terms of HBeAg seroconversion rate (52% vs. 31%). Low baseline HBV DNA concentrations and high baseline ALT levels were favorable factors for HBeAg seroconversion. PegIFN-α-2b therapy for 52 weeks showed 36% of HBeAg loss rate and 29% of seroconversion rate at the end of follow-up. Although combination with lamivudine revealed a higher rate of HBeAg loss (44% vs 29%) at the end of therapy, more patients experienced relapse after the end of therapy. Again, there is no evidence that combination therapy with lamivudine is better than PegIFN-α-2b. Comparison with lamivudine monotherapy or standard IFN therapy was not made. Genotype C showed a poorer response than genotype A (28% vs 47%). In conclusion, the response rate in terms of HBeAg loss/seroconversion with pegIFN-α can be estimated to be around 30% in Korea where prevalence of genotype C is over 95%.

2. Lamivudine

Lamivudine rapidly reduces HBV replication and results in ALT normalization, HBeAg seroconversion and histologic improvement. The cumulative HBeAg seroconversion rates are 17%, 40%, and 50% at 1, 3, and 5 years, respectively. However, these seroconversion rates do not necessarily mean clinical benefits considering the high incidence of lamivudine breakthrough hepatitis and subsequent HBeAg seroconversion. During the breakthrough hepatitis, severe hepatic injuries and progression to cirrhosis can occur. The incidence of lamivudine resistance increases with duration of therapy from 14-32% at 1 year to 60-70% at 5 years. Stopping lamivudine therapy before HBeAg loss/seroconversion usually results in lamivudine withdrawal hepatitis, which also can result in severe flares of hepatitis and hepatic decompensation. Therefore, considering the high rate of lamivudine resistance and withdrawal hepatitis, lamivudine is not recommended as a first-line therapy in AASLD guideline. However, lamivudine therapy is cheaper than other therapies and does not have serious adverse effects associated with the drug itself.
3. Adefovir dipivoxil

Adefovir dipivoxil also reduce serum HBV DNA and ALT levels, and results in increased rates of HBeAg seroconversion and histologic improvement. The HBeAg seroconversion rates are 12% at 1 year, 33% at 2 years, and 46% at 3 years. Resistance to adefovir develops 0% at 1 year, 11% at 3 years, and 29% at 5 years. Adefovir resistance responds to lamivudine therapy, and possibly entecavir and tenofovir. Adefovir has lower potency in terms of serum HBV DNA log\textsubscript{10} reduction (-3.5 log\textsubscript{10} with adefovir, -5.4 log\textsubscript{10} with lamivudine, and -6.9 log\textsubscript{10} with entecavir) and some studies have reported a high rate of primary nonresponse to the 10 mg of adefovir. Adefovir is safe and 10 mg of adefovir does not increase the incidence of renal insufficiency. Currently, adefovir is recommended as a first-line treatment in guidelines from U.S. but is not reimbursed as a first-line treatment in Korea.

4. Entecavir

Entecavir is a potent suppressor of HBV replication and resulted in a higher rate of histologic improvement, HBV DNA reduction, and ALT normalization compared to lamivudine. However, the HBeAg seroconversion rate at 1 year is not different from that with lamivudine (21% vs. 18%). Two-year therapy with 0.5 mg of entecavir resulted in 31% of HBeAg seroconversion (25% with lamivudine), but direct comparison with other studies is difficult because of the study design. Advantages of entecavir are its high potency and a low rate of antiviral resistance. Although some experts have criticized the study design, no entecavir resistance was detected at week 48 or 96. The safety profile over 48 weeks was similar to that with lamivudine. However, long-term safety profile is not available currently. Entecavir is recommended as an initial drug from AASLD guideline and is currently reimbursed for 1 year as an initial therapy in Korea.

5. Telbivudine, clevudine and tenofovir

Telbivudine is also a potent inhibitor of HBV replication. The median change of HBV DNA levels from baseline at week 52 is -6.0 log\textsubscript{10} with telbivudine and -4.6 log\textsubscript{10} with lamivudine. Telbivudine resulted in higher rates of undetectable HBV DNA by PCR assay and ALT normalization than lamivudine. However, the HBeAg loss and seroconversion rates were not statistically different (35% vs. 29%, 30% vs. 25% at year 2). Telbivudine is associated with a lower rate of resistance than lamivudine, but virological breakthrough (≥1 log\textsubscript{10} from nadir) was observed in 4.4% of patients at year 1 and 21.6% at year 2. Telbivudine has an excellent safety profile with no genotoxicity, carcinogenicity or reproductive toxicity. Currently, the AASLD guideline does not recommend telbivudine as a first-line drug because of the relatively high rate of drug resistance.

Thirty milligrams of clevudine reduces HBV DNA by 5.1 log\textsubscript{10} at week 24 (0.27 log\textsubscript{10} in placebo group). Clevudine has a peculiar profile in terms of slow virological rebound after cessation of therapy. Viral suppression was sustained off therapy, with 3.73 log\textsubscript{10} reduction at week 34 and 2.02 log\textsubscript{10} at week 48 (24 weeks after cessation of therapy). Although ALT elevations >5 times the ULN were observed in 7.1% of patients during the post-treatment follow-up period, which was significantly lower than that in the placebo group (19.7%). However, long-term data on HBeAg seroconversion and antiviral resistance rates are not currently available. Clevudine is also reimbursed for 1 year as an initial therapy in Korea.
Tenofovir disoproxil fumarate is originally approved for the treatment of HIV infection. There has been no prospective randomized trial with tenofovir in HBeAg positive naïve patients. Retrospective analyses in patients co-infected with HIV and HBV demonstrated that tenofovir has a potent antiviral activity against HBV. Tenofovir also showed a greater reduction of serum HBV DNA than adefovir in patients with lamivudine-resistant HBV. Tenofovir therapy has been reported to be rarely associated with renal insufficiency and hyperphosphatemia.

Conclusion

Despite the advent of several antiviral agents, all of the drugs have some limitations in long-term control of HBV disease activity. To date, the physicians should consider the strength and weakness of individual drugs in selecting of antiviral agents. More importantly, overzealous antiviral treatment should be avoided in patients with immune tolerant phase or minimal disease activity, considering the emergence of antiviral resistance during long-term antiviral therapy. Liver biopsy can be helpful in patients with minimally elevated ALT levels.

References

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