Recent Advances in the Management of Chronic Hepatitis B Including Suppression of Hepatocellular Carcinoma by Entecavir and Interferon

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Key Words
Chronic hepatitis B · Pegylated interferon-α · Nucleos(t)ide analogues · Entecavir · Tenofovir

Abstract
At present, for adults with chronic hepatitis B virus (HBV) infection, two new analogues, entecavir (ETV) and tenofovir, are recommended as the first-line therapy by the EASL (European Association for the Study of the Liver), AASLD (American Association for the Study of Liver Diseases), and APASL (Asian Pacific Association for the Study of the Liver) guidelines. The use of pegylated interferon-α (PEG IFN-α) is recommended as the first-line therapy instead of standard IFN-α according to the above 3 guidelines. In this paper, the aim was to assess: (1) the long-term efficacy and safety as well as the resistance to ETV and tenofovir disoproxil fumarate (TDF); (2) the efficacy of PEG IFN-α; (3) the role of combination therapy with IFN plus two analogues, such as lamivudine and ETV; (4) the efficacy and safety of two analogues with cirrhosis, and (5) suppression of hepatocellular carcinoma (HCC) by ETV and IFN treatment. The results are as follows: (1) both ETV and TDF showed long-term efficacy and safety; (2) PEG IFN-α resulted in a greater decline in HBV DNA levels and a higher rate of HBeAg seroconversion; (3) combination therapy with IFN plus two analogues did not elevate the rate of sustained responses; (4) both ETV and TDF showed efficacy and safety with cirrhosis (ETV especially displayed efficacy and safety with decompensated cirrhosis), and (5) suppression of HCC was observed by ETV and IFN.

Introduction
It is estimated that over 350 million people are infected with chronic hepatitis B (CHB) worldwide, resulting in 600,000 deaths each year from cirrhosis and hepatocellular carcinoma (HCC) [1].

Clearance of hepatitis B is marked by a loss of HBsAg and resolution of liver inflammation, though hepatitis B virus (HBV) may remain integrated in the host genome as covalently closed circular DNA [2].

Current treatments aim to suppress the HBV DNA replication, reduce inflammation to prevent progressive fibrosis and the development of HCC but not to eradicate
the virus. The practice guidelines EASL (European Association for the Study of the Liver), AASLD (American Association for the Study of Liver Diseases), and APASL (Asian Pacific Association for the Study of the Liver) have been developed to indicate who, how and when to treat [3–5].

We summarize recent findings based on the consensus of the EASL, AASLD, APASL, and the JSH (Japan Society of Hepatology) guidelines [3–5]. In addition, we summarize the recent developments in the management of CHB based on the recent available data, results, and reviews [6–9].

Published Results Based on Consensus of the EASL, AASLD, and APASL Guidelines

Three guidelines recommend that treatment should be started in noncirrhotic CHB patients with serum HBV DNA levels >20,000 IU/ml and persistently increased alanine aminotransferase (ALT) levels and/or histologic evidence of moderate/severe inflammation or fibrosis. The AASLD guideline recommends an arbitrary HBV DNA level of 20,000 IU/ml for starting treatment [4]. The APASL guideline recommends an HBV DNA threshold of 20,000 IU/ml for HBeAg-positive patients and 2,000 IU/ml for HBeAg-negative patients, whereas the EASL guideline recommends a cutoff value of 2,000 IU/ml irrespective of the HBeAg status [3, 5]. For patients who meet the criteria for HBV DNA, the EASL guideline recommends treating them with ALT levels greater than the upper limit of normal (ULN) if a liver biopsy reveals moderate to severe inflammation and/or at least moderate fibrosis; however, the AASLD and APASL guidelines recommend treatment for patients with an ALT level greater than 2 times the ULN. The AASLD guideline recommends that lower values be used to define the ULN for an ALT level of 30 U/l for men and 19 U/l for women, and a liver biopsy be performed in patients with mildly increased ALT levels, particularly in patients older than age 40 years [4]. The AASLD and APASL guidelines recommend antiviral therapy in patients with compensated liver cirrhosis (LC) and a serum HBV DNA level >2,000 IU/ml regardless of the ALT level [4, 5].

The 3 guidelines recommend 3–6 months of observation in HBeAg-positive patients and treatment if spontaneous HBeAg seroconversion is not observed. Recommendations for treatment of noncirrhotic CHB HBeAg-positive and HBeAg-negative patients are summarized in figures 1 and 2 [8].

The management algorithm used during therapy includes measuring HBV DNA and ALT levels every 12 weeks and HBeAg or anti-HBe levels every 24 weeks in CHB patients who are HBeAg-positive. HBeAg-negative CHB patients should be similarly checked for efficacy and safety during 48 weeks of treatment. All CHB patients treated with pegylated interferon-α (PEG IFN-α) should be monitored for the known adverse effects of IFN.

For HBV-related LC patients with increased ALT levels, the AASLD guideline recommends treatment regardless of the HBV DNA level [4]. The EASL guideline recommends treatment of HBV-related LC patients with any detectable level of serum HBV DNA [3]. There is growing evidence that long-term treatment with nucleos(t)ide analogues (NAs) not only prevents disease progression but also reverses fibrosis and cirrhosis. In a double-blind, randomized, placebo-controlled study of 651 patients with advanced fibrosis or cirrhosis, who were HBeAg-positive or had high levels of HBV DNA (>150,000 IU/ml), lamivudine (LAM) therapy was shown to decrease the progression of liver disease [10]. A follow-up report of the phase 3 tenofovir disoproxil fumarate (TDF) versus adefovir dipivoxil (ADV) trial including 348 patients who had paired biopsies at baseline and year 5 showed that 51% of the patients had a decrease in fibrosis stage by 1 or more, and 71 of 96 (74%) patients with cirrhosis on initial biopsy had regression of cirrhosis [11].

Antiviral Effect of NA

Table 1 summarizes the efficacy of NA treatment in a 48-week large, randomized, controlled trial with HBeAg-positive and -negative CHB patients [12–17].

Entecavir

A daily dose of 0.5 mg of entecavir (ETV) was found to be superior to 100 mg of LAM in terms of suppression of HBV DNA by 6.9 log copies/ml in HBeAg-positive CHB patients and by 5.0 log copies/ml in HBeAg-negative CHB patients. Histological improvement was achieved in 72% of ETV-treated CHB patients compared to 62% in LAM-treated CHB patients (HBeAg-positive), and in 70% of ETV-treated versus 61% of LAM-treated CHB patients (HBeAg-negative). In addition, at the end of year 2, HBsAg loss was recorded in 5% of ETV-treated and in 2% of LAM-treated patients [18, 19]. In the follow-up study of 96 weeks of treatment with 0.5 mg of ETV in naïve Japanese patients, resistance was reported in only 1.7% [20].
For 55 patients with decompensated liver function treated with ETV for ≥12 months, improvements from baseline in the Child-Turcotte-Pugh score and its components (albumin, total bilirubin, and prothrombin time) and in the model for end-stage liver disease score were observed (p < 0.05 for all) [21].

Long-term studies report the safety and efficacy of ETV in NA-naïve patients with undetectable HBV DNA in over 90 and 0.4% developing resistance at 4 years of treatment [22]. Achieving a complete viral response with HBV DNA <80 IU/ml on ETV decreased the risk of decompensation, HCC, or death by 71% during a median...
of 20 months of follow-up [23]. Results of the multicenter international BE-LOW study (NCT00410072) investigating ETV monotherapy versus ETV and TDF combination in nucleos(t)ide-naive HBeAg-positive and -negative CHB patients showed no difference at week 96 in viral suppression, ALT level, HBeAg, or HBeAg seroconversion. However, combination therapy did lead to a greater reduction in the viral load in HBeAg-positive CHB patients with baseline HBV DNA of at least 10^8 IU/ml, suggesting a potential benefit in this subset of patients [24].

Greater decreases in serum HBV DNA levels (<10^4 copies/ml) during follow-up were associated with a lower risk of HCC. HCC occurred more frequently (2.3 vs. 7.5%, p < 0.001) in nonresponding patients or in patients with a viral breakthrough compared with those who experienced remission [25].

The efficacy of ETV therapy in suppressing hepatocarcinogenesis was evaluated in a cohort study that matched clinical backgrounds using propensity scores. 90% of the ETV-treated patients had sustained viral suppression at year 1, and drug resistance was minimal (0.8%) during the median follow-up period of 3.2 years. ETV therapy reduced the hepatocarcinogenesis risk ratio to 0.37 and also suppressed hepatocarcinogenesis in patients with LC [26]. Furthermore, in a recent cohort study with patients with LC, the 5-year hepatocarcinogenesis rate was reduced to a risk ratio of 0.55 for the ETV-treated group compared to the historical control group [27].

Based on the above two results, the JSH suggests that ETV therapy suppresses hepatocarcinogenesis [9].

**Tenofovir**

In HBeAg-positive CHB patients, TDF reduced HBV DNA levels by 4.5 log copies/ml (12-week results) and suppressed HBV DNA to undetectable levels (<10^2 IU/ml) in 76% of patients versus in only 13% in the ADV group. TDF and ADV treatments resulted in similar rates of histological benefit (74 vs. 68%) and HBeAg seroconversion (21 vs. 18%). An important finding was HBsAg loss in 3% of CHB patients during the first 48 weeks of therapy in the TDF group [17]. In the HBeAg-positive group, at the end of year 2 of continuous TDF treatment, HBeAg seroconversion increased to 27% and HBsAg loss increased to 6% [28]. In HBeAg-negative CHB patients, TDF reduced HBV DNA levels by 3.0 log copies/ml (12-week results) and suppressed HBV DNA to undetectable levels (<10^2 IU/ml) in 93% of patients versus in only 63% in the ADV group.

Patients after 3 years of TDF monotherapy reported viral suppression with HBV DNA <400 copies/ml in 72% of HBeAg-positive CHB patients and in 87% of HBeAg-negative CHB patients, with normalization of ALT in 74 and 81%, respectively. No resistance was reported, and 8% of HBeAg-positive CHB patients had a loss of HBsAg [29].

### Table 1. Summary of NA treatment in patients with HBeAg-positive and -negative CHB: 48-week post-treatment results

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>HBeAg status</th>
<th>HBV DNA suppression (log 10 copies/ml)</th>
<th>HBV DNA undetectable, %</th>
<th>ALT normalization, %</th>
<th>HBeAg seroconversion, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAM [12, 13]</td>
<td>positive</td>
<td>–5.4</td>
<td>36</td>
<td>60</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>negative</td>
<td>–4.5</td>
<td>72</td>
<td>71</td>
<td>–</td>
</tr>
<tr>
<td>ADV [14, 15]</td>
<td>positive</td>
<td>–3.5</td>
<td>21</td>
<td>48</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>negative</td>
<td>–3.9</td>
<td>51</td>
<td>72</td>
<td>–</td>
</tr>
<tr>
<td>ETV [12, 13]</td>
<td>positive</td>
<td>–6.9</td>
<td>67</td>
<td>68</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>negative</td>
<td>–5.0</td>
<td>90</td>
<td>78</td>
<td>–</td>
</tr>
<tr>
<td>TBV [16]</td>
<td>positive</td>
<td>–6.4</td>
<td>60</td>
<td>77</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>negative</td>
<td>–5.2</td>
<td>88</td>
<td>74</td>
<td>–</td>
</tr>
<tr>
<td>TDF [17]</td>
<td>positive</td>
<td>–4.5 (12 weeks)</td>
<td>76</td>
<td>68</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>negative</td>
<td>–3.0 (12 weeks)</td>
<td>93</td>
<td>76</td>
<td>–</td>
</tr>
</tbody>
</table>

Adapted from Kim et al. [6].
total of 99% of the 348 CHB patients had viral suppression with HBV DNA <400 IU/ml, with histologic improvement in 87% and regression of fibrosis in 51%. Of the 98 patients who had cirrhosis at baseline, 71% had regression of fibrosis and were no longer cirrhotic at year 5 [11].

Of 641 patients initially randomized, 585 (91.3%) entered the open-label phase; 437/585 (74.7%) remained in the study at year 7. For patients on treatment at year 7, 99.3% maintained viral suppression (HBV DNA <69 IU/ml), 80.0% achieved serum ALT normalization, and in HBeAg-positive patients, 84/154 (54.5%) and 25/154 (11.8%) achieved HBeAg and HBsAg loss, respectively. 1/375 (0.3%) HBeAg-negative patients achieved HBsAg loss. No resistance to TDF was detected during 7 years [30]. In total, 136 patients (median age 49 years, 96 males, 94 HBeAg-positive, and 51 with LC) were included. Sixty-two patients were NA-naïve and 74 patients received prior NA therapy (NA-exp group); 31 patients in the NA-exp group showed LAM resistance (LAM-R group; 5.9 ± 2.0 vs. 3.9 ± 2.0 vs. 4.2 ± 1.7 log IU/ml, p < 0.01). The complete virological response rate at week 48 in the NA-naïve group (71.4%) did not differ significantly from that in the NA-exp (71.3%) and LAM-R (66.1%) groups [31].

Following a 48-week randomized, double-blind evaluation of once-daily TDF versus once-daily ADV, open-label TDF for up to 240 weeks was evaluated. Patients with both baseline and week 240 liver biopsies were evaluated for histologic changes. At baseline, 189/641 (29%) randomized patients were Asian. Sixty-eight percent of Asian patients were male; 50% were HBeAg-positive. At week 240, similar proportions of Asian (88%) and non-Asian (87%) patients demonstrated improvement in liver histology, and 19/22 (86%) Asian patients with baseline cirrhosis were no longer cirrhotic [32].

A retrospective analysis found no decrease in the renal function associated with ETV [33].

Antiviral Resistance to NAs

Although LAM has the most extensive safety record, its current use is limited by the high frequency of LAM-R (24% in year 1 and 70% in year 4) [34].

Even though resistance to ADV is slow to emerge, resistant variants increase progressively after the first year, reaching 29% in year 5 [35]. The advantages of ADV are its limited resistance during the first 2 years, the absence of cross-resistance with LAM and other L-nucleos(t)ides and, therefore, its value as treatment for LAM-resistant CHB [36, 37] and for hepatic decompensation associated with LAM-R prior to and after liver transplantation [38]. ETV and TDF are potent HBV inhibitors, and they have a high barrier to resistance [12, 28, 39]. In a study of 96 weeks of treatment with TDF, no evidence of TDF resistance was found [40].

The frequency of antiviral resistance to telbivudine (TBV) at 1 year was 5% of HBeAg-positive and only 2% of HBeAg-negative patients [16].

Resistance should be identified as early as possible before the clinical breakthrough (i.e. increased ALT) by means of HBV DNA monitoring; if possible, the pattern of resistance mutations should be identified to adapt therapeutic strategies. Indeed, clinical and virological studies have demonstrated the benefit of an early treatment adaptation – as soon as the viral load increases (table 2) [41, 42]. Adding a second drug without cross-resistance is the only efficient strategy:

• LAM-R: add TDF (add ADV if TDF is not yet available);
• ADV resistance: it is recommended to switch to TDF if available and add a second drug without cross-resistance. If an N236T substitution is present, add LAM, ETV or TBV, or switch to TDF plus emtricitabine. If an A181T/V substitution is present, add ETV (the safety of the TDF-ETV combination is unknown) or switch to TDF plus emtricitabine;
• TBV resistance: add TDF (add ADV if TDF is not yet available). The long-term safety of these combinations is unclear;

### Table 2. Frequency of antiviral resistance to NA treatment

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Treatment duration, years</th>
<th>Antiviral resistance, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAM [34]</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>70</td>
</tr>
<tr>
<td>ADV (naïve patients) [15]</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>29</td>
</tr>
<tr>
<td>ETV (naïve patients) [19]</td>
<td>4</td>
<td>&lt;1</td>
</tr>
<tr>
<td>TBV (naïve patients) [16, 43]</td>
<td>1</td>
<td>2–5</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>11–25</td>
</tr>
<tr>
<td>TDF (naïve patients) [40]</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Adapted from Kim et al. [6].
• ETV resistance: add TDF (the safety of this combination is unknown);
• TDF resistance: resistance to TDF has not been described so far. It is recommended that genotyping and phenotyping be done by an expert laboratory to determine the cross-resistance profile. ETV, TBV, LAM, or emtricitabine could be added (the safety of these combinations is unknown).

**Treatment Failure**

Drug resistance starts with polymerase gene mutations, followed by a virological breakthrough, biochemical relapse with increased ALT, and progression of liver disease. The identified mutation and the percentage of resistance with length of treatment are outlined in Table 2 [44]. Primary nonresponse defined as <1 log copies/ml decline in HBV DNA after 12 weeks of therapy is rarely seen with a highly potent NA, but can occur in up to 20% treated with ADV. When observed in a compliant patient, treatment should be quickly modified to prevent a selection of drug-resistant mutants. Partial response can occur with any of the NAs and is defined as detectable HBV DNA at week 24 or 48 of treatment. On the basis of TBV phase III data showing high rates of resistance at 2 years of treatment if >4 log copies/ml, a road map approach has been proposed in which a second drug is added if the patient is viremic at week 24. This approach is currently being evaluated in a prospective trial but has been recommended in the most recent European guidelines [3, 45]. However, in patients with high baseline viral loads, the slope of decline must also be considered with the more potent and high genetic barrier drugs, ETV and TDF, before changing the therapy [46]. Virological breakthrough with confirmed genetic mutation necessitates treatment modification with an add-on or switch strategy (Table 2).

**Rescue Therapy**

TDF added to ETV therapy was studied as a rescue strategy in 57 CHB patients with multidrug resistance or prior partial response. Fifty-one patients had undetectable HBV DNA after a mean of 6 months, proving this to be an effective and well-tolerated strategy in a difficult-to-treat population [47]. In contrast, switching to ADV or ETV monotherapy was associated with drug resistance in 24 and 18% at a median of 18 months and failure to suppress HBV DNA. The addition of ADV to LAM was not as effective as ETV plus ADV in suppressing the viral load, but did achieve normalization of ALT in 93% at 1 year, with a resistance rate of 6%. The authors conclude that although ETV plus ADV is preferred, adding ADV to LAM-resistant patients is a reasonable option at a lower cost [48]. In 90 patients with resistance to LAM and ADV where TDF was not available, ETV and ADV was superior to continuing LAM and ADV with a 1-year viral suppression of 63 versus 15% [49].

**Long-Term Therapy with NAs**

HBV DNA levels should be monitored at week 12 to ascertain virological response, and then every 12–24 weeks. HBV DNA reduction to undetectable levels by real-time PCR (i.e. <10–15 IU/ml) should ideally be achieved to avoid resistance. Thus, HBV DNA monitoring is crucial to detect treatment failure. In HBeAg-positive patients, HBeAg and subsequently anti-HBe antibodies once HBeAg is negative should be measured at intervals of 6–12 months.

The HBsAg decline is slow and does not correlate with HBV DNA levels during NA therapy. However, a rapid HBsAg decline during NA therapy may identify patients who will finally clear HBsAg. A 6- to 12-monthly assessment of the HBsAg level could be considered during NA therapy. Taking these lines of evidence together, quantitative HBsAg can complement HBV DNA levels to optimize the management of CHB patients [50, 51]. Renal impairment has rarely been reported in patients with HIV infection receiving anti-HBV drugs, or in patients receiving nephrotoxic drugs and being treated with TDF or ADV; thus, appropriate monitoring for nephrotoxicity and dose adjustments are necessary.

**Treatment with PEG IFN-α**

PEG IFN offers a finite duration of therapy, with approximately 30% of HBeAg-positive patients achieving HBeAg seroconversion with 12 months of therapy. Given the high cost of IFN therapy associated with frequent side effects, there have been attempts to identify patients most likely to benefit from this treatment, which is recommended for those with high ALT levels (>2–5 times ULN), low HBV DNA (<2 × 10^8 IU/ml), and genotype A [3–5].

When compared to the standard IFN-α 2a at a dose of 4.5 million units 3 times weekly, PEG IFN at a dose of 180 μg once weekly for 12 months resulted in a greater decline in HBV DNA levels and a higher rate of HBeAg seroconversion (33 vs. 25%) [52]. Three large multicenter trials of PEG IFN therapy have been published – 2 in HBeAg-positive [53, 54] and 1 in HBeAg-negative CHB patients (Table 3) [55].

In a multinational European study, PEG IFN-α 2a, was given at a dose of 100 μg weekly for 32 weeks followed by
50 μg weekly until completion of 52 weeks of treatment with or without LAM (100 mg daily) in 266 CHB patients who were HBeAg-positive [53]. A comparison group receiving LAM alone was not included. In a second larger multicenter trial, a total of 814 patients with HBeAg-positive CHB were given either PEG IFN-α 2a alone (180 μg once weekly), LAM alone (100 mg daily), or the combination of both for 48 weeks [54]. Finally, in another large multicenter trial, patients with HBeAg-negative hepatitis B were treated with PEG IFN-α 2a alone (180 μg once weekly), LAM alone (100 mg daily), or the combination of both for 48 weeks [55]. These 3 studies showed that adding LAM to PEG IFN did not elevate the rate of sustained responses (table 4).

Regarding the combination therapy with IFN plus ETV, 24 HBeAg-positive CHB patients (23 men and 1 woman; mean age 39 ± 7 years) received ETV 0.5 mg alone for 36–52 weeks, followed by ETV plus IFN-α for 4 weeks, and lastly IFN-α alone for 46 weeks. Twenty-three patients had genotype C infection, and 1 had genotype A infection. The rate of response to sequential therapy with ETV and IFN-α in Japanese patients with HBeAg-positive CHB was not higher than the rate in previous studies of LAM therapy followed by IFN [56].

Earlier studies showed that HBV genotypes A and B had a better response to IFN and PEG IFN treatment than genotypes D and C, respectively [57]. Patients with genotype C had a lower response than those with genotype B when treated with a lower dosage of PEG IFN-α 2a (90 μg) or for a shorter duration (24 weeks) [52]. However, the most recent NEPTUNE study has confirmed a comparable response to PEG IFN-α 2a 180 μg weekly for 48 weeks between genotype B and C patients [58]. Pooled data from the 2 largest studies of HBeAg-positive patients receiving PEG IFN treatment showed that genotype A patients with higher levels of baseline ALT or lower levels of HBV DNA, and genotype B and C patients with both higher ALT levels and lower HBV DNA levels had a high predicted probability of treatment response [59].

### Table 3. Antiviral resistance and rescue therapy

<table>
<thead>
<tr>
<th>Resistance</th>
<th>Rate of resistance</th>
<th>Mutation</th>
<th>First-line therapy</th>
<th>Second-line therapy</th>
<th>Third-line therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAM</td>
<td>80% at 5 years</td>
<td>M204I/V</td>
<td>EASL: switch to TDF</td>
<td>EASL: add ADV</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>L180M</td>
<td>APASL: add ADV or LAM</td>
<td>APASL: switch to TDF</td>
<td></td>
</tr>
<tr>
<td>ADV</td>
<td>42% of HBeAg⁺ and 29% of HBeAg⁺ at 5 years</td>
<td>N236T</td>
<td>EASL: switch to ETV or TDF + entecựcabine</td>
<td>Switch to ETV 1 mg daily (an option, but not preferred)</td>
<td></td>
</tr>
<tr>
<td>ADV + LAM</td>
<td>20% of LAM resistance at 1 year</td>
<td>A181T/Y</td>
<td>EASL: switch to TDF and add ETV or LAM</td>
<td>EASL: add ADV</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>A181T/V + N236T</td>
<td>APASL: switch to TDF + ETV</td>
<td>APASL: switch to TDF + ETV; may have decreased response to TDF; TDF monotherapy not recommended</td>
<td></td>
</tr>
<tr>
<td>TBV</td>
<td>25% of HBeAg⁺ and 11% of HBeAg⁺ at 2 years</td>
<td>M204I/V</td>
<td>EASL: switch to or add TDF</td>
<td>EASL: add ADV</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>L180M</td>
<td>APASL: add ADV or switch to TDF</td>
<td>APASL: add ADV or TDF</td>
<td></td>
</tr>
<tr>
<td>ETV</td>
<td>1.2% at 6 years, 56% of LAM-R at 6 years</td>
<td>L180M + M204I/I ± I169T ± V173L ± M250V</td>
<td>EASL: switch to or add TDF</td>
<td>EASL: add ADV</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>L180M + M204I/I ± I169T ± V173L ± M250V</td>
<td>APASL: add ADV or switch to TDF</td>
<td>APASL: add ADV or TDF</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>L180M + M204I/I ± I169T ± V173L ± M250V</td>
<td>AASLD: add ADV or TDF</td>
<td>AASLD: add ADV or TDF</td>
<td></td>
</tr>
<tr>
<td>TDF</td>
<td>No mutations identified</td>
<td>No mutations identified</td>
<td>EASL: add ADV</td>
<td>EASL: add ADV</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Tujios and Lee [7].

* Rate of ETV resistance 56% at 6 years in those with LAM resistance.

* A181T/Y + N236 mutations may have a decreased response to TDF, and TDF monotherapy is not recommended.
Several studies have now analyzed the effect of the IL28B genotype on HBeAg-positive CHB patients with variable results [60–63].

Retrospective analysis of HBeAg-positive CHB patients enrolled in the NEPTUNE study revealed that none of the patients with HBsAg >20,000 IU/ml at week 12 had anti-HBe 6 months after the end of IFN treatment [58].

According to prior studies, a week 12 stop rule for a lack of HBsAg decline or an HBsAg level >20,000 IU/ml may be employed to prevent futile treatment [64].

In HBeAg-negative patients, a >10% decline in HBsAg at weeks 12 and 24 predicted sustained response (HBV <2,000 IU/ml and normal ALT level 6 months after treatment), whereas no HBsAg decline and <2 log copies/ml HBV DNA predicted no response. Even in the HBeAg-negative patients with an HBsAg decline at week 12, sustained response to IFN remains around 50% [65].

Although there was no difference at the end of treatment, 29% of those treated for 96 weeks had HBV DNA <2,000 IU/ml compared to 12% of those treated for 48 weeks (p = 0.03); 3 patients in the 96-week group had a loss of HBsAg versus none in the other group [66]. A personalized, response-guided, extended IFN treatment regimen looms on the horizon [67].

Concerning suppression of hepatocarcinogenesis by IFN therapy, 4 available data analyses were published. One analysis of 11 studies comprising 1,006 patients treated with IFN and 1,076 untreated controls found that IFN therapy significantly reduced the carcinogenesis risk ratio to 0.59 [68]. Another meta-analysis of 8 studies found that, although hepatocarcinogenesis was suppressed in IFN-treated patients compared to untreated controls (risk difference 5.0%), the hepatocarcinogenesis suppression effect was found in a subgroup of ethnic Asians [69]. A meta-analysis of 7 studies evaluated the therapeutic effect of IFN in patients with cirrhosis, 122 cases of HCC developed in 1,505 patients with LC, and a hepatocarcinogenesis risk difference of 6.4% in IFN-treated patients compared to untreated controls [70]. Lastly, in a meta-analysis of 12 studies examining 1,292 IFN-treated patients and 1,450 untreated controls, IFN therapy significantly reduced the hepatocarcinogenesis risk ratio to 0.66 [71].

Based on these results, the JSH suggests that suppression of hepatocarcinogenesis by IFN therapy has been confirmed by meta-analyses [9].

### Conclusions

At present, for adults with HBV infection, 2 new analogues, i.e. ETV and TDF, are recommended as the first-line therapy by the EASL, AASLD, and APASL guidelines. On the other hand, regarding IFN therapy, the use of PEG IFN-α is recommended as the first-line therapy instead of standard IFN-α by the above-mentioned 3 guidelines.

These treatments should suppress the incidence of HCC although surveillance of HCC, and risk assessment by ultrasound elastography [72], CT, MRI [73–75], and tumor markers [76, 77] are necessary during these treatments to detect HCCs in their early stage.

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**Table 4. Summary of combination therapy of PEG INF and LAM in CHB patients 24 weeks following treatment**

<table>
<thead>
<tr>
<th>HBeAg status</th>
<th>Treatment arms</th>
<th>n</th>
<th>HBV DNA suppression, %</th>
<th>HBV DNA undetectable, %</th>
<th>ALT normalization, %</th>
<th>HBeAg seroconversion, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>PEG IFN 100 μg/week × 32 weeks -&gt;50 μg × 20 weeks</td>
<td>136</td>
<td>27</td>
<td>7</td>
<td>32</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>PEG IFN 100 μg/week × 32 weeks -&gt;50 μg × 20 weeks + LAM</td>
<td>130</td>
<td>32</td>
<td>9</td>
<td>35</td>
<td>29</td>
</tr>
<tr>
<td>Positive</td>
<td>PEG IFN 180 μg/week × 48 weeks</td>
<td>271</td>
<td>32</td>
<td>14</td>
<td>41</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>PEG IFN 180 μg/week + LAM 48 weeks</td>
<td>271</td>
<td>34</td>
<td>14</td>
<td>39</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>LAM for 48 weeks</td>
<td>272</td>
<td>22</td>
<td>5</td>
<td>28</td>
<td>19</td>
</tr>
<tr>
<td>Negative</td>
<td>PEG IFN 180 μg/week × 48 weeks</td>
<td>177</td>
<td>43</td>
<td>19</td>
<td>59</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>PEG IFN 180 μg/week + LAM 48 weeks</td>
<td>179</td>
<td>44</td>
<td>20</td>
<td>60</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>LAM for 48 weeks</td>
<td>181</td>
<td>29</td>
<td>7</td>
<td>44</td>
<td>–</td>
</tr>
</tbody>
</table>

Adapted from Kim et al. [6].
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Disclosure Statement

The authors declare that they have no financial conflicts of interest.

References

Management of Chronic Hepatitis B


