Review of Hepatitis B Therapeutics

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Currently, there are 7 approved therapies for chronic hepatitis B virus (HBV) infection, an increase from just 3 agents 5 years ago. This review will focus on the pharmacology, potency, and adverse events associated with immunomodulatory agents and nucleos(t)ide analogues, with an emphasis on targets of therapy within the HBV life cycle. We will also offer guidelines for the use of available anti-HBV agents and review the emerging challenges in hepatitis B management, including HBV drug resistance, its management, and the potential role of combination therapy.

Hepatitis B virus (HBV) infection affects ~350 million people globally and is a leading cause of end-stage liver disease, hepatocellular carcinoma, and mortality [1]. New therapeutic agents have increased the options for HBV treatment, but because the current agents often require lifelong administration, optimizing initial therapy is essential. This review will focus on the pharmacology and adverse events associated with anti-HBV drugs and offer guidelines for their use.

LIFE CYCLE OF HBV

Knowledge of the HBV life cycle is important for understanding therapeutic approaches to HBV infection [2]. HBV is an enveloped, partially double-stranded DNA virus with 4 overlapping reading frames: the precore/core gene; the polymerase gene; the L, M, and S genes, which encode for the 3 envelope proteins; and the X gene (Figure 1). HBV enters the hepatocyte through an unidentified receptor and is uncoated in the cytoplasm; then the DNA is transported to the nucleus. There, the relaxed, circular, partially double-stranded DNA is converted to covalently closed circular DNA (cccDNA), a stable episomal form that becomes the template for viral messenger RNA transcription. In the cytoplasm, the pregenomic RNA (pgRNA) is translated into the core protein and the viral polymerase, and the subgenomic RNA is translated into the 3 envelope proteins and the X protein. pgRNA is reverse transcribed into DNA by the HBV polymerase, the site of action of the oral anti-HBV therapeutics. The DNA can either be reimported into the nucleus to form additional cccDNA or be enveloped for secretion. Because the available anti-HBV therapeutic agents do not work directly against the cccDNA, eradication of HBV is difficult.

CURRENTLY APPROVED THERAPIES

Standard Interferon Alfa and Pegylated Interferon Alfa

Interferon alfa enhances the innate immune response by binding to the type 1 interferon receptor, resulting in activation of the Jak-Stat pathway [4] and up-regulation of multiple interferon-stimulated genes, which limit viral dissemination. With the addition of polyethylene glycol, pegylated interferon alfa has a longer half-life than interferon alfa. Although there are 2 formulations of pegylated interferon alfa—2a and 2b—only the former is approved in the United States for chronic hepatitis B treatment.

The dose of pegylated interferon alfa-2a is 180 μg given subcutaneously once per week. The maximum concentration occurs 72–96 h after administration, with levels sustained for up to 168 h. It is cleared by both the kidney and liver but should be used with caution in patients with creatinine clearance (CrCl) <50 mL/min, with dose adjustment required for patients undergoing hemodialysis (Table 1). It should also be used with caution in patients receiving theophylline, whose level it increases. Adverse events occurring in >25% of patients include pyrexia, myalgia, and headache, which can be ameliorated by pretreatment with nonsteroidal anti-inflammatory agents. Other adverse events include fatigue, arthralgia, alopecia, diarrhea, anorexia, insomnia, hypo- or hyperthyroidism, irritability, and depression. Pegylated interferon alfa is contraindicated in patients with untreated or severe depression and with decompensated cirrhosis [5].
In hepatitis B e antigen (HBeAg)-positive subjects, pegylated interferon alfa is superior to standard interferon alfa [6]. The recommended 48 weeks of pegylated interferon alfa results in HBV DNA loss in 25% and 63% of patients with HBeAg-positive and HBeAg-negative chronic hepatitis B, respectively (Table 2) [7].

Nucleos(t)ide Analogues
Nucleos(t)ide analogues are oral agents that can be grouped by structure and function into 3 groups: the L-nucleosides, acyclic phosphonates, and others.

L-nucleosides. The L-nucleosides include lamivudine, emtricitabine, and telbivudine. Lamivudine and emtricitabine are cytidine analogues, and telbivudine is a thymidine analogue. They are phosphorylated intracellularly to 5'-triphosphate active metabolites and inhibit HBV DNA polymerase by competing with natural substrates for incorporation into viral DNA, with resulting chain termination [8–10]. As a class, adverse events include hepatic steatosis, lactic acidosis, and hepatic flares after discontinuation of drug. L-nucleosides do not affect the cytochrome P450 system and do not have significant drug-drug interactions. Their bioavailability is not affected by food and all are excreted renally, requiring dose adjustment for patients with CrCl <50 mL/min (Table 1). Lamivudine and emtricitabine are active against human immunodeficiency virus (HIV), whereas the anti-HIV activity of telbivudine is controversial [11, 12].

Lamivudine is potent but is limited by the rapid development of resistance. The 100-mg dose of lamivudine results in a peak plasma concentration of 1.28 ± 0.56 μg/mL, which occurs between 0.5 and 2 h after administration. The mean half-life is 5–7 h [9].

In patients with chronic hepatitis B, lamivudine is associated with histologic improvement, HBeAg antibody (anti-HBe) seroconversion, and normalization of alanine aminotransferase (ALT) level in 56%, 16%, and 72% of patients, respectively [13].

Emtricitabine, given at a dose of 200 mg orally, is not approved by the US Food and Drug Administration for HBV treatment, but it has been extensively used with tenofovir in HIV/HBV-coinfected patients. It reaches a peak plasma concentration of 1.8 ± 0.7 μg/mL at 1–2 h and has a plasma half-life of 10 h [8]. It has slightly greater potency and efficacy than lamivudine but cannot be used as monotherapy because of high rates of resistance [14].

Telbivudine is effective at 600 mg daily and is excreted renally unchanged. A peak plasma concentration of 3.69 ± 1.25 μg/mL is reached 1–4 h after administration, and the drug has a long intracellular half-life (15 h) [10]. Unique adverse events that are uncommon include myopathy, elevation in creatine kinase level, and peripheral neuropathy. Although it has been demonstrated that telbivudine produces improved reductions in HBV DNA level compared with lamivudine, there is no difference in normalization of ALT level, HBeAg loss, or anti-HBe seroconversion (Table 2) [15].

Acyclic diphosphonates. The 2 drugs in this group are adefovir dipivoxil (adefovir) and tenofovir disoproxil fumarate (TDF), with adefovir being the least potent anti-HBV agent and TDF being one of the most potent. This difference in potency is due to the achievable drug levels of these 2 agents...
Table 1. Dose Adjustments for Renal Insufficiency

<table>
<thead>
<tr>
<th>Drug, creatinine clearance</th>
<th>Recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pegylated interferon alfa-2a</strong></td>
<td></td>
</tr>
<tr>
<td>&gt;50 mL/min</td>
<td>180 µg subcutaneously every week</td>
</tr>
<tr>
<td>ESRD (HD patients)</td>
<td>135 µg subcutaneously every week</td>
</tr>
<tr>
<td><strong>Lamivudine</strong></td>
<td></td>
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<tr>
<td>&gt;50 mL/min</td>
<td>100 mg orally every day</td>
</tr>
<tr>
<td>30–49 mL/min</td>
<td>100 mg for first dose, then 50 mg every day</td>
</tr>
<tr>
<td>15–29 mL/min</td>
<td>35 mg for first dose, then 25 mg every day</td>
</tr>
<tr>
<td>5–14 mL/min</td>
<td>35 mg for first dose, then 15 mg every day</td>
</tr>
<tr>
<td>&lt;5 mL/min</td>
<td>35 mg for first dose, then 10 mg every day</td>
</tr>
<tr>
<td><strong>Emtricitabine</strong></td>
<td></td>
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<tr>
<td>&gt;50 mL/min</td>
<td>200 mg every 24 h</td>
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<tr>
<td>30–49 mL/min</td>
<td>200 mg every 48 h</td>
</tr>
<tr>
<td>15–29 mL/min</td>
<td>200 mg every 72 h</td>
</tr>
<tr>
<td>&lt;15 mL/min or HD</td>
<td>200 mg every 96 h (after dialysis)</td>
</tr>
<tr>
<td><strong>Telbivudine</strong></td>
<td></td>
</tr>
<tr>
<td>&gt;50 mL/min</td>
<td>600 mg every day</td>
</tr>
<tr>
<td>30–49 mL/min</td>
<td>600 mg every 48 h</td>
</tr>
<tr>
<td>&lt;30 mL/min (without dialysis)</td>
<td>600 mg every 72 h</td>
</tr>
<tr>
<td>ESRD (dialysis patients)</td>
<td>600 mg every 96 h after HD</td>
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<tr>
<td><strong>Adefovir</strong></td>
<td></td>
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<tr>
<td>&gt;50 mL/min</td>
<td>10 mg every day</td>
</tr>
<tr>
<td>30–49 mL/min</td>
<td>10 mg every other day</td>
</tr>
<tr>
<td>10–29 mL/min</td>
<td>10 mg every third day</td>
</tr>
<tr>
<td>HD patients</td>
<td>10 mg every week after dialysis</td>
</tr>
<tr>
<td><strong>Tenofovir</strong></td>
<td></td>
</tr>
<tr>
<td>&gt;50 mL/min</td>
<td>300 mg every 24 h</td>
</tr>
<tr>
<td>30–49 mL/min</td>
<td>300 mg every 48 h</td>
</tr>
<tr>
<td>10–29 mL/min</td>
<td>300 mg every 72–96 h</td>
</tr>
<tr>
<td>&lt;10 mL/min with dialysis</td>
<td>300 mg every week or after 12 h of dialysis</td>
</tr>
<tr>
<td>&lt;10 mL/min without dialysis</td>
<td>No recommendation available</td>
</tr>
<tr>
<td><strong>Entecavir</strong></td>
<td></td>
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<tr>
<td>&gt;50 mL/min</td>
<td>1 mg every day</td>
</tr>
<tr>
<td>30–49 mL/min</td>
<td>0.5 mg every day or 1 mg every 48 h</td>
</tr>
<tr>
<td>10–29 mL/min</td>
<td>1 mg every 72 h</td>
</tr>
<tr>
<td>&lt;10 mL/min or HD or CAPD</td>
<td>1 mg every 7 days (after dialysis)</td>
</tr>
</tbody>
</table>

**NOTE.** Adapted from Lok and McMahon [7]. CAPD, continuous ambulatory peritoneal dialysis; ESRD, end-stage renal disease; HD, hemodialysis.

Lamivudine, emtricitabine, telbivudine, and entecavir are all available in oral solution. Oral solution dosing can be found in the package inserts. Dosing information is given for 1-mg dose. Entecavir 0.5-mg dosing information can be found in the package insert.

at their recommended doses. They are analogues of adenosine monophosphate that undergo intracellular phosphorylation to their active metabolite, which inhibits the HBV polymerase by competitive inhibition with deoxyadenosine 5’-triphosphate, resulting in chain termination [16, 17].

The major adverse event of this class is nephrotoxicity. Adefovir was first associated with proximal renal tubular dysfunction and Fanconi syndrome in HIV infection at doses of 60 and 120 mg daily [18, 19]. Although significant elevations in creatinine levels were absent at a 10-mg dose at 48 weeks in HBV infection [20], renal impairment has been reported during long-term follow-up [16, 21]. Thus, caution is advised for those with underlying renal dysfunction and for patients taking concomitant nephrotoxic agents [16, 17]. Hepatic flares after discontinuation are noted in both. In addition to class adverse events, decreased bone mineral density has been associated with TDF in HIV infection [17]. These agents do not affect the cytochrome P450 system.

The dose of adefovir is 10 mg daily, which results in peak plasma concentrations of 0.018 ± 0.006 µg/mL between 0.6
Table 2. Comparisons of Antiviral Agent Efficacy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo/control groups from studies</th>
<th>Pegylated interferon for 48 weeks</th>
<th>Adefovir for 48 weeks</th>
<th>Lamivudine for 48–52 weeks</th>
<th>Telbivudine for 52 weeks</th>
<th>Entecavir for 48 weeks</th>
<th>Tenofovir for 48 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of serum HBV DNAa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>HBeAg positive</td>
<td>0–17</td>
<td>25</td>
<td>21</td>
<td>40–44</td>
<td>60</td>
<td>67</td>
<td>76</td>
</tr>
<tr>
<td>HBeAg negative</td>
<td>0–20</td>
<td>63</td>
<td>51</td>
<td>60–73</td>
<td>88</td>
<td>90</td>
<td>93</td>
</tr>
<tr>
<td>Loss of HBeAg</td>
<td>6–12</td>
<td>30/34b</td>
<td>24</td>
<td>17–32</td>
<td>26</td>
<td>22</td>
<td>...</td>
</tr>
<tr>
<td>Anti-HBe seroconversion</td>
<td>4–6</td>
<td>27/32b</td>
<td>12</td>
<td>16–21</td>
<td>22</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Loss of HBsAg</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>HBeAg positive</td>
<td>0–1</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>3.2</td>
</tr>
<tr>
<td>Normalization of ALT level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBeAg positive</td>
<td>7–24</td>
<td>39</td>
<td>48</td>
<td>41–75</td>
<td>77</td>
<td>68</td>
<td>68</td>
</tr>
<tr>
<td>HBeAg negative</td>
<td>10–29</td>
<td>38</td>
<td>72</td>
<td>60–79</td>
<td>74</td>
<td>78</td>
<td>76</td>
</tr>
<tr>
<td>Histologic improvement</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>HBeAg positive</td>
<td>...</td>
<td>38c</td>
<td>53</td>
<td>49–56</td>
<td>65</td>
<td>72</td>
<td>74</td>
</tr>
<tr>
<td>HBeAg negative</td>
<td>33</td>
<td>48</td>
<td>64</td>
<td>60–66</td>
<td>67</td>
<td>70</td>
<td>72</td>
</tr>
<tr>
<td>Durability of response</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBeAg positive</td>
<td>...</td>
<td>...</td>
<td>90</td>
<td>50–80</td>
<td>80</td>
<td>69</td>
<td>...</td>
</tr>
<tr>
<td>HBeAg negative</td>
<td>...</td>
<td>20</td>
<td>5</td>
<td>&lt;10</td>
<td>...</td>
<td>3</td>
<td>...</td>
</tr>
</tbody>
</table>

NOTE. Modified from Lok and McMahon [7]. Data are percentage of patients. Anti-HBe, HBeAg antibody; ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

a Some lamivudine studies used hybridization or branched-chain DNA assays (lower limit of detection, 20,000–200,000 IU/mL). All other studies used polymerase chain reaction assays (lower limit of detection, ∼50 IU/mL).
b Responses at week 48/week 72 (24 weeks after stopping treatment).
c Biopsy performed at week 72 (24 weeks after stopping treatment).

and 4 h. It is unaffected by food and is excreted renally, requiring dose adjustment for patients with CrCl <50 mL/min [16]. Clinical trials with adefovir and placebo have shown modest benefits in HBeAg-positive and HBeAg-negative subjects [20, 22].

The TDF dose is 300 mg daily, with adjustment recommended for patients with CrCl <50 mL/min (Table 1). TDF is excreted renally, with maximum serum concentrations ∼10-fold higher than adefovir (0.30 ± 0.09 µg/mL) being achieved 1 h after administration [17]. The serum elimination half-life is 17 h, whereas the intracellular half-life is 95 h [23]. TDF oral bioavailability is increased after a high-fat meal.

In HIV/HBV-coinfected subjects, there are significant drug interactions between TDF and both atazanavir and didanosine [17]. When administered with TDF, the minimum concentration of atazanavir is reduced by 40%; thus, ritonavir should be given with atazanavir to increase atazanavir levels. When TDF and didanosine are coadministered, the area under the curve for didanosine increases from 14% to 60%; therefore, patients should not receive didanosine and TDF.

In a randomized trial of HBeAg-negative and HBeAg-positive chronic hepatitis B, a higher percentage of subjects receiving TDF had an HBV DNA level <400 copies/mL, compared with subjects receiving adefovir [24]. In HBeAg-positive subjects, the biochemical response was higher with TDF, but anti-HBe seroconversion rates and histologic response were similar between adefovir and TDF [24].

Others. Currently, the only agent in the other group is entecavir, a guanosine analogue that is one of the most potent anti-HBV agents. Its mechanism of action is unique because it inhibits the 3 functions of the HBV DNA polymerase: priming of the HBV DNA polymerase, reverse transcription of the negative strand from the pregenomic messenger RNA, and synthesis of positive-strand HBV DNA [25].

The recommended dose is 0.5 mg for nucleoside-naive patients and 1.0 mg for patients who had used lamivudine previously, with dose adjustment for patients with CrCl <50 mL/min (Table 1). Entecavir is predominantly cleared by the kidneys, with peak plasma concentrations of 0.0082 µg/mL for the 1.0-mg dose occurring between 0.5 and 1.5 h after ingestion [25]. Despite low plasma concentrations, entecavir is potent because of a long intracellular half-life that results in significant accumulation of intracellular entecavir triphosphate [26]. It should be taken on an empty stomach.

In general, adverse events are mild and include headache, diarrhea, arthralgia, and insomnia. However, a recent report documented lactic acidosis in 5 of 16 patients with cirrhosis who were treated with entecavir. All 5 patients had Model for End-Stage Liver Disease scores ≥20 [27]. In randomized trials, HBeAg-positive and HBeAg-negative subjects receiving ente-
cavir had improved histologic responses, higher percentages of 
HBV DNA suppression, and higher percentages of normali-
zation or improvement of ALT levels, compared with subjects 
receiving lamivudine [28, 29]. In HBeAg-positive subjects, there 
was no difference in anti-HBe seroconversion rates [29].

Entecavir is active against HIV and, when given as mono-
therapy, can result in the HIV lamivudine resistance mutation, 
rtM184V, thus limiting HIV therapeutic options [30]. As with 
patients receiving tenofovir, lamivudine, or emtricitabine, pa-
tients receiving entecavir should be tested for HIV infection. 
Entecavir should not be used in HIV/HBV-coinfected patients 
with uncontrolled HIV viremia.

POTENCY AND RESISTANCE

Potency and the genetic barrier to resistance are the 2 most 
important considerations in deciding which agent or agents to 
use. The ideal drug is one that is potent and has a high barrier 
to resistance. Although potency is difficult to quantify, some 
investigators have used a semiquantitative scale based on the 
rapidity of viral load suppression (Figure 2).

The genetic barrier to resistance determines how quickly 
resistance develops and is qualitatively determined by the num-
ber of mutations required for resistance and the ease with which 
those mutations occur. Lamivudine has the lowest barrier to 
resistance, which develops with 1 mutation (rtM204V) [31]. Entecavir has a high barrier to resistance, because at least 3 
mutations are required [32]. Figure 2 illustrates the relative 
potency versus the relative barrier to resistance of each of the 
nucleos(t)ide analogues and shows that TDF and entecavir have 
the most favorable characteristics.

It is easiest to understand drug-resistant HBV on the basis 
of the nucleos(t)ide groups described above. The L-nucleosides 
share the primary resistance mutation, rtM204V/I. Thus, if 
HBV resistant to one of these drugs emerges, then the virus is 
resistant to all others in the group. Because rtM204V/I occurs 
easily, resistance rates are highest with these drugs. After 4 years 
of lamivudine monotherapy, rtM204V/I develops in 70% [33] 
and 90% [34] of patients with HBV monoinfection and HIV/ 
HBV coinfection, respectively. For emtricitabine, the rate of 
resistance among patients with HBV monoinfection is 18% at 
96 weeks [35]; for telbivudine, the rate is 25% after 96 weeks 
among HBeAg-positive patients [36].

Once rtM204V/I emerges, compensatory mutations can de-
velop, including rtV173L and/or rtL180M, which can enhance 
replication fitness [37]. Because of overlapping reading frames, 
HBV polymerase mutations also lead to changes in hepatitis B 
surface antigen (HBsAg), which may potentially lead to serious 
consequences. For example, the rtM204V+rtV173L+rtL180M 
triple-polymerase mutant leads to envelope changes that behave 
as a vaccine escape mutant in vitro [38].

For the acyclic phosphonates, the primary adefovir resistance 
mutation is rtN236T, although rtA181V/T has also been de-
scribed. In one study, either mutation occurred in 20% of 
HBeAg-positive patients after a median of 5 years [39]. Al-
though viruses with rtN236T are not resistant to TDF, they 
have a slower response to TDF than do wild-type viruses [23].

Primary TDF resistance mutations have not been well defined. 
One study reported rtA194T as a TDF resistance mutation [40]; 
however, this pattern was not confirmed in another study [23] 
and was not associated with nonresponse to TDF in a third 
study [41]. Thus, long-term studies of patients receiving TDF 
are needed to define TDF-resistant HBV.

Resistance to entecavir requires a baseline rtM204V/I and 
rtL180M mutation plus either rtT184S/A/I/L, rtS202G/C, or 
rtM250L [32]. Among nucleoside-naive patients the rate of 
entecavir resistance is ≈1% after 5 years [42, 43], whereas 
among patients with preexisting rtM204V/I the rate of enteca-
vir resistance is 51% after 5 years [42].

TREATMENT OF CHRONIC HEPATITIS B

The therapeutic goal of treatment of chronic hepatitis B is to 
decrease the risk of cirrhosis and hepatocellular carcinoma. 
Suppression of HBV replication and anti-HBe seroconversion 
are surrogate markers of this goal. Criteria for initiation of 
therapy from various guidelines use HBV DNA level along with 
an assessment of liver disease (Table 3).

Recommendations for Therapy

In treatment-naive patients, TDF and entecavir are the pre-
ferred choices, because they are potent and have high genetic 
barriers to resistance. In patients with or at risk for renal in-
sufficiency, entecavir is preferred. Peglated interferon alpha 
may be considered in patients who do not have cirrhosis, have a 
low HBV DNA level, and have an elevated ALT level. Although
telsbivudine is a potent agent, its resistance rate precludes its use as first-line therapy. It could be considered as a second-line agent with careful monitoring of HBV DNA levels to minimize the risk of development of resistance. Lamivudine and emtricitabine should not be used as monotherapy, given their high rates of resistance. Because of its low potency, adefovir is not recommended as single-agent therapy.

Special Populations

HIV/HBV coinfection. Several guidelines recommend the use of combination therapy with TDF-emtricitabine and TDF-lamivudine, because these drugs are also used as first-line anti-HIV agents [44]. Entecavir should not be used unless HIV viremia is suppressed (see above). Pegylated interferon alfa has not been tested in HIV/HBV coinfection, but studies of standard interferon alfa therapy before highly active antiretroviral therapy demonstrated poor efficacy [45]; thus, pegylated interferon alfa is a second-line option.

HBV/HCV coinfection. The recommended treatment for HBV/HCV coinfection is pegylated interferon and ribavirin, as per HCV guidelines. Patients in whom HBV DNA is still detectable or rebounds after pegylated interferon discontinuation should subsequently be treated with HBV nucleos(t)ide analogues [46].

Chemotherapy and immunosuppressive therapy. All patients receiving immunosuppressive therapy or chemotherapy, including anti–tumor necrosis factor α agents, should be screened for HBsAg and anti-HBc. Those who are HBsAg positive should have their HBV DNA level determined. If criteria are met for HBV treatment, then treatment should be initiated. Those with an HBV DNA level ≤2000 IU/mL should receive therapy during chemotherapy and for 6 months after completion of chemotherapy. Those with an HBV DNA level >2000 IU/mL should receive therapy until standard treatment end points are met. If treatment criteria are not met and HBV DNA is undetectable, then prophylaxis to prevent reactivation with lamivudine or telsbivudine for short-course immunosuppressive therapy (<12 months) or with tenofovir or entecavir for longer immunosuppressive therapy is recommended. Patients positive for anti-HBc alone or for both anti-HBc and anti-HBs should be monitored closely for elevations in HBV DNA level and treated if HBV viremia occurs [7, 46, 47].

Combination Therapy

Combination therapy has not been consistently associated with increased virologic suppression, but decreased resistance has been demonstrated. In patients with HBV monoinfection, adefovir with either lamivudine or emtricitabine have been associated with greater HBV suppression [48, 49], but this has not been demonstrated for other combinations [50, 51]. In HIV/HBV-coinfected patients naive to therapy, the TDF-lamivudine combination was superior to lamivudine monotherapy, but it was not superior to TDF monotherapy [52]. Similarly, although combination therapy reduces the incidence of resistance to drugs with low barriers of resistance [53], it is unknown whether this will occur with TDF or entecavir combinations, because resistance rates are already low with these agents. Currently, combination therapy is recommended in patients with HIV coinfection [7, 44, 46, 47, 54, 55], patients with drug resistance [7, 46, 47], and patients with decompensated cirrhosis [47].

Suppression with Lamivudine Monotherapy

Despite high resistance rates, some patients experience continued virological suppression during lamivudine monotherapy. Data to guide optimal management of these patients do not exist. Some recommend changing to a more potent agent [7], such as tenofovir, which is preferred over entecavir in this situation because entecavir and lamivudine share resistance mutations. Others recommend basing the decision on the duration of lamivudine therapy, such that lamivudine is continued in those with 2 or more years of lamivudine therapy who experienced suppression within 6–12 months, with careful evalu-
traditional remedy for transaminitis and HBV DNA reactivation [56]; in all others, therapy is changed to tenofovir.

Management of HBV Drug Resistance

Lamivudine resistance. The options for lamivudine resistance include changing to TDF, adding TDF, or changing to TDF-emtricitabine. Some advocate the latter two on the basis of extension of adefovir studies that show a 0%-2% rate of adefovir resistance [57, 58] when added to a failing lamivudine regimen, compared with a 21% (3 of 14) rate of adefovir resistance when lamivudine is replaced by adefovir [58]. Entecavir is not recommended, because rates of entecavir resistance are high with preexisting lamivudine resistance [42]; however, if TDF cannot be used, then it is a second-line option with careful HBV DNA monitoring.

Adefovir resistance. A change to combination TDF-lamivudine or TDF-emtricitabine should be considered for adefovir resistance. Although TDF monotherapy has been used [59, 60], in vitro evidence suggests a 3-4-fold decreased activity of TDF resistance. Although TDF monotherapy has been used [59, 60], in vitro evidence suggests a 3-4-fold decreased activity of TDF resistance. Although TDF monotherapy has been used [59, 60], in vitro evidence suggests a 3-4-fold decreased activity of TDF in this setting [23].

Entecavir resistance. Both adefovir and TDF retain activity against entecavir-resistant virus, with TDF being preferred because of its higher potency. As yet, there are no clinical trial data to further guide management [7].

Duration of Therapy and Follow-up

In HBeAg-positive patients, many consider cessation of therapy 6-12 months after anti-HBe seroconversion [7, 46, 47]. In patients with cirrhosis, for whom rebound hepatitis can be severe, many experts continue therapy indefinitely. In HBeAg-negative patients, duration of therapy with the currently available agents should be lifelong, given the high incidence of rebound viremia and transaminitis after therapy cessation [61].

With the nucleos(t)ide analogues, HBV DNA should be measured at 12 and 24 weeks. If virologic suppression is achieved, then HBV DNA can be monitored every 24 weeks thereafter [47]. In patients with HBeAg-positive chronic hepatitis B, HBeAg and anti-HBe should be monitored every 6 months. In addition, monitoring for hepatocellular carcinoma should occur every 6 months in high-risk patients [7].

SUMMARY

Over the last several years, several new agents have been added to the armamentarium of drugs against HBV infection. Currently, the optimal agents for first-line therapy are entecavir, TDF, and, in some situations, potentially pegylated interferon. Several challenges in this field remain, including the inability to eradicate a latent reservoir of HBV, emerging drug resistance, and the need to define the role of optimal combination antiviral therapy.

References


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