1. Introduction

It is estimated that around 400 million people are infected with chronic hepatitis B (CHB) globally. The majority are from the Asia-Pacific region. Up to 40% of these patients will develop cirrhotic complications and hepatocellular carcinoma (HCC) [1]. In endemic areas such as Asia, HBV is most commonly acquired in the perinatal period or during early childhood. The immune tolerance and immune clearance phases are prolonged [2]. HBV e antigen (HBeAg) seroconversion has been commonly regarded as a sign of disease remission and a treatment end point. However, significant proportions of patients with CHB still have active disease and may develop disease complications after HBeAg seroconversion [2]. High levels of serum HBV DNA is now regarded as the major risk factor for disease progression to end-stage cirrhosis, cirrhotic complication and HCC [3,4]. Long-lasting suppression of HBV replication with effective antiviral therapy has been linked to a reduced risk of disease progression [5]. Hence, the goal of antiviral therapy for CHB is to provide prolonged suppression of HBV replication.

Studies have also demonstrated that profound viral suppression in the early course of therapy is associated with increased likelihood of achieving clinically important treatment end points and lower incidence of viral resistance [6].

The two classes of agents for CHB treatment currently available are the immunomodulatory therapy and the nucleoside/nucleotide analogs (NA). The former includes conventional IFN and PEG IFN-α2a and -α2b. These agents are to be
used with a finite duration of therapy. But the side effects are poorly tolerated, and the long-term benefits in terms of lower incidence of cirrhosis complications and HCC in Asian patients are controversial [7-9].

The five approved oral NAs for the treatment of CHB include lamivudine, adefovir dipivoxil, entecavir, telbivudine (Box 1) and tenofovir disoproxil fumarate (Table 1). These agents have relatively fewer side effects and are generally well tolerated. However, hepatic flares and occasional hepatic decompensation can result from patient non-compliance or the development of drug-resistant mutations in long-term NA therapy [10]. Infrequent but important adverse events such as myopathy, neuropathy, lactic acidosis, pancreatitis and renal impairment have been reported during post-marketing surveillance in individual agents.

2. Mechanism of action and pharmacokinetics of telbivudine

Telbivudine is manufactured by Novartis Pharma, and marketed under the name Sebivo (or Tyzeka in the US) as film-coated tablets with each tablet containing 600 mg of telbivudine. It was approved by the FDA in 2006 and in the EU and China in 2007. The administration route is oral with a dosage regimen of 600 mg/day.

Telbivudine belongs to the β-L2’ deoxyxynoside family and is an L-enantiomer of thymidine. After phosphorylation by host cell kinases to its active triphosphate form, it competes with the naturally occurring thymidine triphosphate for HBV viral DNA elongation. Subsequent incorporation into viral DNA causes obligate chain termination of DNA synthesis. Its hydroxyl group at the 3’ position of the β-L2’ deoxyribose sugar confers the specificity to HBV polymerase [11]. It has no activity towards other human viruses, including HIV, cytomegalovirus, herpes simplex virus types 1 and 2, varicella zoster virus, Epstein–Barr virus, adenovirus type 1, influenza A and B virus, measles virus, parainfluenza virus type 3, rhinovirus type 5 or respiratory syncytial virus type A. (There is one case report of a HBV–HIV co-infected patient suggesting telbivudine combined with adefovir therapy may have some anti-HIV effect in vivo. However, this has not been confirmed [12].)

Telbivudine is rapidly absorbed after oral administration, reaching peak plasma concentration from 0.8 to 3 h [13]. The long intracellular half-life of 14 h allows for once daily dosing. Oral absorption is not affected by food intake and, therefore, can be administered orally with no regard to the timing of meals. It is predominantly excreted unchanged by passive diffusion in the kidneys. For patients with moderate to severe renal impairment (creatinine clearance < 50 ml/min), dose adjustment is required by extending the dosing interval to every 2, 3 or 4 days accordingly [14]. It should be given after hemodialysis. Its pharmacokinetics is not affected in patients with hepatic impairment and so no dosage modifications are required in these patients [15].

3. Clinical studies

In the initial dose escalation study of telbivudine, it was found that the maximal viral suppression was at doses higher than 400 mg/day [16]. In a subsequent Phase IIb study of 104 CHB patients, telbivudine was shown to have significantly greater virologic and biochemical responses at 52 weeks compared with lamivudine. Telbivudine treatment was also associated with a lower rate of mutation at the tyrosine-methionine-aspartate-aspartate (YMDD) motif, compared with lamivudine treatment. This trial also showed that the combination of telbivudine and lamivudine was not superior to telbivudine monotherapy [17].

The Phase III (GLOBE) trial was a large international, multi-centered, randomized double-blind study that compared telbivudine 600 mg/day to lamivudine 100 mg/day in patients with compensated CHB. A total of 1367 patients of whom 921 were HBeAg-positive and 446 were HBeAg-negative were randomized to treatment from 112 academic centers in 20 countries from 4 continents. It is the largest 2 year intention-to-treat CHB study set up to date. Therapeutic response was defined as a reduction in the serum HBV DNA level to lower than 5 log10 copies/ml, coupled with either alanine transaminase (ALT) normalization or loss of HBeAg. Secondary efficacy measures included serum HBV DNA changes from the baseline, proportion of patients with HBV DNA undetectable by a PCR assay (< 300 copies/ml), HBeAg loss and seroconversion, normalization of serum ALT levels, and HBV surface antigen (HBSAg) loss and seroconversion. In HBeAg-positive patients, telbivudine was

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**Box 1. Drug summary.**

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Telbivudine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase</td>
<td>Launched</td>
</tr>
<tr>
<td>Launched indication</td>
<td>Infection, HBV</td>
</tr>
<tr>
<td>Pharmacology description</td>
<td>DNA directed DNA polymerase inhibitor</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Alimentary, by mouth</td>
</tr>
<tr>
<td>Chemical structure</td>
<td></td>
</tr>
</tbody>
</table>

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Pharmaprojects – copyright to Citeline Drug Intelligence (an Informa business). Readers are referred to Pipeline (http://informa-pipeline.citeline.com) and Citeline (http://informa.citeline.com).
post-marketing surveillance in individual agents.

adverse events such as myopathy, neuropathy, lactic acidosis, and potentially myoglobinuria, have been reported with telbivudine therapy, but these are rare [7-9]. The drug is contraindicated in patients with moderate to severe renal impairment (creatinine clearance < 50 ml/min), dose adjustment is required by extending the dosing interval to every 2, 3 or 4 days accordingly [14]. It should be given after hemodialysis. Its pharmacokinetics is not significantly affected by the timing of meals. It is predominantly excreted unchanged with the naturally occurring thymidine triphosphate for DNA synthesis. The chemical structure of telbivudine is similar to lamivudine, with a deoxyribose sugar conferring the specificity to HBV polymerase. The drug is launched into viral DNA causes obligate chain termination of DNA merase [11]. It has no activity towards other human viruses, including HIV, cytomegalovirus, herpes simplex virus types 1, 2 and 3. HBeAg-negative patients have a lower incidence of liver tumor than HBeAg-positive patients [12].

Telbivudine is manufactured by Novartis Pharma, and marketed under the name Sebivo (or Tyzeka in the US) as an HBeAg-positive CHB therapy. Table 1 shows the clinical profiles of nucleoside/nucleotide analog treatments for chronic hepatitis B (HBeAg-positive/ HBeAg-negative).

### Table 1. Clinical profiles of nucleoside/nucleotide analog treatments for chronic hepatitis B (HBeAg-positive/ HBeAg-negative).

<table>
<thead>
<tr>
<th>Rate of HBeAg seroconversion (%)</th>
<th>Lamivudine</th>
<th>Adefovir</th>
<th>Entecavir</th>
<th>Telbivudine</th>
<th>Tenofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Year</td>
<td>16/-</td>
<td>12/-</td>
<td>21/-</td>
<td>27/-</td>
<td>21/-</td>
</tr>
<tr>
<td>2 Years</td>
<td>26/-</td>
<td>29/-</td>
<td>31/-</td>
<td>30/-</td>
<td>27/-</td>
</tr>
<tr>
<td>3 Years</td>
<td>40/-</td>
<td>43/-</td>
<td>39/-</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

### ALT normalization (%)

| 1 Year | 60/71 | 48/72 | 68/78 | 77/74 | 69/77 |
| 2 Years | 50/72 | 74/73 | 87/89 | 70/77 | NANA |
| 3 Years | 41/NA | 80/68 | 90/NA | NANA | NANA |

### Undetectable HBV DNA by PCR (%)

| 1 Year | 36/72 | 21/63 | 67/90 | 60/88 | 76/93 |
| 2 Years | NANA | 40/71 | 80/94 | 56/82 | 77/90 |
| 3 Years | NANA | 48/79 | 82/NA | NANA | NANA |

### Resistance (%)

| 1 Year | 24/21 | 0/0 | < 1/1 | 4.4/2.7 | 0/0 |
| 2 Years | 42/35 | NA/3 | < 1/1 | 25.1/10.8 | 0/0 |
| 5 Years | 76/NA | 20/29 | 1.2/1.2 | NANA | NANA |

### Elevation of creatine kinase (%)

| 1 Year | 2.1, 3.1 | NA | NA | 7.5 [18] | NA |

ALT: Alanine transaminase; HBeAg: HBV e antigen; NA: Not available.

Telbivudine showed a greater HBV DNA suppression compared with adefovir in a multi-centered, randomized, open-label study that involved 135 treatment-naïve HBeAg-negative CHB patients. At 24 weeks, the mean log_{10} HBV DNA reductions were -6.30 versus -4.97 copies/ml, p < 0.001 for the telbivudine and adefovir groups, respectively. The telbivudine group was associated with a higher rate of undetectable HBV DNA than in the adefovir group (39 vs 12%, respectively, p = 0.001). At 52 weeks, the mean log_{10} HBV DNA reductions from baseline were -5.65 versus -5.99 copies/ml, respectively (p = 0.012) [23].

Telbivudine was also compared with entecavir in the treatment of HBeAg-positive patient with compensated CHB in a small multi-centered, randomized, open-label, viral kinetics study. Forty-four patients were enrolled and the reductions in HBV DNA and ALT levels from baseline up to week 12 were examined. The mean HBV DNA reductions at week 12 were -6.6 and -6.5 log_{10} copies/ml (p = NS) in the telbivudine and entecavir groups, respectively [24].

**Table 1. Clinical profiles of nucleoside/nucleotide analog treatments for chronic hepatitis B (HBeAg-positive/ HBeAg-negative).**

### Rate of HBeAg seroconversion (%)

<table>
<thead>
<tr>
<th>Year</th>
<th>Lamivudine</th>
<th>Adefovir</th>
<th>Entecavir</th>
<th>Telbivudine</th>
<th>Tenofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16/-</td>
<td>12/-</td>
<td>21/-</td>
<td>27/-</td>
<td>21/-</td>
</tr>
<tr>
<td>2</td>
<td>26/-</td>
<td>29/-</td>
<td>31/-</td>
<td>30/-</td>
<td>27/-</td>
</tr>
<tr>
<td>3</td>
<td>40/-</td>
<td>43/-</td>
<td>39/-</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

### ALT normalization (%)

<table>
<thead>
<tr>
<th>Year</th>
<th>Lamivudine</th>
<th>Adefovir</th>
<th>Entecavir</th>
<th>Telbivudine</th>
<th>Tenofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60/71</td>
<td>48/72</td>
<td>68/78</td>
<td>77/74</td>
<td>69/77</td>
</tr>
<tr>
<td>2</td>
<td>50/72</td>
<td>74/73</td>
<td>87/89</td>
<td>70/77</td>
<td>NANA</td>
</tr>
<tr>
<td>3</td>
<td>41/NA</td>
<td>80/68</td>
<td>90/NA</td>
<td>NANA</td>
<td>NANA</td>
</tr>
</tbody>
</table>

### Undetectable HBV DNA by PCR (%)

<table>
<thead>
<tr>
<th>Year</th>
<th>Lamivudine</th>
<th>Adefovir</th>
<th>Entecavir</th>
<th>Telbivudine</th>
<th>Tenofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36/72</td>
<td>21/63</td>
<td>67/90</td>
<td>60/88</td>
<td>76/93</td>
</tr>
<tr>
<td>2</td>
<td>NANA</td>
<td>40/71</td>
<td>80/94</td>
<td>56/82</td>
<td>77/90</td>
</tr>
<tr>
<td>3</td>
<td>NANA</td>
<td>48/79</td>
<td>82/NA</td>
<td>NANA</td>
<td>NANA</td>
</tr>
</tbody>
</table>

### Resistance (%)

<table>
<thead>
<tr>
<th>Year</th>
<th>Lamivudine</th>
<th>Adefovir</th>
<th>Entecavir</th>
<th>Telbivudine</th>
<th>Tenofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24/21</td>
<td>0/0</td>
<td>&lt; 1/1</td>
<td>4.4/2.7</td>
<td>0/0</td>
</tr>
<tr>
<td>2</td>
<td>42/35</td>
<td>NA/3</td>
<td>&lt; 1/1</td>
<td>25.1/10.8</td>
<td>0/0</td>
</tr>
<tr>
<td>5</td>
<td>76/NA</td>
<td>20/29</td>
<td>1.2/1.2</td>
<td>NANA</td>
<td>NANA</td>
</tr>
</tbody>
</table>

### Elevation of creatine kinase (%)

<table>
<thead>
<tr>
<th>Year</th>
<th>Lamivudine</th>
<th>Adefovir</th>
<th>Entecavir</th>
<th>Telbivudine</th>
<th>Tenofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.1, 3.1</td>
<td>NA</td>
<td>NA</td>
<td>7.5 [18]</td>
<td>NA</td>
</tr>
</tbody>
</table>
In a study from China, 80 HBV patients with cirrhosis, with a baseline mean HBV DNA of 6.52 log_{10} copies/ml, were treated with telbivudine 600 mg/day or lamivudine 100 mg/day for 48 weeks. The mean reduction of HBV DNA was -3.67 log_{10} copies/ml at 48 weeks, compared with 3.08 log_{10} copies/ml with lamivudine. There was a higher proportion of patients treated with telbivudine with undetectable HBV DNA compared to that with lamivudine at 24 weeks (92.5%, 37/40 vs 75.0%, 30/40, p < 0.05, respectively), while the rate of undetectable HBV DNA at 48 weeks were similar (92.5%, 37/40 vs 77.5%, 31/40, p = NS, respectively). In the telbivudine-treated patients, there was also improvement in the Child-Pugh score at weeks 24 and 48, and 5% had a YMDD mutation [25].

Telbivudine was also evaluated in patients with decompensated HBV cirrhosis. In a double-blind study with 195 patients (98 receiving telbivudine, 97 receiving lamivudine), at the end of 2 years, undetectable HBV DNA was achieved in 47% of telbivudine and 36% of lamivudine patients. However, viral breakthroughs occurred in 29% of patients on telbivudine and 39% of patients on lamivudine [26].

4. Viral resistance

The development of resistance to NA results from mutations in the polymerase gene. This is often followed by an increase in viral load, and increase in serum ALT several weeks to months later, and there may be progression of liver disease [27]. The cumulative annual incidences of resistance for lamivudine from years 1 to 5 are 23, 46, 55, 71 and 80%, respectively [28].

In the GLOBE study, telbivudine was shown to have less viral resistance compared to lamivudine at years 1 and 2. In HBeAg-positive patients, the incidence of virologic resistance with telbivudine was 5% at year 1 and 25.1% at year 2 compared with 11% at year 1 and 39.5% at year 2 with lamivudine (p < 0.001). In HBeAg-negative patients, the incidence of virologic resistance with telbivudine was 2.2% at year 1 and 10.8% at year 2 compared with 10.7% at year 1 and 25.9% at year 2 with lamivudine (p < 0.001) [18,19]. In the study 015, virologic breakthrough was also found to be lower with telbivudine than with lamivudine at 48 weeks (7.5 vs 17.5%, p = 0.009) [20].

A single mutation in position 204 of the reverse transcriptase YMDD domain of the HBV polymerase, from methionine to isoleucine (rtM204I), is associated with viral resistance to telbivudine. Secondary mutations rtL80I/V and L80I/V + L180 M can accompany this signature mutation in ~2 and 0.3% of cases, respectively [18]. Unlike lamivudine where both rtM204I and rtM204V are associated with resistance, the rtM204V remains relatively sensitive to telbivudine [29]. The rtM204I HBV is sensitive to adefovir, tenofovir and, to a lesser extent, entecavir. rtM204I mutation is one of the three prerequisite mutations for entecavir resistance [30]; telbivudine-experienced patients will respond less well to entecavir compared to nucleoside-naive patients.

The importance of early viral suppression, at weeks 24 or 48 of treatment, in predicting long-term outcome has been shown with lamivudine, adefovir and PEG IFN [31-33]. It was also observed in the GLOBE study. Logistic regression analyses showed that serum HBV DNA levels at baseline or at treatment week 24 were significant independent predictors of better outcomes (HBV DNA undetectable, viral resistance, HBeAg seroconversion, ALT normalization) at 104 weeks in the telbivudine-treated patients [19]. In a further multivariate analyses of the GLOBE study data, in telbivudine-treated patients, the viral resistance rate at 104 weeks was 11.3% in HBeAg-positive patients with baseline HBV DNA < 9 log_{10} copies/ml, and 3.1% in HBeAg-negative patients with baseline HBV DNA < 7 log_{10} copies/ml. Furthermore, the viral resistance rate at the end of 104 weeks was lower in patients with low HBV DNA at treatment week 12 or 24, being 6% for HBeAg-positive patients and 3% for HBeAg-negative patients when the serum HBV DNA at week 12 was PCR undetectable (< 300 copies/ml) [34].

The mutation patterns for adefovir and tenofovir, both NAs, are different from the pattern in nucleoside analogs such as telbivudine. In resistance to adefovir, a mutation from asparagine to threonine at position rt236 [35] or a mutation from alanine to threonine at position rt181 is associated with reduction in anti-HBV activities [36]. These mutations are also associated with lower activity with tenofovir [37]. Telbivudine remains effective towards these mutant HBVs while adefovir and tenofovir are both effective for the YMDD mutants [38].

5. Safety evaluation

5.1 Telbivudine

Telbivudine is not associated with significant effects in cytotoxicity, mitochondrial toxicity, myelotoxicity or genotoxicity in in vitro studies. There is also no carcinogenicity, reproductive toxicity or genotoxicity in animal studies. There were no major toxicities in the Phase I and II clinical studies in humans.

In the GLOBE study, telbivudine had similar safety and tolerability profile compared with lamivudine with the exception of creatine kinase (CK) elevation. The frequency of adverse events through week 104 was similar for both medications. Most were constitutional symptoms, mild, transient and not attributed to the study drug. Four percent of patients in both telbivudine (n = 680) and lamivudine groups (n = 687) had adverse events leading to treatment interruption or discontinuation in the 104-week period. A total of three drug-related serious adverse events were reported in the telbivudine recipients (myopathy, liver failure and elevated CK level) [19].

Elevation of CK is more commonly observed in telbivudine-treated patients. In the Phase IIb study, 5/104 patients had elevations of CK (one receiving telbivudine 400 mg/day, three
breakthroughs occurred in 29% of patients on telbivudine and 36% of lamivudine patients. However, viral (98 receiving telbivudine, 97 receiving lamivudine), at the end of HBV cirrhosis. In a double-blind study with 195 patients with a baseline mean HBV DNA of 6.52 log 10 copies/ml, 100 mg/day for 48 weeks. The mean reduction of HBV were treated with telbivudine 600 mg/day or lamivudine and 5% had a YMDD mutation [25].

improvement in the Child-Pugh score at weeks 24 and 48, while the rate of undetectable HBV DNA at 48 weeks able HBV DNA compared to that with lamivudine at years 1 and 10.8% at year 2 compared with 10.7% at year 1 and 39.5% at year 2 with lamivudine (p < 0.001). In HBeAg-negative patients, the incidence of viral resistance compared to lamivudine at years 1 and 2. In

The development of resistance to NA results from mutations in viral load, and increase in serum ALT several weeks to weeks later. The majority of these were transient and resolved by the time of the next visit 4 – 12 weeks later. The grade 3/4 CK elevations were usually limited to one episode. There patients developed reversible myopathy, characterized by muscle pain and weakness and moderately elevated CK necessitating drug discontinuation or interruption [19]. In the 015 study, 8.4% of telbivudine-treated patients had grade 3/4 CK elevation during the 52 weeks study period. The difference in incidence compared with the lamivudine arm (3%) did not reach statistical significance (p = 0.06) [20]. In a retrospective analysis of the Novartis global database of 655 patients treated continuously with telbivudine over 4 years, 14.3% of Asian patients and 17.1% of Caucasians had grade 3/4 CK elevation. The majority (68.3%) experienced a single grade 3/4 elevation, 90% of which either resolved or was downgraded to grade 1/2 by the next study visit. The rate of all muscle-related symptoms (myalgia/myopathy/myositis) during the 208 weeks treatment was 4.1% (27/655), of which 1.1% (7/655) was myopathy/myositis. Of all the patients with muscle-related adverse effects, 29% had a concomitant grade 3/4 CK elevation. Roughly a third of the muscle-related symptoms occurred within 30 days of a grade 3/4 CK elevation episode. Therefore, grade 3/4 CK elevation is a poor predictor for the onset of muscle-related events [39]. The clinician must not merely rely on CK elevation to monitor the muscle-related adverse effects.

Telbivudine is also found to be associated with peripheral neuropathy, especially when used together with PEG IFN. A study of 159 CHB patients was terminated because of an unacceptably high rate of peripheral neuropathy with 9 patients developing peripheral neuropathy, 8 (16%; 8/50) of whom were receiving the combination therapy of telbivudine and PEG IFN and one (1.8%; 1/55) who was on telbivudine monotherapy. The time to onset of peripheral neuropathy ranged from 2 to 6 months in patients receiving the combination therapy. Some of the peripheral neuropathy cases persisted despite cessation of therapy [40]. The incidence of peripheral neuropathy as a severe adverse event with telbivudine monotherapy was 0.45% (10/2200) in the Telbivudine Global Clinical Trial Program data [41]. The concomitant use of telbivudine and PEG IFN should be avoided.

The possible mechanisms of telbivudine-related peripheral neuropathy and myopathy are unknown. Telbivudine is not associated with mitochondrial toxicity from in vitro studies at concentrations of 10 times the maximal clinical dose and has no known effect on human hepatocytes, skeletal muscle or neuronal cells [42].

5.2 Safety in special populations
To date, there have been no published reports of safety and efficacy of telbivudine in patients with renal insufficiency, transplant recipients and or in children.

A placebo-controlled trial with telbivudine in 61 pregnant CHB patients was performed in China. Except for one patient who was enrolled in the telbivudine group at 12 weeks of gestation, the rest (30) enrolled in the telbivudine group were at 28 – 32 weeks of gestation. Compared with the control group (30), the mean HBV DNA was significantly lower in the telbivudine group before parturition. All newborns from both groups received hepatitis B immunoglobulin and HBV vaccination at 0, 1 and 6 months of age. The HBsAg-positive rates of newborns at month 7 were 0 versus 13.3% (4/30) in the telbivudine and control groups, respectively (p < 0.05). There was no adverse effect noted in all patients and the newborns. No birth defects were found in newborns from telbivudine treated patients. No increase in CK was reported [43].

5.3 Comparison with safety of other drugs
5.3.1 Lamivudine
Among the five approved NA for the treatment of HBV in adults, lamivudine, approved for use in HBV treatment in 1998, is no longer recommended as a first-line agent due to its high incidence of viral resistance on long-term use [44,45]. Rare occurrences of reversible myopathy, neuropathy, pancreatitis and Fanconi syndrome have been reported in CHB patients with HIV co-infection [46-50]. The role of lamivudine in these complications is not clear as most of these patients were exposed to multiple anti-retroviral agents. Although lamivudine was regard as Category C (i.e., adverse effects on the fetus have been shown in animal reproduction studies and inadequate studies on human), there were retrospective and prospective series using lamivudine in selected HBsAg-positive mothers in their third trimester to reduce the risk of HBV transmission, and lamivudine was found to be safe. In special populations such as patients with decompensated HBV cirrhosis, solid-organ transplant recipients and patients with cancers who are receiving chemotherapy, lamivudine is also well tolerated [51,52].

5.3.2 Adefovir
Adefovir was approved at the dose of 10 mg/day for HBV treatment in 2002. The most important adverse effect is nephrotoxicity which is dose-dependent. In 5 years continuous treatment with adefovir, 3 – 8% of patients developed elevation of creatinine [53].

5.3.3 Entecavir
Entecavir is a potent anti-HBV agent, with a high genetic barrier for viral resistance, approved in 2005. A higher incidence of solid tumor in animals was noted in preclinical studies using high-dose entecavir compared to placebo. However, there has been no evidence of increased incidence of
Telbivudine is a well-tolerated and potent anti-HBV agent (pregnancy Category B) with efficacy superior to lamivudine and adefovir in the treatment of compensated CHB. The suboptimal viral resistance profile limits the broad applicability to all CHB population. More long-term and post-market surveillance studies for elevation in CK and its association with myopathy are needed. Its long-term use in selected groups of CHB based on baseline and on-treatment characteristics (HBV DNA < 9 log_{10} copies/ml at baseline and PCR undetectable at week 24) is expected to offer good viral suppression and resultant reduction in the morbidity and mortality from chronic HBV infection.

7. Expert opinion

In the treatment of CHB, no therapy has been proven to eradicate the virus completely from the human body due to the persistence of the covalently closed circular HBV DNA in the hepatocytes. Long-term maximal viral suppression is of utmost importance for the prevention of disease progression and HCC development. In clinical practice, this can only be achieved by long-term administration of the NA. This, however, is costly. To ensure the compliance to long-term medication, the cost of the individual NAs is not a negligible issue. Safety and development of viral resistance are also important. Therefore, regular monitoring of treatment response and viremic levels should be performed to prevent biochemical flares and possible hepatic decompensation. The ideal would be the long-term administration of a potent anti-HBV agent with minimal side effects and a high genetic barrier for viral resistance. Entecavir and tenofovir both fulfilled these characteristics and are the ideal first-line agents, but are the most expensive of the five NAs. A proper selection of patients based on the baseline characteristics and on-treatment virologic response may allow for a more cost-effective long-term option using telbivudine. Close attention should be paid to patients having elevated CK or serum creatinine on NA. Prompt switching to an alternative treatment is advised if there is any evidence of myopathy or if CK or serum creatinine elevation has not improved by 1 or 2 weeks.

Declaration of interest

M-F Yuen has received research grants from GlaxoSmithKline, Bristol-Myers Squibb and Novartis. DY-K But has nothing to disclose.
The ideal would be the long-term administration of a potent anti-HBV agent with minimal side effects and a high genetic barrier for viral resistance. Entecavir and tenofovir both optimize long-term outcomes for patients with chronic hepatitis B. Hepatol Int 2006;50:874-9

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