Entecavir is a potent anti-HBV drug superior to lamivudine: experience from clinical trials in China

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Infection with the hepatitis B virus (HBV) can result in chronic hepatitis B (CHB) in many patients. Patients with CHB require regular screening and monitoring to facilitate disease surveillance and to determine if/when treatment is indicated. The current goal of CHB treatment is sustained viral suppression with the aim of reducing or preventing hepatic injury and disease progression. Effective anti-HBV therapy is now available that can suppress, but not eradicate, HBV replication. Among the currently licensed and approved anti-HBV nucleos(t)ides, entecavir demonstrates a potent anti-HBV activity and a low rate of emergence of drug resistance, with good safety and tolerability profiles. These excellent pharmacological characteristics were assessed both in large international clinical trials and in separate studies in China. This article presents results from Phase II and Phase III trials involving 876 Chinese patients with CHB. The results of these studies suggest that entecavir should be recommended as a first-line choice among the currently available anti-HBV nucleos(t)ides.

Keywords: hepatitis B virus, resistance, safety, efficacy, antiviral therapy

Introduction

Hepatitis B virus (HBV) infection is a serious global public health problem. Among the 2 billion people who are infected with HBV, more than 350 million people are chronically infected, and 75% of these live in Asia or the west Pacific regions.1 China has one of the highest rates of prevalence of HBV infection in the world. According to a recent survey, about 9.09% of the population or ~120 million individuals are chronically infected with HBV.2 Around 15% to 40% of chronic hepatitis B (CHB) patients will develop and die from progressive liver diseases, such as liver failure, cirrhosis or hepatocellular carcinoma.3 Therefore, there is an urgent need to treat CHB patients as soon as possible. The discovery and development of anti-HBV nucleos(t)ide analogues represents a major breakthrough in antiviral therapy for CHB patients. Globally, four anti-HBV nucleos(t)ide analogues have been approved, or received a recommendation for approval, for the treatment of CHB: lamivudine, adefovir dipivoxil, entecavir and telbivudine.

Experimental and clinical studies have demonstrated that entecavir is one of the most potent anti-HBV compounds and has an excellent resistance profile.4–8 International clinical trials and further studies in China have shown that entecavir achieved statistically superior virological and biochemical responses compared with lamivudine. This paper summarizes the pharmacokinetics study and the three clinical trials that were performed in China to confirm the efficacy of entecavir for the treatment of CHB in Chinese patients.

Clinical trials of entecavir in China

Several clinical trials were performed in China to evaluate entecavir prior to its registration and manufacture, as outlined in Table 1.

Pharmacokinetics study

Study ETV-018 provided data on the pharmacokinetics of oral entecavir at different doses in healthy male Chinese volunteers. The steady-state pharmacokinetic parameters $C_{\text{max}}$, $T_{\text{max}}$ and AUC at Day 12 in eight subjects who received the entecavir 0.5 mg dose were 6.36 ± 1.43 ng/mL, 0.75 (0.5–1.5) h and 17.42 ± 2.83 ng·h/mL, respectively.9 A comparison of the pharmacokinetic data obtained from studies of oral entecavir in Chinese, Japanese and Caucasian patients reveals similar pharmacokinetic profiles in each group.10

Dose-ranging study

Study ETV-012 was a dose-ranging Phase II study that evaluated entecavir prior to its registration and manufacture, as outlined in Table 1.

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in Chinese adults with CHB infection. A total of 216 nucleoside-naive patients were randomized (1:1:1) and 212 patients received at least one dose of study medication: 72 in the entecavir 0.5 mg arm, 69 in the entecavir 0.1 mg arm and 71 in the placebo arm. The study had four distinct phases; the initial double-blind 28 day dosing phase was followed by a 56 day off-treatment follow-up period. Patients were then eligible to enter the open-label phase where they received 48 weeks of entecavir 0.5 mg and were followed-up for a period of 24 weeks. The primary endpoint was the proportion of patients with an antiviral response at Day 28. Safety was assessed for all patients who received at least one dose of entecavir.

A significantly greater proportion of patients receiving entecavir 0.5 or 0.1 mg achieved an antiviral response [defined as either \( \geq 2\log_{10} \) reduction in HBV DNA by branched DNA (bDNA) assay or undetectable HBV DNA by bDNA assay (<0.7 MEq/mL) plus a \( \geq 2\log_{10} \) reduction in HBV DNA PCR assay] compared with placebo (93%, 86% and 3%, respectively; \( P < 0.0001 \) for both comparisons).11 Mean change in HBV DNA from baseline by bDNA assay is shown in Figure 1. The difference in the mean change from baseline in HBV DNA at Day 28 for entecavir 0.5 mg compared with 0.1 mg was statistically significant (0.3 \( \log_{10} \) MEq/mL; \( P = 0.0005 \)).

**Figure 1.** Mean change in HBV DNA from baseline by bDNA assay over 12 weeks of therapy (ETV-012). ETV, entecavir. Reproduced, with permission, from reference 22.

### Table 1. Clinical trials performed in China

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Trial dosage</th>
<th>Subjects</th>
<th>Number randomized</th>
<th>Objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETV-018 (Phase I)</td>
<td>0.05, 0.1, 0.5, 1.0 mg/day ETV</td>
<td>normal healthy volunteers</td>
<td>68</td>
<td>pharmacokinetics, tolerance, safety</td>
</tr>
<tr>
<td>ETV-012 (Phase II)</td>
<td>placebo, 0.1, 0.5 mg/day ETV</td>
<td>CHB patients</td>
<td>216</td>
<td>dose-ranging study</td>
</tr>
<tr>
<td>ETV-023 (Phase III)</td>
<td>0.5 mg/day ETV 100 mg/day 3TC</td>
<td>nucleoside-naive CHB patients</td>
<td>525</td>
<td>comparison of ETV and 3TC in nucleoside-naive patients</td>
</tr>
<tr>
<td>ETV-056 (Phase III)</td>
<td>1.0 mg/day ETV</td>
<td>3TC-refractory CHB patients</td>
<td>147</td>
<td>safety and efficacy of ETV patients who have failed 3TC therapy</td>
</tr>
</tbody>
</table>

ETV, entecavir; 3TC, lamivudine; CHB, chronic hepatitis B.

**Double-blind, randomized, controlled study of entecavir compared with lamivudine in nucleoside-naive patients**

Study ETV-023 was a multicentre, double-blind, Phase III study that compared the efficacy and safety of entecavir with that of lamivudine for the treatment of CHB.12,13 Initially, 525 nucleoside-naive, Chinese patients with CHB were randomized (1:1) to receive entecavir 0.5 mg/day or lamivudine 100 mg/day. A total of 519 patients received at least one dose of study drug: 258 in the entecavir arm and 261 in the lamivudine arm. The primary efficacy endpoint was a composite of serum HBV DNA \( <0.7 \) MEq/mL by bDNA assay and alanine aminotransferase (ALT) \( <1.25 \times \) upper limit of normal (ULN) at Week 48. Primary analyses were by intent-to-treat, with missing Week 48 measurements counted as non-responses.

Ninety percent of entecavir-treated patients achieved the primary endpoint by Week 48 compared with 67% of lamivudine-treated patients (\( P < 0.0001 \)).12,13 At the first HBV DNA assessment after 12 weeks of treatment, the mean reduction in HBV DNA was significantly greater for the entecavir group (5.07 \( \log_{10} \) copies/mL) than for the lamivudine group (4.53 \( \log_{10} \) copies/mL; \( P < 0.001 \)). The mean change in serum HBV DNA from baseline to Week 48 was also greater with entecavir than with lamivudine (\( -5.90 \) versus \( -4.33 \) \( \log_{10} \) copies/mL by PCR assay; \( P < 0.0001 \); Figure 2). Significantly greater proportions of entecavir-treated than lamivudine-treated patients achieved undetectable serum HBV DNA levels by PCR assay (\( <300 \) copies/mL; 76% versus 43%; \( P < 0.0001 \)) and ALT normalization (ALT \( \leq 1 \times \) ULN; 90% versus 78%; \( P = 0.0003 \)) at Week 48. Among patients who were hepatitis B e antigen (HBeAg)-positive at baseline, entecavir- and lamivudine-treated patients achieved comparable rates of HBeAg seroconversion (15% and 18%, respectively; Table 2). Safety was comparable between the two treatment groups. At Week 52, patients either stopped therapy or continued blinded treatment based on the protocol management criteria. Patients who had achieved a protocol defined consolidated response (defined as patients who achieved HBV DNA \( <0.7 \) MEq/mL by bDNA assay and were HBeAg-negative both for at least 6 months and ALT \( <1.25 \times \) ULN at Week 48) were followed off-treatment for 24 weeks. Of the HBeAg-positive patients who...
were followed off-treatment, 69% (31/45) of entecavir-treated patients and 70% (21/30) of lamivudine-treated patients main-
tained or achieved HBeAg seroconversion.12,13 ALT
normalization was maintained or achieved in 75% (58/77) and
49% (31/63) of entecavir- and lamivudine-treated patients,
respectively, and HBV DNA undetectability was maintained or
achieved in 22% (17/77) and 10% (6/63) of entecavir- and
lamivudine-treated patients, respectively.

Patients with a protocol defined partial response (HBV DNA
<0.7 MEq/mL but had not yet achieved a consolidated response
at Week 48) continued blinded therapy until consolidated
response criteria were met, or until Week 96, whichever
occurred first. Of the 193 entecavir-treated and 145 lamivudine-
treated patients who continued treatment in the second year,
79% of entecavir-treated patients versus 46% of lamivudine-
treated patients achieved undetectable HBV DNA levels (<300
copies/mL) through 96 weeks.13 The rates of ALT normalization
(≤1×ULN) and HBeAg seroconversion were 96% and 21% in
the entecavir group and 92% and 23% in the lamivudine group.

On-treatment ALT flares were observed in 4% of entecavir-
treated patients versus 7% in lamivudine-treated patients through
Week 96.13 After discontinuation of therapy, off-treatment ALT
flares were observed in 5% and 10% of patients who received
entecavir and lamivudine, respectively.13 Entecavir 0.5 mg/day
was well tolerated with a safety profile that was comparable
to that of lamivudine 100 mg/day.12,13

Entecavir treatment for patients who were refractory
to lamivudine therapy

Study ETV-056 was a randomized, double-blind, placebo-
controlled trial that evaluated the efficacy and safety of entecavir
in patients who were refractory to lamivudine therapy.14 A total
of 147 CHB patients were randomized (4:1) and 145 received at
least one dose of blinded study drug: 116 in the entecavir
1.0 mg arm and 29 in the placebo arm. Of the 145 patients who
started the study, 144 completed the 12 weeks blinded treatment
phase, after which all patients received open-label entecavir
1.0 mg daily for 36 weeks.

The mean change in HBV DNA level from baseline was
assessed at the end of the blinded treatment phase (Week 12).
Patients who received entecavir during this period had a mean
change of −4.3 log_{10} copies/mL compared with −0.15 log_{10}
copies/mL for patients who received placebo (P < 0.001); a
significant reduction in HBV DNA level was seen as early as
Week 2 (mean change: −2.65 log_{10} copies/mL).14 By Week 48,
patients who had initially been randomized to receive entecavir
(for the blinded dosing phase) had achieved a mean change in
HBV DNA level of −5.08 log_{10} copies/mL (Figure 3) and 27%
had undetectable HBV DNA levels (<300 copies/mL). Patients
who were randomized to placebo during the blinded dosing
phase, received 36 weeks of entecavir 1.0 mg therapy during the
open-label phase, and had a mean change in HBV DNA level
from baseline of −4.86 log_{10} copies/mL by Week 48 (Figure 3).

Among patients initially randomized to entecavir and who
were HBeAg-positive at study entry, 8% lost HBeAg and 6%
developed HBeAg seroconversion (loss of HBeAg and gain of
HBeAb) by Week 48.14

ALT normalization was assessed in patients who had ALT
levels >1×ULN at baseline. At Week 12, 68% of patients who

Table 2. Virological, biochemical and serologic endpoints in nucleoside-naive patients at Week 48 of Study ETV-023

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Entecavir 0.5 mg (n = 258)</th>
<th>Lamivudine 100 mg (n = 261)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite endpoint (HBV DNA &lt;0.7 MEq/mL by bDNA assay and ALT &lt;1.25×ULN)</td>
<td>231 (90%)</td>
<td>174 (67%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HBV DNA by PCR assay mean (SE) change from baseline at Week 48, log_{10} copies/mL</td>
<td>−5.90 (0.071)</td>
<td>−4.33 (0.122)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HBV DNA &lt;300 copies/mL at Week 48</td>
<td>197 (76%)</td>
<td>112 (43%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ALT normalization (ALT ≤1×ULN)</td>
<td>231 (90%)</td>
<td>203 (78%)</td>
<td>0.0003</td>
</tr>
<tr>
<td>HBeAg loss and seroconversion (acquisition of antibodies to HBeAg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBeAg loss, no./no. HBeAg-positive at baseline</td>
<td>41/225 (18%)</td>
<td>44/221 (20%)</td>
<td>NS</td>
</tr>
<tr>
<td>HBeAg seroconversion, no./no. HBeAg-positive at baseline</td>
<td>33/225 (15%)</td>
<td>39/221 (18%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; SE, standard error; NS, not significant; ULN, upper limit of normal.

For all analyses with the exception of mean reduction in HBV DNA by PCR assay, patients with a missing value for an endpoint were considered non-
responders for that endpoint.
received entecavir had achieved ALT normalization (ALT ≤ 1× ULN) compared with only 6% of patients who received placebo (P < 0.0001). By Week 48, the proportion of patients with ALT normalization had increased to 85% in patients initially randomized to entecavir.

The on-treatment safety profiles of both drugs were comparable in this study. The proportions of patients experiencing any adverse event during the blinded dosing phase were comparable in the two treatment arms: 33% and 28% of patients receiving entecavir and placebo, respectively.

Discussion

Entecavir is a potent inhibitor of the hepatitis B virus and has been shown to be effective and well tolerated in a range of HBV-infected patients. By competing with the natural substrate deoxyguanosine triphosphate, entecavir inhibits all three activities of the HBV polymerase: (i) base priming; (ii) reverse transcription; and (iii) synthesis of HBV DNA. In vitro studies have shown entecavir to be a highly potent inhibitor of HBV with an EC₅₀ of around 4 nM; making it at least 100-fold more potent than lamivudine or adefovir. In large, multinational Phase III studies in nucleoside-naive and lamivudine-refractory patients, 48 weeks of entecavir treatment resulted in rates of histological, virological and biochemical improvement that were significantly higher than with lamivudine treatment.

CHB is highly prevalent in China and there is a higher prevalence of HBV genotypes B and C in this region compared with other parts of the world. Although HBV genotype was not expected to affect the response to antiviral therapy, it is important to confirm the efficacy of any new anti-HBV agent in this population. The results of entecavir clinical trials performed in mainland China are encouraging since they demonstrate the superior efficacy of entecavir compared with lamivudine in Chinese patients, with comparable safety and tolerability.

Persistently elevated HBV DNA levels increase the risk of development of cirrhosis and hepatocellular carcinoma in persons with CHB and treatment guidelines cite the suppression of HBV replication as the primary goal of therapy. In nucleoside-naive Chinese patients, the reduction in HBV DNA levels during entecavir treatment was rapid and profound, resulting in a >5 log₁₀ reduction by Week 12 and undetectable levels of HBV DNA in 76% of cases by Week 48. A rapid reduction in HBV DNA was also seen in lamivudine-refractory Chinese patients treated with entecavir. This rapid reduction in HBV DNA levels, coupled with a high genetic barrier to resistance explains another important advantage of entecavir; that the emergence of drug resistance in the nucleoside-naive patients has been shown to be very rare. Thus, the benefits of entecavir treatment in nucleoside-naive patients may be expected to continue over long periods of treatment. Furthermore, entecavir has been shown to be safe and well tolerated; the adverse events profile for entecavir is similar to that of lamivudine and no new events were seen to occur in Chinese patients. Therefore, the most recent practice guidelines of China (December 2005) recommend entecavir as one of the first choices for the treatment of active CHB.

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Transparency declarations

G. Y. serves as an advisor for Bristol-Myers Squibb Company and is a principle investigator involved in entecavir studies.

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