Up to 40% of patients with CHB will develop cirrhotic complications and hepatocellular carcinoma (HCC). The natural history of CHB has been traditionally divided into three phases: (1) Immune tolerance phase, (2) Immune clearance phase and (3) Residual phase. The immune tolerance phase is characterized by hepatitis e-antigen (HBeAg) positivity, high hepatitis B virus (HBV) DNA levels and minimal inflammation on liver histology, occurring in childhood and early adulthood. The intermediate immune clearance phase is associated with fluctuating or elevated alanine aminotransferase (ALT) levels, active inflammation on liver histology and finally HBeAg seroconversion with antibody against HBeAg (anti-HBe). In the residual phase, the ALT usually becomes normal with low HBV DNA level. Although HBeAg seroconversion has been commonly regarded as a sign of disease remission and therefore as a treatment endpoint, more recent evidence suggests that in fact the majority of patients who acquire HBV early in life and subsequently develop complications of cirrhosis and HCC are HBeAg negative. These complications develop during the residual phase of CHB.

The ideal treatment goal for CHB would be the complete eradication of HBV, rarely achieved with the current available therapies. Instead current treatment goals adopted in clinical trials and practice include HBeAg seroconversion, normalization of ALT levels, suppression of HBV DNA and improvement in liver histology. It is still debatable whether these short-term goals can translate into clinical long-term benefit. Long term goals including the prevention of cirrhotic complications and HCC are achievable by prolonged maximal suppression of viral replication, as illustrated in a study of patients with advanced fibrosis or established cirrhosis.

Current treatment for CHB

The two main classes of treatment for CHB currently available are immunomodulatory therapy and nucleoside/nucleotide analogues. Interferon-alpha (IFN-α) and its pegylated form are the only immunomodulatory agents approved for the treatment of CHB. The exact mechanism of IFN-α is unknown although likely antiviral mechanisms include up-regulation of class I MHC antigen expression on infected hepatocytes, inhibition of viral DNA and RNA replication and activation of cytokines. Previous meta-analysis with IFN-α has shown it to be effective in promoting HBeAg seroconversion and in suppressing HBV DNA. More recently pegylated IFN-α has been
shown to be effective in treating both HBeAg-positive and HBeAg-negative CHB.\textsuperscript{7,8} However, IFN-\(\alpha\) therapy is associated with significant side effects including flu-like symptoms, thrombocytopenia, mood instability and potential for worsening flare-up of hepatitis. Moreover, IFN-\(\alpha\) is less effective in the Asian population where HBV infections largely occur during early childhood.\textsuperscript{3} IFN-\(\alpha\) therapy is also rarely effective in immuno-compromised patients thus excluding this mode of therapy in this important group of patients.\textsuperscript{9}

Current available nucleoside and nucleotide analogues (NAs) include lamivudine, adefovir dipivoxil and more recently entecavir. Lamivudine, a cytosine analogue, is the first NA to be approved for the treatment of CHB. Lamivudine is effective in promoting HBeAg seroconversion, HBV DNA suppression, normalization of ALT and in decreasing the progression of liver fibrosis.\textsuperscript{10,11} In cirrhotic and pre-cirrhotic patients, lamivudine has been shown to decrease the occurrence of cirrhotic complications including HCC after 3 years of treatment.\textsuperscript{12} However, treatment with lamivudine is limited by the development of viral resistance, with up to 68% of patients developing resistance after 4 years of treatment.\textsuperscript{13} Lamivudine resistance occurs as a result of mutations occurring within the tyrosine-methionine-aspartate-aspartate (YMDD) motif of the reverse transcriptase gene at position 204, with substitution of methionine with valine or isoleucine (M204V and M204I, respectively).\textsuperscript{13} Adefovir is the second NA approved for the treatment of CHB and has been shown to be effective in both HBeAg-positive and HBeAg-negative CHB.\textsuperscript{14,15} Adefovir is also effective against lamivudine resistant HBV harboring the YMDD mutation, whether given alone or in combination with lamivudine and in pre- and post-transplant patients.\textsuperscript{16-18} Viral resistant mutations occur at a slower rate compared with lamivudine, with up to 28% HBeAg-negative patients developing resistance after 5 years of treatment.\textsuperscript{19,20} Mutations associated with adefovir resistance occurs at position 181 of the HBV polymerase with substitution of alanine to valine or threonine (A181V or A181T, respectively) and from asparagine to threonine at position 236 (N236T).\textsuperscript{21} Development of resistance to adefovir has been associated with flares of hepatitis and decompensation.\textsuperscript{22} This mutant strain remains sensitive to lamivudine. Adefovir has been associated with potential nephrotoxicity and may therefore limit its use in patients with pre-existing renal impairment. This renal toxicity is mediated via the human renal organic anion transporter 1 with the accumulation of excess drug within the proximal tubule.\textsuperscript{23} However, with the current recommended dose of 10 mg, the risk of renal toxicity is low, except for post-transplant patients.

Entecavir, the latest NA approved for the treatment of CHB, is a carbocyclic analogue of 2’-deoxyguanosine. Entecavir has been shown to be more effective than lamivudine in the suppression of HBV DNA and also in promoting histological improvement in both HBeAg-positive and HBeAg-negative patients.\textsuperscript{24,25} Viral resistance has not been observed after 2 years of treatment with entecavir in treatment-naive patients. To date, entecavir resistance occurs only in patients with pre-existing lamivudine resistant mutations at M204V and L180M. In addition, further mutations at T184G (substitution of threonine with glycine) with S202I (substitution of serine with isoleucine) or M250V (substitution of methionine with valine) are required.\textsuperscript{26} This may explain the low rate of resistance seen with entecavir, which requires at least three different mutations, as compared to lamivudine or adefovir, which only requires a single amino acid substitution. The low rate of resistance may also be partly related to its potency with maximal early suppression of the virus within 24 weeks in a large proportion of patients. However, data are limited with regard to its long-term use.

Accordingly newer agents are required given the limitations associated with the current available treatments.

The \(\beta\)-L-2’ deoxynucleosides

With the approval of lamivudine for the treatment of CHB, increasing interest has been focused on the L-nucleosides as an antiviral agent. \(\beta\)-L2 deoxynucleosides differ with natural nucleosides by their stoichiometric configuration of the sugar and base moieties, being in the L- rather than the D-configuration. Members of the structurally unsubstituted and unmodified \(\beta\)-L-2-deoxynucleosides include \(\beta\)-L-thymidine (LdT or telbivudine), \(\beta\)-L-2’-deoxycytidine (val-LdC) and \(\beta\)-L-2’ deoxyadenosine (LdA). The chemical structure of telbivudine is shown in Figure 1. The 3’-hydroxyl group of the \(\beta\)-L-2’-deoxyribose molecule confers high selectivity of \(\beta\)-L-2-deoxynucleosides against human HBV, woodchuck hepatitis virus (WHV) and duck hepatitis B virus. This specific anti-HBV activity
Mechanism of action

β-L2 deoxyuridines interacts with viral polymerase results in obligate chain termination of DNA synthesis. Despite their similar molecular structure, telbivudine and LdC display slightly different mode of action. For telbivudine, inhibition of DNA synthesis preferentially occurs during the synthesis of anti-complement DNA (or second strand DNA) [Figure 2], whereas for LdC, inhibition occurs also during reverse transcription with synthesis of DNA from RNA (first strand DNA). Lamivudine also inhibits DNA synthesis at the reverse transcription stage and therefore combination of lamivudine or LdC with telbivudine may be complementary in theory.

Preclinical studies

Studies using HepG2 cells lines and human hepatocytes in primary culture have shown that telbivudine undergoes phosphorylation to its active triphosphate form effectively, peaking at 24 hours. The intracellular half-life of telbivudine is estimated to be 15 hours. The effective concentration (EC\textsubscript{50}) of telbivudine is around 0.19 µM in human hepatoma cell lines and with a 50% cytotoxic concentration (CC\textsubscript{50}) of >1000 µM, resulting in a high selectivity index of telbivudine.

As with the treatment of HIV, there are always concerns with potential mitochondrial toxicities with nucleoside analogues, resulting in delayed toxicities such as peripheral neuropathy, myopathy and pancreatitis. Replication of mitochondrial DNA (mtDNA) is dependent on human DNA polymerase γ, inhibition of which may lead to depletion or mutation of mtDNA with subsequent mitochondrial toxicity and increase lactic acid production. There is no demonstrable inhibition of human polymerase α, β and γ by telbivudine after phosphorylation. No mitochondrial toxicity is observed after 14 days of incubation with telbivudine in HepG2 cell line, with no effect on lactic acid production, mtDNA content and morphology and no incorporation of the drug compound into mtDNA. Another study shows that neither LdC or telbivudine are substrates for human HBV polymerase.

Further studies on human hepatoma cell line 2.2.15, primary human peripheral blood mononuclear cells, human foreskin fibroblasts...
and other cell types of mammalian and avian origin show no cytotoxic effect exerted by telbivudine. In addition, telbivudine has no effect on granulocyte-macrophage colony-forming unit (GM-CFU) and erythrocyte burst-forming unit (E-BFU) precursors in clonogenic assays, which would otherwise suggest potential haematotoxicity.27

In animal studies, telbivudine given to rats and cynomolgus monkeys for 6 and 9 months, respectively is not associated with clinical toxicity at a maximal dose of 1000 mg/kg/day. A 2-year carcinogenic study in Sprague-Dawley rats shows no evidence of oncogenicity in doses of up to 2000 mg/kg/day for more than 85 weeks. Carcinogenic studies performed in transgenic mice shows no differences after 26 weeks in the incidence of neoplastic or non-neoplastic changes between high-dose 2000 mg/kg/day group and control group. In the developmental and reproductive toxicity studies, no significant effects are observed in reproductive fertility in rats treated with 2000 mg/kg/day and in embryo-fetal or postnatal development in rats and rabbits treated with 1000 mg/kg/day.33

**Antiviral activity**

Using the woodchuck model, telbivudine, LdC and LdA have been given orally at a daily dose of 10 mg/kg. Inhibition of WHV DNA is observed within the first few days of treatment and is maintained throughout the period of treatment. Following drug withdrawal, WHV DNA returns to pre-treatment levels by week 8. Of the three β-L2 deoxynucleosides, telbivudine is the most potent in the WHV model, reducing WHV DNA levels by 8 logs compared with 6 logs and 1.5 logs with LdC and LdA, respectively.27 For this reason telbivudine is the first of the β-L2 deoxynucleosides selected for development in clinical trials.

**Clinical pharmacokinetics**

The pharmacokinetic profile of telbivudine has been evaluated in an early phase I/II trial in healthy subjects and in patients with CHB infection. In healthy subjects, telbivudine has been given at doses of 25, 50, 100, 200, 400 or 800 mg once daily for 4 weeks. Telbivudine is well-tolerated with no observed dose-related or treatment-related adverse events compared with placebo. Telbivudine is rapidly absorbed after oral administration with the median times to the maximum plasma concentration ranging from 0.8 to 3 hours after administration. A dose-proportional virological response is observed across the dose range, with reduction of serum HBV DNA of 3.5 to 4.0 logs with 400-800 mg/day after 4 weeks of treatment. Over the dose range studied, telbivudine exhibits linear plasma pharmacokinetics with respect to maximal plasma concentration (C_{max}) and area under curve, with slightly enhanced levels at steady-state explained by the slower second-phase elimination. The long intracellular half-life of 14 hours supports once-daily dosing with relatively high doses to achieve optimal antiviral effect.34 Oral absorption of telbivudine is not altered by food intake immediately before oral dosing and therefore can be administered orally with no regard to the timing of meals.35

Given the potential for combination therapy with other antiviral medications, the drug-drug interaction of telbivudine has been studied with lamivudine and adefovir in healthy subjects. There is no bilateral pharmacokinetic drug-drug interaction between telbivudine and lamivudine or adefovir.36 Further drug-drug interaction study using telbivudine with peginterferon α-2a or cyclosporine A in healthy subjects shows no significant interaction between oral telbivudine, cyclosporine A and single-dose peginterferon α-2a with respect to the pharmacokinetics of telbivudine. Although no effect on the pharmacokinetics of cyclosporine A has been observed, no firm conclusion can be made on the effects of telbivudine on peginterferon α-2a given the high variability in the pharmacokinetic data of peginterferon α-2a and small sample size of the study.37 As telbivudine is predominantly excreted by the kidneys, interaction with cytochrome P450 isoforms is unlikely and hepatic impairment has no significant effect on the pharmacokinetic parameters of telbivudine.38

**Phase I/II trial**

The first human phase I/II clinical trial of telbivudine is a double blind, placebo-controlled dose escalation study looking at the safety, antiviral efficacy and pharmacokinetic profile. Doses of 25, 50, 100, 200, 400 and 800 mg daily have been studied, with a cohort of seven patients with HBeAg-positive CHB randomised at a ratio of 6:1 to receive telbivudine or matching placebo for each dosing level. Treatment was given for a period of 4 weeks and patients were followed-up for an additional 12 weeks. Following oral administration, telbivudine is rapidly absorbed with a mean time to maximum concentration ranging from 0.8 to 2.8 hours after dosing. Plasma elimination of telbivudine follows a monophasic pattern over
an 8-hours sampling period. The observed mean terminal half-life ranges from 2.5 to 5.0 hours.

After 4 weeks of telbivudine treatment, a dose-related virological response is observed. Treatment with telbivudine at doses of 25, 50, 100, 200, 400 and 800 mg resulted in 2.5, 2.68, 3.19, 2.89, 3.63 and 3.75 log copies/mL decline in serum HBV DNA respectively. This compares to a 0.13 log decrease in the placebo group. None of the patients in the placebo group achieved a 2 log reduction in serum HBV DNA, compared to 97% of patients in telbivudine recipients (P<0.0001).

Additional pharmacodynamic assessment was performed using maximal effect (E_{max}) modeling, which describes the antiviral activity of each dose as a function of the dose required to produce a 50% viral load reduction or undetectable HBV DNA. Near-maximal reduction of viral load is observed with telbivudine doses between 400 and 800 mg daily.

Further viral dynamics modeling shows a biphasic pattern of viral clearance with rapid decline in viral load during the first week of treatment corresponding to the first-phase clearance, indicating the suppression of free circulating HBV. No effect on the suppression of serum HBV DNA is observed with increasing doses of telbivudine during this first phase clearance. After the first week, a more gradual decline in viral load is observed, corresponding to the second phase of viral clearance, indicating the suppression of HBV in infected hepatocytes. In contrast, viral suppression is dose-related during the second phase of viral clearance at doses of up to 400-800 mg daily. In addition, patients given telbivudine of 400-800 mg daily are associated with a slower rebound of HBV DNA after stopping treatment.39

**Phase IIb trial**

Given the favorable results in phase I/II study, an international multi-centered phase IIb trial has been initiated in 104 patients with compensated HBeAg-positive CHB. Telbivudine doses of 400 and 600 mg daily were selected from the complementary E_{max} modeling and viral dynamics analysis of the phase I/II study. Five daily oral antiviral treatment regimens given for 1 year were investigated, including telbivudine 400 mg, telbivudine 600 mg, telbivudine 400 mg plus lamivudine 100 mg, telbivudine 600 mg plus lamivudine 100 mg or lamivudine 100 mg. Patients who completed 1 year of treatment were offered a subsequent follow-on study. The primary endpoint was the reduction in serum HBV DNA from baseline. The secondary endpoints were normalization of serum ALT levels, serum HBeAg loss and seroconversion and serum HBsAg loss and seroconversion. In addition to efficacy endpoints, safety assessments were also included.

Compared with patients treated with lamivudine monotherapy, a greater antiviral effect was achieved in patients treated with telbivudine, which was evident after the fourth week. At week 52, the median reduction from baseline serum HBV DNA levels were greater than 6 log in those treated with telbivudine compared to 4.66 log in those treated with lamivudine alone. No significant differences were observed in those treated with 400 mg of telbivudine, 600 mg of telbivudine or in those treated with combination telbivudine and lamivudine. The mean log reductions of serum HBV DNA at week 52 for patients on lamivudine monotherapy, telbivudine monotherapy and combination telbivudine and lamivudine therapy were 4.57, 6.01 and 5.99, respectively, with significantly greater reductions of mean serum HBV DNA levels seen in both telbivudine monotherapy and with combination therapy compared with lamivudine monotherapy. (P<0.05). At 52 weeks, 61% of patients receiving telbivudine had undetectable serum HBV DNA by polymerase chain reaction (PCR) (<200 copies/mL) compared with 32% in those treated with lamivudine (P<0.05) and 49% in those treated with combination therapy (P=NS).

Normalization of ALT at week 52 was observed in 86% of those treated with telbivudine compared with 63% of those treated with lamivudine alone (P<0.05) and in 78% of patients treated with combination therapy (P=NS). HBeAg seroconversion occurred in 31, 15 and 22% in those treated with telbivudine, combination therapy and lamivudine monotherapy respectively (P=NS). No HBsAg loss was seen across all three groups.

At week 48, virological breakthrough was seen in 21, 5 and 12% in those treated with lamivudine, telbivudine and combination treatment, respectively. Further analysis by DNA sequencing showed presence of YMDD mutation in 21% of those treated with lamivudine, 5% of those treated with telbivudine and 10% of those treated with...
combination treatment. The specific mutation for telbivudine will be discussed in the next section.

This phase IIb trial shows that telbivudine monotherapy has superior antiviral efficacy compared with lamivudine alone and there are no additional benefits with combining lamivudine and telbivudine together. Telbivudine is associated with a lower chance of developing YMDD mutations compared with those treated with lamivudine either alone or with telbivudine.

**Phase III GLOBE trial**

From the phase II clinical trial, a large international multi-centered randomized double-blinded study comparing the efficacy of telbivudine at a daily dose of 600 mg against lamivudine 100 mg has been undertaken. From 112 centers, 1367 patients with compensated CHB were recruited for this 2-year study, of which 921 were HBeAg positive and 446 were HBeAg negative. Primary analysis was performed at week 52 with further interim analysis at week 76 and final analysis at week 104.

At week 52, patients treated with telbivudine had significantly higher therapeutic response rate compared with lamivudine (75 and 67%, respectively, \( P < 0.05 \)), as defined by suppression of HBV DNA to 5 log or less and normalization of ALT or loss of HBeAg. About 65% of patients treated with telbivudine had a histological response of 2 points or greater improvement in Knodell necroinflammatory score without progression of fibrosis, as compared with 56% in those treated with lamivudine (\( P < 0.05 \)). The mean decline in log HBV DNA levels and rates of undetectable HBV DNA by PCR was higher in the telbivudine group compared with those on lamivudine (-6.5 vs. -5.5 and 60 vs. 40%, respectively, \( P < 0.05 \)). The benefits in therapeutic responses as defined above, mean decline in log HBV DNA from baseline and rates of undetectable HBV DNA by PCR appears more marked by week 76 (75 vs. 58%, -6.6 vs. -5.2 and 69 vs. 41%, respectively, \( P < 0.05 \)). The mean log HBV DNA change from baseline in HBeAg positive patients and also the rates of achieving undetectable HBV DNA by PCR is shown in Figures 3 and 4, respectively. In addition, higher rates of HBeAg loss and normalization of ALT was seen in those treated with telbivudine compared with lamivudine at week 76 (40 vs. 26%, 78 vs. 68%, respectively, \( P < 0.05 \)).

![Figure 3: Mean logarithmic reduction of HBV DNA from baseline in HBeAg-positive patients treated with lamivudine 100 mg or telbivudine 600 mg.](http://www.hepatitisbannual.org)

![Figure 4: Time to PCR-negativity in patients treated with telbivudine 600 mg and lamivudine 100 mg daily.](http://www.hepatitisbannual.org)
Viral resistant mutation

At 48 weeks, 81 patients had viral breakthrough as defined by (1) increase in HBV DNA $>10^5$ after initial decline below this level or (2) a 1 log increase after a prior 2 log drop in those who never achieved HBV DNA $<10^5$. Of these 81 patients, 19 occurred during telbivudine therapy with 17 showing genotypic resistance and the remaining 62 occurred during lamivudine therapy of which 52 had genotypic resistance. The genotypic resistance all showed evidence of YMDD mutation and no new telbivudine-specific resistant mutants were found.

The YMDD mutations detected in the telbivudine group were single M204I mutations in 16 patients (94%), with only 1 (6%) patient having mixed M204I and M204V mutations. In the lamivudine group and YMDD mutations were more variable, with 25 (48%) having M204I, 15 (29%) having M204V and 12 (23%) having a mixture of M204I and M204V mutations. In vitro findings have shown that the antiviral efficacy of lamivudine is reduced against M204V and M204I mutant viruses. In contrast, telbivudine shows reduced activity against M204I mutants, but retains its antiviral efficacy against M204V mutants. This is consistent with the finding that telbivudine resistance is almost exclusively due to the M204I mutation and does not include M204V mutants.

The genotypic resistant rates at week 48 were higher overall in the lamivudine group compared with the telbivudine group (8.3 and 2.7%, respectively, $P=0.001$) and also in HBeAg positive patients (8.2 and 3.0%, respectively, $P=0.001$) and in HBeAg negative patients (8.5 and 2.1%, respectively, $P=0.005$). In vitro studies have shown telbivudine resistant mutants to remain sensitive to adefovir. Conversely, telbivudine is 2-fold more active against the N236T adefovir resistant mutations compared with wild-type HBV.\textsuperscript{42}

This phase III trial concludes that telbivudine is superior to lamivudine in all virological endpoints with greater mean HBV DNA reduction, higher rate of undetectable HBV DNA by PCR, lower chances of YMDD mutation and treatment failure in both HBeAg-positive and HBeAg-negative patients. In HBeAg-positive patients, telbivudine shows greater therapeutic response and histological improvement compared to lamivudine. The final results of this phase III study will become available in late 2006.

Core promoter/precore mutation

Examining 446 patients with HBeAg CHB enrolled in the phase III GLOBE trial, 414 patients (93%) had precore (PC) and/or core promoter (CP) mutations. There was no difference in treatment outcomes at 1 year between those that had CP, PC, combined CP and PC and those with neither mutation, with telbivudine showing greater antiviral efficacy compared to lamivudine across all groups.\textsuperscript{43}

Early viral suppression

The importance of effective early viral suppression with antiviral treatment and its prognostic significance on long term therapy has been well documented in several studies. In patients treated with lamivudine, reduction of serum HBV DNA to less than 3 log copies/mL after 24 weeks of treatment results in a lower YMDD mutation rate during subsequent prolonged therapy.\textsuperscript{44} Similarly, in patients treated with adefovir, a higher HBV DNA at week 48 is predictive of emergence of subsequent adefovir resistance.\textsuperscript{19} For patients treated with 48 weeks of peginterferon $\alpha$-2a, reduction of HBV DNA below 400 copies/mL at week 12 is associated with a sustained response at week 72.\textsuperscript{45}

The prognostic significance of early viral suppression at 24 weeks has been assessed with patients treated with telbivudine in the phase Ib clinical study. All patients with undetectable serum HBV DNA at week 24 had undetectable HBV DNA by PCR at week 52. In patients with detectable serum HBV DNA at week 24, the chance of an undetectable HBV DNA level at week 52 was inversely related to the viral load at week 24. In those patients with serum HBV DNA less than 3 log copies/mL at 24 weeks, none developed virological breakthrough. These patients also had higher rates of normalization of ALT and loss of HbeAg.\textsuperscript{40}

The effect of early HBV suppression is also investigated in the larger phase III study. Patients with serum HBV DNA less than 3 log copies/mL at 24 weeks had higher HBeAg seroconversion rates (38 vs. 8%, respectively, $P<0.0001$), higher negative HBV DNA by PCR in HBeAg-positive and HBeAg-negative patients (85 vs. 14 and 86 vs. 28%, respectively, $P<0.0001$) and a 8 to 61-fold reduced odds of viral breakthrough ($P<0.0001$) at week 52 when compared with those patients with higher viral loads at week 24.
The same effect is observed in both patients treated with telbivudine and with lamivudine.\textsuperscript{41}

**Safety profile**

In pre-clinical studies using animal models, no significant effects in chronic toxicity, carcinogenicity, reproductive and developmental toxicity have been observed, suggesting minimal risk for toxicity in humans. Telbivudine is now proven to be safe and well-tolerated in earlier dose-evaluation studies and in subsequent clinical trials. To date, no reports of serious adverse effects or dose-limiting toxicities have been observed in humans. In the initial dose-finding studies, the overall safety profile of telbivudine was comparable to placebo. Most of the adverse events reported in the phase 2b trial were not attributed to the telbivudine and the two serious events reported were not treatment-related. The clinical side-effects profile was similar to that of lamivudine in the phase III study.

**CONCLUSION**

Telbivudine has been proven to be safe both in \textit{in-vitro}, animal and human studies. Recent phase III study results have shown potent antiviral effects with superior efficacy to lamivudine in reduction of HBV DNA, normalization of ALT and in the rate of HBeAg seroconversion. In addition, viral resistant mutations occurred at a lower rate compared with lamivudine.

Given that complete eradication of HBV has eluded all current therapies, the next best alternative is through prolonged maximal suppression of HBV DNA. By this mechanism, the ultimate goal of lowering the chance of developing cirrhotic complications and HCC can be achieved. However, to achieve this goal, more potent antiviral therapies are required. Whether this requires monotherapy or combination therapy is still under exploration. Though combination therapy has certainly been the strategy for successful HIV treatment, combinations of lamivudine and telbivudine, lamivudine and adefovir and lamivudine and peginterferon α-2a have not shown any additional benefit in antiviral efficacy over monotherapy.\textsuperscript{7,8,40,46}

This may reflect the current limited number of antiviral agents available for this disease, mostly acting on the polymerase region of the virus.

The development of drug resistance continues to be a problem, again highlighting the need for newer agents and supporting the use of combination treatment. Through adequate viral suppression the chance of developing drug resistant mutations are likely to decrease. Different drugs targeting different stages of HBV viral replication and the immune response to HBV infection, along with the use of drugs with complementary resistant profiles may lower the rate of resistance allowing for better viral suppression.

Telbivudine has been shown to be a promising up-and-coming agent for the treatment of CHB given its excellent safety profile and potent antiviral effect. Further studies are required to determine its long-term efficacy in the prevention of cirrhosis and its related complications including HCC.

**REFERENCES**


Bridges E. Telbivudine preclinical safety studies suggest minimal risk of chronic toxicity, reproductive toxicity or carcinogenicity. J Hepatol 2006;44:S147.


Zhou X. Clinical pharmacokinetics of telbivudine, a potent antiviral for hepatitis B, in subjects with impaired hepatic or renal function. Hepatology 2004;40:672A.


Lai C. Telbivudine (LdT) vs Lamivudine for Chronic Hepatitis B: First year results from the International Phase III GLOBE Trial. Hepatology 2005;42:S748A.


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