

FRESH FROM THE PIPELINE

Telbivudine

Jules Dienstag, Chris Easley and Peter Kirkpatrick

Telbivudine (Tyzeka; Idenix/Novartis), a nucleoside analogue that inhibits the hepatitis B virus polymerase, was approved by the US FDA in October 2006 for the treatment of adults with chronic hepatitis B.

Despite the availability of effective vaccines, more than 350 million people worldwide have chronic infection with hepatitis B virus (HBV). Hepatitis B is a leading cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma and accounts for ~1 million deaths a year¹. There is therefore a need for antiviral drugs with the potential to suppress viral replication or eliminate infection and thereby halt the progression of liver injury.

Two types of anti-HBV drugs — interferons, which some classify as immunomodulators, and nucleoside/nucleotide analogues — have been approved so far^{2,3}. A recombinant form of interferon- α -2b (Intron A; Schering-Plough) became the first FDA-approved drug for treating HBV in 1992. It has the advantages of a finite duration of therapy (4–6 months) and a lack of emergence of resistance, but its use has been limited by adverse effects and the need for frequent injections. A long-acting PEGylated interferon, PEG-interferon- α -2a (Pegasys; Roche), was subsequently approved in the United States and Europe in 2005.

In 1998, the first nucleoside analogue, lamivudine (Epivir-HBV; GlaxoSmithKline) was approved for treating HBV. It has since been joined on the market by the nucleotide analogue adefovir dipivoxil (Hepsera; Gilead) and the nucleoside analogues entecavir (Baraclude; Bristol-Myers Squibb) and telbivudine (Tyzeka; Idenix/Novartis).

Basis of discovery

The nucleoside/nucleotide analogues that are approved for the treatment of HBV all target the HBV polymerase^{2,3}, which, as well as acting as a conventional DNA polymerase, also has a reverse transcription function for RNA intermediates. Inhibition of this enzyme by these agents suppresses viral replication^{2,3}.

Lamivudine became a popular treatment option following its approval in 1998, but resistance to lamivudine resulting from mutations in the HBV polymerase emerges rapidly, which limits its long-term use^{2,4}.

The proportion of patients with lamivudine resistance attributable to the common YMDD mutation has been reported to rise from ~15–25% after 1 year to 70% after 4 years⁴. This problem, and also the goal of achieving greater suppression of viral replication than lamivudine can deliver, has stimulated efforts to develop new, more potent agents that have activity against lamivudine-resistant HBV and/or for which resistance might be slower to emerge. Studies so far with adefovir and entecavir, which both have activity against lamivudine-resistant HBV, indicate that resistance rates for these drugs, especially for entecavir, are considerably lower^{2,3}.

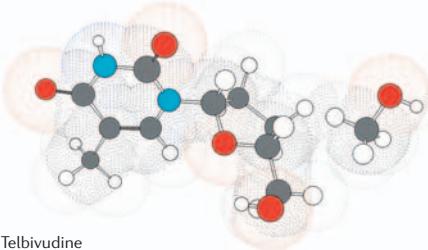
Drug properties

Studies with a series of simple ‘unnatural’ nucleosides that differ in stereochemical configurations showed that the β -L-enantiomer of the natural nucleoside thymidine, LdT (FIG. 1) — now known as telbivudine — had potent and specific anti-HBV activity⁵. Telbivudine is phosphorylated by cellular kinases to the active triphosphate form, which inhibits HBV DNA polymerase by competing with its natural substrate thymidine 5'-triphosphate, resulting in the inhibition of HBV replication^{6,7}. Importantly, telbivudine 5'-triphosphate does not inhibit human DNA polymerases α , β or γ ^{5,7}, which has been associated with the mitochondrial toxicity of some of the other nucleoside analogues used in antiviral therapy.

Clinical data

The safety and efficacy of telbivudine were assessed in a randomized, double-blind, active-controlled clinical trial involving 1,367 patients aged 16 years or older with chronic hepatitis B^{7,8}. All patients had evidence of HBV infection with viral replication (positive for serum hepatitis B surface antigen

Telbivudine



(HBsAg), positive for hepatitis Be antigen (HBeAg) or HBeAg-negative with HBV DNA detectable by a PCR assay), elevated alanine aminotransferase (ALT) levels to ≥ 1.3 times the upper limit of normal and chronic inflammation on liver biopsy compatible with chronic viral hepatitis⁷.

Telbivudine (600 mg orally, once daily) was compared with lamivudine (100 mg orally, once daily) for a treatment period of up to 104 weeks; the primary data analysis was conducted after all subjects had reached week 52 (REF. 7). Clinical and virological efficacy endpoints were evaluated separately in the HBeAg-positive and HBeAg-negative patient populations⁷. The primary endpoint of therapeutic response at week 52 was a composite serological endpoint requiring suppression of HBV DNA to $< 5 \log_{10}$ copies per ml in conjunction with either loss of serum HBeAg or ALT normalization⁷. Secondary endpoints included histological response, ALT normalization and various measures of antiviral efficacy⁷.

In HBeAg-positive patients, 75% of the patients receiving telbivudine and 67% of the patients receiving lamivudine had a therapeutic response⁷. In HBeAg-negative patients, 75% of the patients receiving telbivudine and 77% of the patients receiving lamivudine had a therapeutic response⁷. For HBeAg-positive patients, the mean reduction in HBV from the baseline after 52 weeks was $-6.45 \log_{10}$ copies per ml (60% with undetectable HBV DNA by PCR with a sensitivity threshold of 400 copies per ml) in the telbivudine group and $-5.54 \log_{10}$ copies per ml (40% with undetectable HBV DNA) in the lamivudine group. For HBeAg-negative patients, the reductions were $-5.23 \log_{10}$ copies per ml (88% HBV DNA undetectable) in the telbivudine group and $-4.40 \log_{10}$ copies per ml (71% HBV DNA undetectable) in the lamivudine group⁷.

Indications

Telbivudine is approved by the FDA for the treatment of chronic hepatitis B in adult patients with evidence of viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or aspartate transaminase; AST) or histologically active disease⁷.

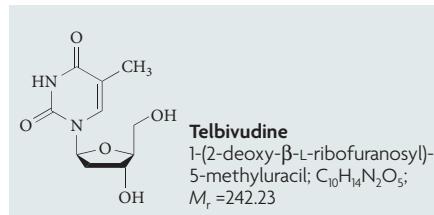


Figure 1 | Telbivudine.

ANALYSIS | DRUGS FOR HEPATITIS B

► Analysing clinical issues for drugs for hepatitis B is Jules Dienstag, M.D., Carl W. Walter Professor of Medicine at Harvard Medical School and Physician in the Gastrointestinal Unit (Medical Services) at Massachusetts General Hospital, Boston, USA.

Recent trials of novel anti-HBV drugs have highlighted the importance of potent viral suppression in achieving clinical endpoints such as HBeAg seroconversion and in preventing the emergence of resistance. During Phase II trials, reports of telbivudine's potential efficacy and resistance profile were very promising⁹. Phase III trials for telbivudine, however, indicate that although it has convincing superiority over lamivudine, it does not quite measure up to entecavir, which was approved by the FDA in 2005. Although entecavir and telbivudine were not studied head-to-head in the same trial, the baseline features of the study populations were very similar in the trials of each drug, and the performance of the lamivudine active control arm in both sets of trials was almost identical^{8,10,11}, which facilitates comparison.

Among HBeAg-positive patients in the trials for the two drugs, after 1 year, entecavir suppressed HBV DNA to undetectable levels in 69% of subjects¹⁰, whereas telbivudine treatment achieved undetectable HBV DNA in 60% of patients^{7,8}. For HBeAg-negative

patients, baseline levels of HBV DNA were lower in both trials, and the new drugs showed similar efficacy in this population, achieving an undetectable level of HBV DNA by PCR in ~90% of patients compared with ~70% for lamivudine^{7,8,11}. Of interest and concern, however, is that despite greater suppression of HBV DNA (~1–1.5 log₁₀ copies per ml) by telbivudine and entecavir than by lamivudine, the higher antiviral potency of the two new drugs did not translate into a higher rate of HBeAg seroconversion compared with lamivudine (~20% at 1 year)^{7,8,10}.

Turning to the issue of resistance, in the Phase III trial of telbivudine (involving treatment-naïve patients), resistance was reported to have emerged in 3% of the telbivudine group versus 8% of the lamivudine group^{7,8}. The resistance profile of telbivudine in this trial was therefore not as good as that of entecavir, which was not associated with any resistance during a year of therapy in treatment-naïve subjects^{10,11}. These differences become more significant after 2 years of treatment. Although no resistance emerged among treatment-naïve subjects treated with entecavir for 2 years¹², resistance emerged in ~20% (versus ~30% for lamivudine in these trials) of HBeAg-positive and ~8% (versus ~20% for lamivudine) of HBeAg-negative patients treated with telbivudine¹³.

Although benefit continues to increase with longer duration of treatment with both entecavir and telbivudine, viral suppression by entecavir is higher (for example, for HBeAg-positive patients, at 2 years, HBV DNA was undetectable in 87% of an entecavir group¹² compared with 54% of a telbivudine group¹³). In summary, although telbivudine has demonstrated superiority to lamivudine, its niche among the options for treatment of chronic hepatitis B remains to be determined. For HBV therapy in general, combination therapy is likely to be required to maintain potent HBV suppression in the long term and pre-empt the emergence of resistance, and several nucleoside and nucleotide analogues, including telbivudine, are now being evaluated in various combinations in clinical trials.

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Competing interests statement

J.D. declares competing financial interests; see web version for details.

Box 1 | Market for hepatitis B drugs

Analysing the market for hepatitis B drugs is Chris Easley, Engagement Manager, Product and Portfolio Development Practice, IMS Management Consulting, London, UK.

An estimated 350 million people worldwide are infected with the hepatitis B virus (HBV), of whom ~80% are in Asia (China has the largest incidence). The prevalence of HBV infection in western countries is lower — for example, around 1.25 million are affected in the United States — and is decreasing, which is in part due to the effective introduction of vaccination programmes. Conversely, the number of prescriptions for HBV is expected to continue growing in the short-medium term as diagnosis and treatment rates improve.

Although acute infection can, in rare cases, result in liver failure, it is patients who progress to chronic HBV infection who are at greatest risk of developing serious co-morbidity, including cirrhosis, liver failure and hepatocellular carcinoma. Despite the recently increased range of therapeutic options, unmet needs in HBV infections persist, not least because many HBV carriers do not exhibit symptoms and hence go untreated.

Treatment of chronic HBV infection aims to reduce viral replication and thereby slow disease progression. Although interferon-α-2b and lamivudine are the established treatment options for HBV, telbivudine joins a range of newer HBV-polymerase inhibitors, which have started to replace older therapies — a trend that is expected to continue. Telbivudine was approved in the United States in October 2006 and received a positive opinion from the European Committee for Medicinal Products for Human Use in February 2007. Three nucleoside antivirals are also currently in Phase III trials for HBV — emtricitabine, clevudine and tenofovir — as well as a non-nucleoside antiviral compound (NOV-205) and a PEG-interferon-α-2b candidate. Telbivudine as a fixed-dose combination with valtorcitabine is also currently in Phase IIb trials; this combination is being targeted as a treatment alternative for patients who do not respond adequately to single-agent therapy. Analysts' sales expectations for telbivudine range from US\$250–543 million in 2012.