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Novel anti-hepatitis B agents: a focus on telbivudine

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SUMMARY

Although preventable by vaccination, hepatitis B infection is common, affecting more than 350 million individuals worldwide. Chronic hepatitis B infection is associated with the complications of chronic liver disease including cirrhosis and hepatocellular carcinoma. Current agents designed to target hepatitis B are hindered by the development of resistance, poor tolerability or limited efficacy and a demand for new agents and strategies continues. This review focuses on telbivudine, a novel agent in the fight against hepatitis B.

Keywords: Hepatitis B; telbivudine; novel agents

INTRODUCTION

Despite being a vaccine preventable illness, in the USA alone more than 8000 cases of hepatitis B infection were reported in the year 2000 (1). The WHO estimates that more than 350 million individuals are infected worldwide, constituting 5% of the global population (2). Because of the frequently asymptomatic nature of the infection (and continued underreporting) the proportion of individuals living with hepatitis B is likely to be even greater. Modelling data from the National Health and Nutrition Examination Surveys has estimated that there were more than 80,000 new infections in the USA in 2000 (3). These patients are at risk of the complications of chronic hepatitis B infection – liver disease including cirrhosis and hepatocellular carcinoma. Because of the significant morbidity and mortality associated with the infection, antiviral agents targeting hepatitis B have emerged as a major area of research.

This article focuses upon telbivudine, an oral nucleoside agent, with encouraging data to support its introduction into the anti-hepatitis B armoury.

PREVENTION

Hepatitis B vaccination has been available for more than 20 years. In the USA, the hepatitis B eradication programme has targeted all pregnant women and initiated immunoprophylaxis in exposed infants. It has also advised routine immunisation of children, screening of teenagers and vaccination in those who have missed childhood vaccination. High-risk individuals including those with multiple sexual partners, men who have sex with men, injecting drug users, prison residents, contacts of individuals with acute or chronic hepatitis B, healthcare workers and those with renal failure are also targeted.

Despite this vaccination strategy, hepatitis B infection remains common and physicians are encouraged to recognise the symptoms, signs and complications of hepatitis B infection, and remain abreast of novel therapies.

TREATMENT OF HEPATITIS B

The primary aim of hepatitis B therapy is the durable suppression of hepatitis B replication halting the progression of liver inflammation and fibrosis, potentially reversing it. Studies have illustrated a link between the level of hepatitis B virus replication and the degree of hepatic injury (4,5). The FDA currently approves entecavir, lamivudine, interferon alpha-2b, pegylated interferon alpha-2a, and adefovir dipivoxil, as monotherapeutic agents. However, their use is compounded by the development of resistance, poor tolerability and limited efficacy.

Interferon is an injectable compound with a plethora of side-effects, leading to intolerance in many individuals. Lamivudine and adefovir are limited by the development of resistance. Although resistance is less frequent with adefovir, this agent may be restricted by nephrotoxicity and a lack of potency. Care must also be taken when using entecavir in individuals with renal dysfunction. A number of new drugs – telbivudine, tenofovir, emtricitabine, clevudine, pradefovir

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and valtorcitabine – are under investigation. Among these, telbivudine is currently undergoing FDA review and forms the focus of this editorial.

TELBIVUDINE

Telbivudine (LdT) is a novel agent for the treatment of chronic hepatitis B. It acts by targeting HBV DNA polymerase, particularly synthesis of the positive strand of HBV DNA, in contrast to lamivudine which primarily targets the negative strand (6). This selective targeting is associated with a slower development of resistance mutations. At present, telbivudine has undergone head-to-head trials with the FDA-approved agents, adefovir and lamivudine only.

In preclinical studies telbivudine was investigated in rats and monkeys at concentrations substantially greater than the anticipated dose in humans. No significant toxic effects were observed in animal models, suggesting a minimal risk of cumulative, carcinogenic or reproductive toxicity in humans (7).

A phase IIb clinical trial compared telbivudine monotherapy, and telbivudine/lamivudine in combination, with a control arm of lamivudine monotherapy (8,9). A total of 104 individuals with hepatitis B e antigen (HBeAg)-positive chronic hepatitis B were enrolled to receive 1 year of either:

1. Telbivudine 400 mg qd
2. Telbivudine 600 mg qd
3. Telbivudine 400 mg and lamivudine 100 mg qd
4. Telbivudine 600 mg and lamivudine 100 mg qd
5. Lamivudine 100 mg qd.

After 52 weeks, the telbivudine doses were increased to 600 mg qd throughout. At 104 weeks, individuals exposed to telbivudine monotherapy had a 1.3 $\log_{10}$ greater mean viral load reduction compared with those receiving lamivudine monotherapy. Suppression of HBV DNA was superior in the telbivudine monotherapy arm, where 71% of individuals achieved an undetectable viral load, compared with only 32% of those in the lamivudine monotherapy arm ($p < 0.05$). The telbivudine monotherapy group also showed greater normalisation of serum ALT and higher rates of HBeAg seroconversion. Of note, the rate of treatment failure was significantly lower in the telbivudine monotherapy arm (4.5%) than in the lamivudine monotherapy arm (21%) ($p < 0.05$). There was no significant difference between the use of telbivudine alone and telbivudine/lamivudine in combination. Interestingly, as with many of the later telbivudine studies, there was a correlation between early reduction of HBV DNA (24-week data) and long-term efficacy outcomes, suggesting that individuals benefit from rapid suppression of HBV viral load.

The Globe study (10) has investigated the use of telbivudine compared with standard therapy – lamivudine. Globe is a phase III, double-blinded, randomised clinical trial designed to compare telbivudine vs. lamivudine in over 1300 individuals with chronic hepatitis B, over a 2-year period. It is an international, multicentre centre study, recruiting from over 112 clinical centres.

Individuals entered into the study were screened for HBeAg positivity, and required HBV DNA >6 $\log_{10}$ copies/ml by COBAS PCR assay, an ALT greater or equal to 1.3–10 times the upper limit of normal and compensated liver disease. They were stratified for HBeAg status (positive or negative) and ALT value (less or greater than 2.5 times the upper limit of normal). Individuals were randomised to receive 2 years of either:

1. Lamivudine 100 mg qd or
2. Telbivudine 600 mg qd.

The primary end-point of Globe was 'Therapeutic Response', a composite serological end-point comprising suppression of serum HBV DNA to below 5 $\log_{10}$ copies/ml. Secondary end-points included reduction in serum HBV DNA, normalisation of serum ALT, HBeAg loss, seroconversion, and safety. The baseline characteristics are shown in Table 1.

At 1 year, a significant *reduction* in HBV DNA in the telbivudine exposed individuals compared with lamivudine was observed, there being a greater HBV *clearance* to PCR non-detectable levels in this group also. Telbivudine exposed individuals who were HBeAg positive had a -6.4 $\log_{10}$ copies/ml HBV DNA fall vs. -5.5 $\log_{10}$ in the lamivudine-treated individuals ($p < 0.01$). In HBeAg-negative patients, similar results were achieved, -5.2 $\log_{10}$ in the telbivudine group vs. -4.4 $\log_{10}$ in the lamivudine arm ($p < 0.01$). Significantly greater clearance of HBV DNA to PCR non-detectability was observed in the telbivudine arm with 60% of HBeAg-positive individuals having an undetectable HBV DNA compared with 40% in the lamivudine arm ($p < 0.01$). In HBeAg-negative individuals, 88% in the telbivudine arm, vs. 71% in the lamivudine arm, achieved undetectability ($p < 0.01$). There was also less treatment

Table 1 Baseline characteristics of individuals in the Globe study

	HBeAg-positive patients		*HBeAg-negative patients*	
	Telbivudine (n = 450)	*Lamivudine (n = 453)*	*Telbivudune (n = 222)*	*Lamivudine (n = 221)*
Mean baseline HBV DNA ($\log_{10}$ copies/ml)	9.5	9.5	7.7	7.4

Table 2 Efficacy at 1 year against virological suppression at 24 weeks in HBeAg-positive individuals in the Globe study

	Virological suppression at week 24 (%)			
HBeAg-positive patients at week 52	*< 300 copies/ml*	*300–1000 copies/ml*	*100–10,000 copies/ml*	*> 10,000 copies/ml*
HBV DNA (< 300 copies/ml)	90	70	30	5
ALT normalisation	90	89	80	54
Viral breakthrough	1	3	8	11

Table 3 Efficacy at 1 year against virological suppression at 24 weeks in HBeAg-negative individuals in the Globe study

	Virological suppression at week 24 (%)			
HBeAg-negative patients at week 52	*< 300 copies/ml*	*300–1000 copies/ml*	*100–10,000 copies/ml*	*> 10,000 copies/ml*
HBV DNA (< 300 copies/ml)	93	66	38	10
ALT normalisation	83	74	63	36
Viral breakthrough	0	9	18	32

failure with telbivudine (HBV DNA remained above 5 $\log_{10}$ copies/ml): 5% in HBeAg-positive patients, compared with 13% for lamivudine ($p < 0.01$), and 0% in HBeAg-negative patients, vs. 3% for lamivudine (p = ns). For all clinical and virological efficacy parameters, efficacy at 1 year was proportional to HBV DNA level at week 24 (see Tables 2 and 3).

Achieving HBV DNA < 300 copies/ml at week 24 with lamivudine or telbivudine was highly predictive of not developing resistance at week 52. Overall, significantly less resistance was seen in the telbivudine arm than the lamivudine arm (2–3% vs. 7–8%). The ability to predict subsequent outcomes at 24 weeks enables clinicians to estimate response and plan future therapeutic interventions.

Telbivudine was associated with fewer flares of serum ALT levels when compared with lamivudine. The most common adverse events, seen with both agents, were upper respiratory tract infection, head-ache, fatigue and nasopharyngitis, with little difference in occurrence in either arm of the study. ALT elevation was seen more frequently in the lamivudine-exposed population, whereas, transient elevations in creatinine kinase (not requiring intervention) were seen more commonly with telbivudine.

On reviewing histological findings, 65% of HBeAg-positive individuals exposed to telbivudine had a significant improvement in histology (defined as a two-point improvement in Knodell inflammatory score, with no worsening in fibrosis score) vs. 56% of those exposed to lamivudine ($p < 0.01$). In HBeAg-negative individuals, there was no difference in histological outcomes between the two arms.

There was no significant difference in seroconversion rates in either arm of the study, nor was there a significant difference in loss of HBeAg alone.

Another phase III trial with telbivudine, reported by Hou et al. (11), compared telbivudine with lamivudine in Chinese individuals with chronic hepatitis B, 87% of whom were HBeAg-positive. At 52 weeks, 70% of telbivudine exposed individuals had undetectable HBV DNA levels (defined as < 300 copies/ml by PCR) compared with only 43% of lamivudine-treated individuals ($p < 0.001$). When reviewing secondary end-points, telbivudine was superior to lamivudine in normalising ALT levels (89% vs. 76%, respectively, $p < 0.005$). In telbivudine-exposed individuals who were HBeAg-positive on entering the study, 25% had seroconverted at 52 weeks, compared with 18% of those treated with lamivudine. Although this was not statistically significant, HBeAg loss was greater in the telbivudine group (31% vs. 20%, respectively, $p < 0.05$). Both telbivudine and lamivudine were equally well tolerated.

A third major study, reported by Heathcote et al. (12), has compared the use of telbivudine with adefovir in HBeAg-positive individuals with chronic hepatitis B. This was a multicentre trial which enrolled 135 patients. As with Globe, individuals were chronically infected with HBV without evidence of liver decompensation. Participants were HBeAg-positive, treatment naïve, with a serum HBV DNA greater than 10^6 copies/ml and ALT values of 1.3–10 times the upper limit of normal.

Individuals were randomised to receive:

1. Telbivudine 600 mg qd or
2. Adefovir 10 mg qd.

The primary endpoint of the study was serum HBV reduction at 24 weeks. Secondary end-points were rates of HBV non-detectability, HBeAg loss, and ALT normalisation. Of the 133 participants, 44 individuals were randomised to the telbivudine arm, 89 to adefovir.

At 24 weeks, a significantly greater HBV DNA reduction was seen in those individuals exposed to telbivudine (6.37 vs. 5.11 $\log_{10}$ copies/ml; $p < 0.01$). In individuals exposed to adefovir, 42% failed to reach a HBV DNA below

5 $\log_{10}$ copies/ml, compared with 5% in the telbivudine arm ($p < 0.01$). There was no significant difference in HBeAg loss or normalisation of ALT levels between the study arms. There was no difference in adverse events between arms of which the most common was upper respiratory tract infection.

PRECORE/CORE PROMOTOR MUTANTS

HBeAg-negative chronic hepatitis B has been associated with the accumulation of HBV mutations in the precore (PC) and/or core promoter (CP) regions of the genome (13,14).These mutations decrease HBeAg transcription and secretion and studies have illustrated a link between the development of PC and CP mutations and HBV genotype (15,16). However, the impact of CP or PC mutations on treatment response has not been investigated.

Within Globe, there were 446 HBeAg-negative individuals whose results were analysed to elucidate a potential relationship between CP/PC mutations and demographic/disease parameters at baseline, and the influence of these parameters on treatment outcomes at 1 year. As discussed above, telbivudine had greater antiviral efficacy than lamivudine. The majority (93%) of HBeAg-negative individuals had detectable CP and PC mutations amplified from their baseline sera. CP mutations were found most frequently in those individuals with HBV genotype A, being least common in those with genotype B. PC mutations were observed most commonly in individuals with genotype B, least commonly in genotype A. The majority of individuals with HBV genotypes C or D had both PC and CP mutations. At 1 year, there was no difference in efficacy outcomes in HBeAg-negative individuals, regardless of PC or CP pattern at baseline (17).

RESISTANCE

Of the 1367 individuals included in the Globe ITT analysis, 81 patients experienced viral breakthrough. Among these, genotypic resistance was confirmed in 69: 17 telbivudine-treated patients and 52 lamivudine recipients. Following sequencing, all resistance was associated with M204 variants in the YMDD motif of the genome (18). Individuals failing lamivudine had acquired either M204I, M204V or a mixed picture of M204M/I/V. In those exposed to telbivudine, M204I was the only mutation detected in 16 of 17 telbivudine patients with resistance; the other patient carried a mixture of M204M/I/V. The M204V lamivudine resistant mutation was associated with the 180M compensatory mutation, thus forming a double mutant, whereas the M204I telbivudine mutation was not. These results imply that telbivudine may suppress the emergence of fully resistant HBV via the M204V pathway that is dominant with lamivudine.

CONCLUSION

In the era of an effective vaccine, it is a travesty that so many of the world's population suffer the consequences of chronic hepatitis B infection. There remains a clear demand for novel antiviral agents. In trials to date, telbivudine appears to be efficacious, easy to take, with a good safety profile, proving to be an attractive therapeutic option in the management of hepatitis B.

DISCLOSURES

Mark Nelson has served on the advisory board to Idenix, and has served as an advisor and speaker for, and received research grants from, Gilead, Glaxo Smith Kline and Roche.

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