Drugs 2005; 65 (11): 1451-1460
0012-6667/05/0011-1451/$39.95/0

Drugs in Development for Hepatitis B

Maria Buti and *Rafael Esteban*

Liver Unit, Hospital General Universitari Vall d'Hebron, Barcelona, Spain

Abstract

The management of chronic hepatitis B (CHB) has improved dramatically over the last decade with the development of new drugs such as lamivudine and adefovir dipivoxil, in addition to the now standard interferon (IFN)-α therapy. These new drugs can achieve a significant reduction or inhibit replication of hepatitis B virus (HBV) DNA during therapy. However, in the majority of patients, particularly in those who are hepatitis B e antigen (HBeAg)-negative, the sustained off-therapy suppression of HBV DNA is rare. For this reason, several new antiviral and immunomodulatory agents are currently being evaluated.

Among the immunomodulatory agents, pegylated IFNα (peginterferon-α) has been shown to be more effective for HBeAg-positive CHB than either lamivudine or standard IFNα monotherapy, particularly in those patients infected by HBV genotypes A and B. The new antivirals entecavir, tenofovir disoproxil fumarate and telbivudine exhibit a more potent viral inhibitory effect than the currently approved drugs (IFNs, lamivudine and adefovir dipivoxil). However, the emergence of viral resistance has been witnessed and this could be one of the major limitations to the clinical use of these new drugs, particularly during prolonged therapy.

In HBeAg-negative patients it is more and more common for oral antiviral therapy to be administered for prolonged periods, as the sustained off-therapy response rates of short-term therapy are very low. Different studies are currently evaluating combination therapy, using lamivudine with adefovir dipivoxil or peginterferon-α with lamivudine; the preliminary results show virological responses no better than those achieved by monotherapy. However, as combination therapy is associated with a low likelihood of developing HBV drug resistance, this could result in a higher virological response during prolonged therapy.

In the near future the most realistic therapeutic option for the majority of patients with CHB will be long-term use of these new, more potent antiviral drugs, if they can achieve good safety profiles while maintaining low resistance rates at affordable costs.

Three agents are currently approved for the treatment of chronic hepatitis B (CHB): interferon (IFN)-α, lamivudine and adefovir dipivoxil. Each of these agents has limitations, and none demonstrates an excellent efficacy profile. Lamivudine and adefovir dipivoxil have the advantage of being administered orally, and both display excellent safety profiles.

Further therapies need to be developed as the sustained virological response rates of the three agents approved for the treatment of CHB, particularly when off-therapy, is still low. Drug resistance

limits their efficacy and new drugs are necessary for patients with CHB in particular clinical situations, such as immunocompromised and decompensated patients, patients with normal ALT levels, those resistant to lamivudine or to adefovir dipivoxil, and those who do not respond to the approved therapies.[1,2]

CHB can be divided into two major categories depending on the presence of the hepatitis B e antigen (HBeAg) and its antibody (anti-HBe): the HBeAg-positive and the HBeAg-negative forms.[1-3] HBeAg-positive CHB is characterised by an extremely high rate of hepatitis B virus (HBV) replication and persistent or intermittently increasing aminotransferase levels.[2] HBeAg-positive CHB may occur almost immediately after the acute phase of HBV infection or develop after several years of maintaining an immunotolerant state. Although between 5% and 15% of untreated HBeAg-positive patients achieve spontaneous clearance of HBeAg, development of anti-HBe and transition to the inactive carrier phase,[3-6] the majority maintain a high rate of HBV DNA replication, running the risk of severe liver necroinflammation with worsening fibrosis and development of cirrhosis increasing the risk of hepatocellular carcinoma (HCC).[6,7]

HBeAg-negative CHB, also referred to as anti-HBe-positive CHB, represents a late phase in the course of chronic HBV infection. It develops in those patients who lose HBeAg and, therefore, seroconvert to anti-HBe.[2-5,8] HBeAg-negative CHB may develop immediately following HBeAg loss or after reactivation of an inactive HBV carrier state. In the vast majority of patients, HBeAg-negative CHB is associated with the replication of HBV variants unable to produce HBeAg as a result of mutations at either the precore or basic core promoter regions of the viral genome.[3,9] HBeAg-negative CHB is a progressive and potentially severe form of chronic liver disease, often resulting in cirrhosis and an increased risk of developing HCC;[10,11] spontaneous remissions are very rare.

This review explores the potential benefits, for both HBeAg-positive and -negative CHB patients, of the new antiviral and immunomodulatory agents currently being developed; peginterferon-α, entecavir, emtricitabine, clevudine, tenofovir disoproxil fumarate and β-L nucleosides (table I). Information regarding these drugs remains limited, as they are only recently approved or in late phase clinical trials.

Table I. Therapeutic agents or approaches that are currently under evaluation for the treatment of chronic hepatitis B

Peginterferon-α
Newer antiviral agents
entecavir
emtricitabine
clevudine
L-nucleosides (e.g. telbivudine, torcitabine, L-deoxyadenosine)
tenofovir disoproxil fumarate
Combination therapies
peginterferon-α plus lamivudine
two antiviral agents (e.g. adefovir dipivoxil plus lamivudine, telbivudine plus lamivudine)
IFNα plus therapeutic vaccine(s)
antiviral agent(s) plus therapeutic vaccine(s)

IFN = interferon.

1. Peginterferon-α

Pegylation technology has been used to increase the pharmacokinetic and pharmacodynamic profile of the standard IFNα therapy; hence, achieving steady and durable serum IFNα concentrations with a single weekly administration. Two different peginterferon-α formulations have been developed, differing mainly in the polyethylene glycol molecule. Peginterferon-α-2b has a linear polyethylene glycol molecule, with a low molecular weight (12 kDa) [PegIntron®][1], and peginterferon-α-2a has a large (40 kDa), branched polyethylene glycol molecule (Pegasys®). Both forms of peginterferon-α have been licensed for use in the treatment of chronic hepatitis C, where they have replaced the standard IFNα because of their superior efficacy without the appearance of any new adverse effects and their easier administration mechanism. However, peginterferon-α-2a has recently been approved for use in the treatment of CHB.

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Some new data are available from the clinical trials of these peginterferons. The efficacy of peginterferon-α-2a in the treatment of patients with HbeAg-positive CHB was initially evaluated in a phase II trial using a small number of patients. The results of this trial showed that a 24-week course of peginterferon-α-2a is more effective than a 24-week course of standard IFNα (4.5MU three times weekly).[12] In a more recent large 52-week phase III trial investigating 266 HBeAg-positive CHB patients, peginterferon-α-2b was found to have an off-therapy efficacy equal to that of the combination therapy with peginterferon-α-2b plus lamivudine, achieving HBeAg loss rates of 36% and 35%, respectively, 24 weeks after termination of therapy.[13] These results are very similar to those reported when standard IFN and lamivudine were combined for a short period. An important feature of HBeAg-positive CHB is that the response to peginterferon-α is higher in those patients infected by genotypes A and B: HBeAg loss rates of 47% for genotype A, 44% for genotype B, 28% for genotype C and 25% for genotype D have been recorded.[13] Another trial investigating patients with HBeAg-positive CHB randomised 814 patients to receive either a 48-week course of peginterferon-α-2a monotherapy, peginterferon-α-2a plus lamivudine combination therapy or lamivudine monotherapy for equal periods. Both peginterferon-α-2a monotherapy and the combination of peginterferon-α-2a and lamivudine were superior to lamivudine monotherapy at week 72, that is, 6 months after the discontinuation of treatment. In this study, combination therapy performed no better than peginterferon-α-2a monotherapy. The HBeAg seroconversion rates witnessed were 32%, 27% and 19%, respectively, with normal ALT levels being observed in 41%, 39% and 28%, respectively[14] (table II).

In a 48-week trial, HBeAg-negative patients were randomised to receive either peginterferon-α-2a, lamivudine or the combination of peginterferon-α-2a plus lamivudine. Peginterferon-α-2a with or without lamivudine sustained a response superior to that of lamivudine 24 weeks after discontinuation of therapy. Undetectable HBV DNA (<400 copies/mL) was observed in 19% of patients treated with peginterferon-α-2a, 20% of those treated with the combination and 7% of those treated with lamivudine. Normal ALT levels were achieved in 59%, 60% and 44%, respectively.[15] These results suggest that peginterferon-α-2a monotherapy is equally effective as combination therapy and is more effective than lamivudine monotherapy. However, mean suppression of HBV DNA 6 months after therapy termination was degraded substantially in all three arms (mean reduction 1.6–2.3 $\log_{10}$ copies/mL), suggesting that relapses would eventu-

Table II. Efficacy of peginterferon-α in the treatment of patients (pts) with hepatitis B e antigen (HBeAg)-positive chronic hepatitis B. Studies of ≥1 year of therapy

Study/dosage	No. of pts	HBeAg loss (% pts)	HBeAg seroconversion (% pts)
Cooksley et al.[12]			
IFNα-2a 4.5MU tiw for 24 weeks	51		25
Peginterferon-α-2a 90 μg/week for 24 weeks	49		37
Peginterferon-α-2a 180 μg/week for 24 weeks	46		33
Peginterferon-α-2a 270 μg/week for 24 weeks	48		27
Janssen et al.[13]			
Peginterferon-α-2b for 52 weeks	136	36	
Peginterferon-α-2b + lamivudine for 52 weeks	130	35	
Lau et al.[14]			
Peginterferon-α-2a 180μg for 48 weeks	271	34	
Peginterferon-α-2a 180μg + lamivudine 100mg for 48 weeks	271	28	
Lamivudine 100 mg/day for 48 weeks	272	21	

IFN = interferon; **tiw** = three times weekly.

ally follow. This study has shown that longer follow-up periods are necessary in HBeAg-negative patients, as relapses often appear after an extended period.

The role of peginterferon-α therapy, with or without the addition of a nucleoside analogue, merits additional consideration; however, the development of more potent oral agents is likely to present very competitive alternatives to the peginterferon-α therapies. Although results of the combinations of peginterferon-α plus lamivudine do not seem to have been encouraging, an additional complimentary effect of these two drugs cannot be excluded, as not all combination regimens have been evaluated. Thus, the timing and duration of the administration of each drug, and the need for sequential or concurrent use, deserve further evaluation, as they may be important factors influencing the efficacy of this combination therapy in all or certain subgroups of CHB patients.

In summary, peginterferon-α is a useful drug, particularly for those HBeAg-positive patients infected by genotypes A or B, which allows a limited duration of HBV therapy. However, the optimal dose and duration of therapy remains to be defined.

2. Entecavir

Entecavir, a cyclopentyl guanosine analogue, is a potent inhibitor of HBV DNA polymerase, inhibiting both the priming and elongation steps of viral DNA replication.[1,2] Entecavir is effective against lamivudine-resistant mutants, but less effective against wild-type HBV.[2,3] Several studies have shown that at daily dosages of between 0.1 and 1.0mg, entecavir is well tolerated and effectively suppresses HBV replication, in both treatment-naive CHB patients and those with lamivudine-resistant disease.[16-20]

In a 24-week, double-blind, multicentre clinical trial 169 HBeAg-positive and -negative CHB patients were randomised to receive one of three oral dosages of entecavir (0.01, 0.1 or 0.5 mg/day) or lamivudine 100 mg/day.[18] Both entecavir 0.1 and 0.5 mg/day reduced viral load more effectively than lamivudine. Compared with the lamivudine therapy, entecavir 0.1 mg/day reduced HBV DNA by an additional 0.97 $\log_{10}$ and entecavir 0.5 mg/day by an additional 1.28 $\log_{10}$ ($p < 0.0001$). The entecavir 0.5 mg/day was more effective than 0.1 mg/day ($p = 0.018$), with 83.7% of patients treated with entecavir 0.5 mg/day experiencing a decrease in HBV DNA levels below the lower limit of detection compared with 57.5% treated with lamivudine 100 mg/day and 62% treated with entecavir 0.1 mg/day. Entecavir was well tolerated at all dosage levels, with most adverse events being mild or moderate and transient.

In a 48-week phase III study of 715 HBeAg-positive, nucleoside-naive patients, comparing the efficacy and safety of entecavir 0.5 mg/day and lamivudine 100 mg/day, patients were randomised 1 : 1 to receive either lamivudine or entecavir.[21] The primary endpoint, histological improvement, defined by a >2-point decrease in necroinflammatory activity and no worsening fibrosis, was observed in 72% of patients receiving entecavir and in 62% of those receiving lamivudine (p = not significant). A higher proportion of patients who received entecavir achieved normal ALT levels (78%) and undetectable HBV DNA (69%) when compared with those treated with lamivudine (70% achieved normal ALT levels and 38% undetectable HBV DNA). At week 48, HBeAg seroconversion occurred in 21% of entecavir- and 18% of lamivudine-treated patients; no patients developed entecavir resistance.[21] A similar study was designed in nucleoside-naive HbeAg-negative patients with CHB. 648 patients were randomised to receive either entecavir 0.5 mg/day or lamivudine 100 mg/day for 48 weeks.[22] The primary endpoint of histological improvement was observed in 70% of patients treated with entecavir and 61% of those treated with lamivudine. Undetectable HBV DNA (<400 copies/mL by polymerase chain reaction [PCR]) was observed in 91% of the entecavir group and 73% of the lamivudine group (p = not significant). No entecavir resistance was observed during the 48 weeks of therapy. Studies in both HBeAg-positive and -negative patients have demonstrated that entecavir achieves a superior histological, virological and biochemical re-

sponse, and maintained a similar safety profile to that of lamivudine.

Finally, a phase III study has been conducted in 286 lamivudine refractory patients. This study compared a high dosage of entecavir (1 mg/day) with lamivudine 100 mg/day for 48 weeks.[23] The dosage was selected after the results of a previous study investigating 181 patients who failed to respond to lamivudine and were later treated with either one of three different doses of entecavir for 24 weeks (0.1, 0.5 and 1 mg/day) or continued with lamivudine for 24 weeks. At the end of therapy, the percentage of patients receiving entecavir who achieved undetectable HBV DNA, as measured by branched DNA, was 19% with the 0.1mg, 53% with the 0.5mg and 79% with the 1 mg/day dosage; only 13% of patients who received lamivudine achieved undetectable HBV.[20] After 48 weeks of entecavir therapy a higher proportion of patients achieved a histological improvement of 55% compared with only 28% treated with lamivudine ($p < 0.0001$).

The composite endpoint, undetectable HBV DNA and normal ALT levels, was observed in 55% of patients treated with entecavir and in only 4% of those treated with lamivudine. In the group of patients previously treated with lamivudine, two distinct classes of entecavir-resistant mutations were identified, rtM250V and rtI169T, each of which interact cooperatively with the lamivudine-resistant mutations at rtM204I/V providing a structural basis for the observed cross-resistance between the two antiviral drugs.[24]

Results of these phase III trials have been submitted to the US FDA, which has recently approved the use of entecavir as a treatment for HBV. In patients who exhibit lamivudine resistance, entecavir significantly decreases hepatitis B viraemia and, in this setting, entecavir 1 mg/day seems to be the optimal dosage. This is in contrast with the 0.5mg dose recommended for previously untreated patients.

The role of entecavir in the treatment of HBV will be determined over the next few years. Preliminarily results of phase III trials suggest that entecavir will achieve a greater inhibition of HBV DNA than either lamivudine or adefovir dipivoxil; however, more data regarding longer follow-up periods and drug costs are necessary.

3. Emtricitabine

Emtricitabine is the 5-fluorinated derivative of lamivudine[25] which requires activation by intracellular phosphorylation resulting in a potent inhibition of HBV replication.[25] A potential disadvantage of this agent is that it may be ineffective against lamivudine-resistant, YMDD mutant, HBV strains and may be associated with development of similar HBV-resistant mutants.[26]

In a 48-week, randomised, double-blind study, the efficacy of three doses (25, 100 or 200 mg/day) of emtricitabine were compared in 98 Asian patients (77 HBeAg-positive and 21 HBeAg-negative).[27] At week 48, HBeAg loss was observed in 40% of the 77 HBeAg-positive patients. The median decrease in viral load was 2.59 $\log_{10}$ copies/mL for the 25mg dose, 3.12 $\log_{10}$ copies/mL for the 100mg dose and 2.92 $\log_{10}$ copies/mL for the 200mg dose. The proportion of patients achieving undetectable HBV DNA at week 48 were 38%, 42% and 61% for the 25, 100 and 200mg dose groups, respectively. Genotypic analysis at week 48 showed that 12% of patients receiving the 100mg dose and 6% of those receiving the 200mg dose had detectable viraemia with phenotypic changes, associated with HBV drug resistance. These results suggest that the optimal emtricitabine dosage is 200mg once daily. This dosage is well tolerated, produces the highest rate of HBV suppression and is associated with the lowest occurrence of drug-resistant mutants. A 48-week, phase III randomised study comparing emtricitabine 200 mg/day with placebo has been also been performed: 167 patients received emtricitabine and 81 received placebo. The primary endpoint, histological response at week 48 of therapy, was observed in 62% of those treated with emtricitabine and in 25% of those treated with placebo. Serum ALT was normal in 65% and 25% of emtricitabine- and placebo-treated patients ($p < 0.001$), respectively. Undetectable HBV DNA was achieved in 56% and 7% ($p < 0.001$) of patients, respectively, and similar adverse effects were reported in both groups.[28]

Table III. New agents for the treatment of patients with hepatitis B e antigen (HBeAg)-positive chronic hepatitis B (CHB) in phase III development. Studies of ≥1 year of therapy

Parameter	Entecavir (Chang et al.[21])	Emtricitabine (Shiffman et al.[28])	Telbivudine (LdT) [Han et al.[30]]
Dosage (mg/day orally)	0.5	200	400–600mg
Duration (wk)	48	48	52
No. of patients	354	167	44
Viral resistance	Yes	Yes	Yes
Efficacy in HBeAg-positive CHB (% patients)			
HBeAg loss	22	Not reported	33
HBeAg seroconversion	21	12	31
normal ALT	78	65	86
undetectable hepatitis B virus DNA	69	56	61

Treatment-emergent mutations associated with resistance to emtricitabine occurred in 13% of patients, suggesting that emtricitabine is similar to lamivudine. Therefore, emtricitabine is being developed as a combination nucleoside-nucleotide therapy for CHB; a similar combination has already been developed for HIV infection. For this reason, some clinical trials comparing emtricitabine monotherapy with the combination of emtricitabine and adefovir dipivoxil or adefovir dipivoxil monotherapy are currently being conducted. Preliminary results at week 48 of one such randomised, double-blind study investigating 30 treatment-naive HBeAg-positive patients have shown that the combination of adefovir dipivoxil plus emtricitabine has a greater antiviral effect than lamivudine monotherapy, displaying a median $\log_{10}$ reduction of viraemia of −3.48 and −2.22, respectively. In addition, this combination therapy achieved a faster and greater HBV suppression when compared with lamivudine monotherapy[29] (table III).

The role of emtricitabine monotherapy seems to be limited because of it has a similar efficacy and resistance profile to lamivudine. However, the combination of emtricitabine and adefovir dipivoxil should be investigated further as it could yield new advantages in HBV therapy.

4. Clevudine

Clevudine [L-FMAU; 1-(2-fluoro-5methyl-β-L-arabinosyluracil)], a pyrimidine analogue, has a marked *in vitro* activity against HBV but not HIV.[1,2] The active triphosphate is not an obligate chain terminator but inhibits HBV DNA polymerase. Clevudine has an *in vitro* concentration that produces a 50% effective response (EC_{50}) value ranging from 0.02 to 0.15 μmol/L, a mean of 0.08 μmol/L. *In vitro* studies suggest that it may also be effective against lamivudine-resistant HBV mutants.[31-33] *In vivo* studies of the infected woodchuck model have demonstrated that a single daily dose of clevudine 10mg can result in as much as a 9 $\log_{10}$ decrease in viral load. Clevudine was not found to be incorporated into mitochondrial DNA or to be associated with significant *in vitro* lactic acid production.[32]

Initial results from a 4-week, phase I/II dose escalation study of clevudine in HBeAg-positive and -negative CHB patients have been published.[34] A daily dose of 10–100mg of clevudine achieved a ≥2 $\log_{10}$ reduction in serum HBV DNA levels in >70% of patients. Some degree of sustained antiviral effect was reported to occur, as median serum HBV DNA remained below baseline levels during the 6-month period following the end of the study.[34] Clevudine was well tolerated and was not associated with any adverse events. These preliminary results show that clevudine has a potent antiviral activity at the doses tested and maintains a sustained post-treatment antiviral effect, for at least 6 months, after the termination of treatment. In a second phase II study, 31 patients were randomised to receive clevudine 10, 30 or 50 mg/day for 12 weeks. The results of this study demonstrated that the three doses of clevudine produced potent viral

suppression. Dosages >10 mg/day have been deemed suitable for further development.[35] One important finding observed in this study was the continued viral suppression after termination of therapy, an effect not witnessed in other oral antiviral drugs. The reason behind this more durable, off-therapy, viral inhibition is unknown. The safety profile was excellent but mutations within the polymerase region have been observed. More data regarding the use of clevudine in the treatment of CHB are expected.

5. Tenofovir Disoproxil Fumarate

Tenofovir is administered orally as a prodrug, tenofovir disoproxil fumarate, which has already been licensed for the treatment of HIV.[36] Tenofovir is a nucleotide reverse transcriptase inhibitor, with potent antiviral activity against both HIV and wild-type or lamivudine-resistant strains of HBV.[37,38] Tenofovir disoproxil fumarate has been shown to achieve significant reductions in serum HBV DNA levels in HIV/HBV co-infected patients, with or without previous anti-HIV therapy.[39,40] Since adefovir dipivoxil therapy at the recommended dosage for CHB (10 mg/day) has no effect on HIV RNA or CD4+ cell count,[40,41] tenofovir disoproxil fumarate will probably become the preferable agent used in this setting, as part of a highly active antiretroviral regimen.

Recently, an open-labeled study investigating 53 patients with HBV DNA replication and genotypic evidence of lamivudine resistance compared tenofovir disoproxil fumarate with adefovir dipivoxil.[42] Thirty-five patients received tenofovir disoproxil fumarate for between 72 and 130 weeks, and 18 received adefovir dipivoxil for between 60 and 80 weeks. All patients treated with tenofovir disoproxil fumarate showed a strong suppression of HBV DNA within a few weeks of starting therapy, whether co-infected with HIV or without comorbidity. In contrast, considerable variations in HBV DNA decline were observed within the adefovir dipivoxil group. At week 48 only 44% of the adefovir group, in comparison with 100% of the tenofovir group, exhibited HBV DNA levels $<10^5$ copies/mL ($p < 0.001$). No severe adverse effects emerged in either group, and no evidence of long-term (up to 130 weeks) phenotypic viral resistance was demonstrated in the tenofovir-treated patients. However, the results of this study have to be interpreted with caution as it was not randomised. The patient population was heterogeneous: some were immunosuppressed and some received concomitant lamivudine therapy. These results do, however, support the development of tenofovir disoproxil fumarate as a new therapy for CHB, particularly for those patients with lamivudine-resistant HBV infection.

6. β-L-Nucleosides

L-Nucleosides, the natural nucleosides in the β-L-configuration, including telbivudine (L-deoxythymidine; L-dT), torcitabine (L-deoxycytidine; L-dC) and L-deoxyadenosine (L-dA),[43] represent a new class of antiviral agent available for the treatment of CHB. All L-nucleosides have been shown to have potent, selective and specific inhibitory activity against the hepadnaviruses.[44,45] However, a recent *in vitro* study suggested that telbivudine and torcitabine may be inactive against lamivudine-resistant, YMDD mutant, HBV strains.[45] Of these L-nucleosides, telbivudine has undergone the most extensive clinical trials to date.[46]

The initially encouraging results with telbivudine[47] have recently been confirmed in an international multicentre trial. In this phase IIb, double-blind trial,[30,48] 104 CHB patients were randomised to receive either 400 or 600mg of telbivudine as monotherapy or combination therapy with telbivudine (400 or 600 mg/day plus lamivudine 100 mg/day), or lamivudine monotherapy (100 mg/day) for 52 weeks. Significantly greater antiviral activity was seen in both these groups than with lamivudine 100 mg/day for 48 weeks, with a median decrease in serum HBV DNA levels of 6.1–6.4 $\log_{10}$ compared with the 4.7 $\log_{10}$ decrease seen with lamivudine. HBeAg loss was observed in 28% of the patients treated with lamivudine, 33% of those treated with telbivudine and 17% of those treated with telbivudine plus lamivudine. A viral dynamics anal-

ysis, based on data from the 1-year phase IIb clinical trial, showed that patients treated with telbivudine demonstrate faster and more profound first-phase clearance as well as significantly improved second-phase clearance when compared with lamivudine monotherapy. Viral dynamics modeling indicated that the greater second-phase viral clearance achieved with telbivudine was associated with a more rapid clearance of HBV-infected cells. This correlates with an improved clinical outcome for the telbivudine-treated patients at 1 year.[49] Phase III clinical trials of telbivudine in patients with HBeAg-positive and -negative CHB are in progress. The ongoing international phase III clinical study, referred to as the GLOBE study, is designed to evaluate telbivudine head-to-head against lamivudine. The GLOBE study, which involves >1300 patients, is one of the largest hepatitis B studies to date and will assist our understanding of the role of telbivudine as a therapy for CHB.

Another promising β-L-nucleoside compound is valtorcitabine (val-LdC), a prodrug of torcitabine with improved oral bioavailability, which is currently in phase I/II testing.[50] This phase I/II study comprised of seven valtorcitabine dosage cohorts ranging from 50 to 1200 mg/day administered in a single daily oral dose for 4 weeks, with a 12-week follow-up period following treatment. The study investigated adult HBeAg-positive CHB patients. At baseline, patients had serum HBV DNA >7 $\log_{10}$ copies/mL and serum ALT levels 1–5 times the upper limit of normal. Results indicate that valtorcitabine treatment produced substantial dose-dependent viral load reductions. Patients receiving the 900 mg/day dosage of valtorcitabine achieved a mean 3.04 $\log_{10}$ reduction in serum HBV DNA levels, representing a 99.9% reduction in viral load with only 4 weeks of treatment. Valtorcitabine also demonstrated a favourable safety profile.[50] The results of the phase I study[50] support continued development of valtorcitabine as part of a fixed-dose combination with telbivudine.

Combinations of β-L-nucleosides appear to have additional or synergistic effect against the HBV. *In vitro* studies and animal testing have shown no evidence of cellular or mitochondrial toxicity. The combination of telbivudine and valtorcitabine has been analysed in woodchucks. Over a 12-week treatment period, the combination of telbivudine and valtorcitabine cleared PCR-detectable HBV DNA in each of the five animals tested, with no adverse reactions reported. If similar antiviral effects are observed in humans, achieving a relatively rapid clearance of HBV viraemia may be a realistic goal.

These combination therapies aim to increase the sustained off-therapy response rates, after a finite therapeutic course and reduce the probability of viral resistance during extended treatment periods.[51,52] A limitation will certainly be an increase in the cost and, possibly, an increase in adverse effects. To date, the results from investigating these combination therapies have been conflicting and rather disappointing. Clinical trials investigating combinations of these new drugs have not been performed, as it is necessary to have the separate approval for each drug before evaluating any combination therapies. When approval is obtained, these drugs will be evaluated as combination therapies.

7. Conclusion

The results of phase III trials investigating the use of new antiviral agents have been promising; however, as yet, none are approved. Once approval has been gained, the majority of these antiviral agents will be recommended as long-term antiviral monotherapies, or perhaps as part of a combination therapy used with other antiviral or immunomodulatory agents.[53] The agent that demonstrates the greatest antiviral efficacy while maintaining the best safety and tolerability profile will be developed further. Naturally, in this new competitive setting, drug cost will be another important issue.

Acknowledgements

The authors have provided no information on sources of funding or on conflicts of interest directly relevant to the content of this review.

References

1. EASL International Consensus Conference on Hepatitis B. J Hepatol 2003; 39 Suppl. 1: S3-25

2. Lok AS, Heathcote EJ, Hoofnagle JH. Management of hepatitis B: 2000 – summary of a workshop. Gastroenterology 2001; 120: 1828-53
3. Hadziyannis SJ, Vassilopoulos D. Hepatitis B e antigen-negative chronic hepatitis B. Hepatology 2001; 34: 617-24
4. Lok ASF, McMahon BJ. Chronic hepatitis B. Hepatology 2001; 34: 1225-41
5. Hoofnagle JH, Dusheiko GM, Seeff LB, et al. Seroconversion from hepatitis B e antigen to antibody in chronic type B hepatitis. Ann Intern Med 1981; 94: 744-8
6. Fattovich G, Rugge M, Brollo L, et al. Clinical, virologic and histologic outcome following seroconversion from HBeAg to anti-HBe in chronic hepatitis type B. Hepatology 1986; 6: 167-72
7. Yang H-I, Lu S-N, Liaw Y-F, et al. Hepatitis B e antigen and the risk of hepatocellular carcinoma. N Engl J Med 2002; 347: 168-74
8. Hadziyannis SJ. Hepatitis B e antigen negative chronic hepatitis B: from clinical recognition to pathogenesis and treatment. Vir Hep Rev 1995; 1: 7-36
9. Hunt CM, McGill JM, Allen ML, et al. Clinical relevance of hepatitis B virus mutations. Hepatology 2000; 31: 1037-44
10. Bonino F, Rosina F, Rizzetto M, et al. Chronic hepatitis in HBsAg carriers with serum HBV-DNA and anti-HBe. Gastroenterology 1986; 90: 1268-73
11. Brunetto MR, Giarin M, Oliveri F, et al. Wild type and e antigen-minus hepatitis B virus in course of chronic hepatitis. Proc Natl Acad Sci U S A 1991; 88: 4186-90
12. Cooksley WG, Piratvisuth T, Lee SD, et al. Peginterferon alpha-2a (40 kDa): an advance in the treatment of hepatitis B e antigen-positive chronic hepatitis B. J Viral Hepat 2003; 10: 298-305
13. Janssen HLA, von Zonneveld M, Senturk H, et al. Pegylated interferon α-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomised trial. Lancet 2005 Jan 8; 365 (9454): 123-9
14. Lau G, Piratvisuth T, Luo KX, et al. Peginterferon alfa2a monotherapy and in combination with lamivudine is more effective than lamivudine monotherapy in HBeAg-positive chronic hepatitis B: results from a large, multinational study. Hepatology 2004; 40 Suppl. 1: 171A
15. Marcellin P, Lau GKK, Bonino F, et al. Peginterferon-alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. N Engl J Med 2004; 351: 1206-17
16. Yamanaka G, Wilson T, Innaimo S, et al. Metabolic studies on BMS-200475, a new antiviral compound active against hepatitis B virus. Antimicrob Agents Chemother 1999; 43: 190-3
17. Nevens F, de Man RA, Chua D, et al. Effectiveness of a low dose of entecavir in treating recurrent viremia in chronic hepatitis B [abstract]. Hepatology 2000; 32 Suppl.: 377A
18. Lai C-L, Rosmawati M, Lao J, et al. Entecavir is superior to lamivudine in reducing hepatitis B virus DNA in patients with chronic hepatitis B. Gastroenterology 2002; 123: 1831-8
19. de Man RA, Wolters L, Nevens F, et al. A study of oral entecavir given for 28 days in both treatment-naive and pre-treated subjects with chronic hepatitis [abstract]. Hepatology 2000; 32 Suppl.: 376A
20. Tassopoulos N, Hadziyannis S, Cianciara J, et al. Entecavir is effective in treating patients with chronic hepatitis B who have failed lamivudine therapy [abstract]. Hepatology 2001; 34: 340A
21. Chang TT, Gish R, de Man R, et al. Entecavir is superior to lamivudine for the treatment of HBeAg positive chronic hepatitis B: results of phase III study ETV-022 in nuclesoide naive patients [abstract]. Hepatology 2004; 40 Suppl. 1: 193A
22. Shouval D, Lai CLL, Cheinquer H, et al. Entecavir demosntrates superior histologic and virologic efficacy over lamivudine in nucleoside-naive HBeAg-negative chronic hepatitis B: results of phase III trial ETV-027 [abstract]. Hepatology 2004; 40 Suppl. 1: 728A
23. Sherman M, Yurdaydin C, Sollano J, et al. Entecavir is superior to continued lamivudine for the treatment of lamivudine-refractory, HbeAg-positive chronic hepatitis B: results of phase III study ETV-026 [abstract]. Hepatology 2004; 40 Suppl. 1: 664A
24. Delanay WE, Yang H, Sabogal A, et al. In vitro cross-resistance testing of adefovir, lamivudine, telvibudine, entecavir and other anti-HBV compounds against four major mutational patterns of lamivudine-resistant HBV [abstract]. Hepatology 2004; 40 Suppl. 1: 244A
25. Korba BE, Schinazi RF, Cote P, et al. Effect of oral administration of emtricitabine on woodchuck hepatitis virus replication in chronically infected woodchucks. Antimicrob Agents Chemother 2000; 44: 1757-60
26. Ladner SK, Miller TJ, Otto MJ, et al. The hepatitis B virus M539V polymerase variation responsible for 3TC resistance also confers cross-resistance to other nucleoside analogues. Antiviral Chemother 1998; 9: 65-72
27. Wang C, Correy L, Leung N, et al. Antiviral activity of 48 weeks of emtricitabine (FTC) treatment in patients with HBeAg negative/HBV DNA positive chronic hepatitis B (CHB) [abstract]. Hepatology 2001; 34: 323A
28. Shiffman ML, Ng TM, Krastev Z, et al. A double-blind, placebo-controlled trial of emtrcitabine (FTC, Emtriva) administered once-daily for treatment of chronic Hepatitis B virus infection [abstract]. Hepatology 2004; 40 Suppl. 1: 172A
29. Lau G, Cooksley H, Ribeiro RM, et al. Randomized, double, blind study comparing adefovir dipivoxil plus emtricitabine combination therapy versus adefovir alone in HBeAg-positive chronic hepatitis B: efficacy and mechanisms of treatment response [abstract]. Hepatology 2004; 40 Suppl. 1: 272A
30. Han SH, Leung NWY, Teo EK, et al. Results of a one-year international phase IIb trial of LdT, and LdT plus lamivudine in patients with chronic hepatitis B [abstract]. Hepatology 2004; 40 Suppl. 1: 16
31. Chu CK, Boudinot FD, Peek SF, et al. Preclinical investigation of L-FMAU as an anti-hepatitis B virus agent. Antivir Ther 1998; 3 Suppl. 3: 113-21
32. Peek SF, Cote PJ, Jacob JR, et al. Antiviral activity of clevudine [L-FMAU, (1-(2-fluoro-5-methyl-beta, l-arabinofuranosyl) uracil)] against woodchuck hepatitis virus replication and gene expression in chronically infected woodchucks (*Marmota monax*). Hepatology 2001; 33: 254-66
33. Abdelhamed AM, Kelley CM, Miller TG, et al. Comparison of anti-hepatitis B virus activities of lamivudine and clevudine by a quantitative assay. Antimicrob Agents Chemother 2003; 47: 324-36
34. Marcellin P, Mommeja-Marin H, Sacks SL, et al. A phase II dose-escalating trial of clevudine in patients with chronic hepatitis B. Hepatology 2004; 40: 140-8
35. Marcellin P, Leung N, Hann H-WL, et al. A phase II, randomized trial evaluating the safety, pharmacokinetics and antiviral activity of clevudine for 12 weeks in patients with chronic hepatitis B [abstract]. Hepatology 2004; 40 Suppl. 1: 652A

36. Benhamou Y, Poynard T. Treatment of chronic hepatitis B virus infection in patients co-infected with human immunodeficiency virus. J Hepatol 2003; 39 Suppl. 1: S194-9
37. Lessells R, Leen C. Management of hepatitis B in patients coinfected with the human immunodeficiency virus. Eur J Clin Microbiol Infect Dis 2004; 23: 366-74
38. Benhamou Y. Antiretroviral therapy and HIV/hepatitis B virus coinfection. Clin Infect Dis 2004; 38 Suppl. 2: S98-103
39. Dore GJ, Cooper DA, Pozniak AL, et al. Efficacy of tenofovir disoproxil fumarate in antiretroviral therapy-naive and -experienced patients coinfected with HIV-1 and hepatitis B virus. J Infect Dis 2004; 189: 1185-92
40. Lerbaek A, Kristiansen TB, Katzenstein TL, et al. Tenofovir treatment in an unselected cohort of highly antiretroviral experienced HIV positive patients. Scand J Infect Dis 2004; 36: 280-6
41. Benhamou Y, Bochet M, Thibault V, et al. Safety and efficacy of adefovir dipivoxil in patients co-infected with HIV-1 and lamivudine-resistant hepatitis B virus: an open-label pilot study. Lancet 2001; 358: 718-23
42. Van Bömmel F, Wünche T, Mauss S, et al. Comparison of adefovir and tenofovir in the treatment of lamivudine-resistant Hepatitios B virus infection. Hepatology 2004; 40: 1421-5
43. Standring DN, Bridges EG, Placidi L, et al. Antiviral beta-L-nucleosides specific for hepatitis B virus infection. Antivir Chem Chemother 2003; 12 Suppl. 1: 119-29
44. Bryant ML, Bridges EG, Placidi L, et al. Antiviral L-nucleosides specific for hepatitis B virus infection. Antimicrob Agents Chemother 2001; 45: 229-35
45. le Guehier F, Pichoud C, Jamard C, et al. Characterization of the antiviral effect of 2′3′-dideoxy-2′-3′didehydro-beta-L-5-fluorocytidine in the duck hepatitis B virus infection model. Antimicrob Agents Chemother 2000; 44: 111-22
46. Delaney W, Yang H, Miller M, et al. Lamivudine-resistant HBV is cross-resistant to L-dT and L-dC in vitro. J Hepatol 2002; 36 Suppl. 1: 89
47. Lai C-L, Lim SG, Brown NA, et al. A dose-finding study of once-daily oral telvivudine in HBeAg-positive patients with chronic hepatitis B virus infection. Hepatology 2004; 40: 719-26
48. Lai C-L, Leung NWY, Teo E-K, et al. Results of a one-year international phase IIb comparative trial of telbivudine, lamivudine, and the combination, in patients with chronic hepatitis B [abstract]. Hepatology 2003; 38 Suppl. 1: 262A
49. Neumman AV, Zhou XJ, Boehme RE, et al. Viral dynamics for LDT (Telbuvidine) treated Hepatitis B patients: high degree of initial inhibition with dose-dependent second phase HBV clearance suggests a new model for HBV dynamics [abstract]. Hepatology 2004; 40 Suppl. 1: 246A
50. Lai CL, Brown N, Myers M, et al. Valtorcitabina provides potent suppression of hepatitis B virus in patients with chronic hepatitis B: results of a phase I/II clinical trial. J Hepatol 2004; 40 Suppl. 1: 173A
51. Shaw T, Locarnini S. Combination chemotherapy for hepatitis B virus: the final solution? Hepatology 2000; 32: 430-2
52. Mailliard ME, Gollan JL. Suppressing hepatitis B without resistance: so far, so good. N Engl J Med 2003; 348: 848-50
53. Keeffe EB, Dieterich DT, Han SH, et al. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States. Clin Gastroenterol Hepatol 2004; 2: 87-10652

Correspondence and offprints: Dr *Maria Buti*, Liver Unit, Hospital General Universitari Vall d'Hebron, Paseo Valle de Hebron 119, Barcelona, 08035, Spain.
E-mail: mbuti@vhebron.net