Expert Opinion

Monotherapy versus combination therapy for the treatment of chronic hepatitis B

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Background: Nucleos(t)ide analogues, active against hepatitis B polymerase, suppress viral replication and improve clinical outcome. However, the emergence of drug-resistant mutants can result in treatment failure. *Objectives*: We describe how the choice of first-line therapy is critical to long-term treatment success. *Methods*: A review of current drug therapies is provided. *Results/conclusions*: Monotherapy with early-generation drugs (lamivudine or adefovir) was associated with a high rate of viral drug resistance and combination therapy with these agents was shown to reduce the incidence of resistance. The latest-generation drugs (entecavir and tenofovir) are potent inhibitors of viral replication and, in treatment-naive subjects, viral resistance to entecavir is uncommon and is not yet reported to tenofovir. Therefore, monotherapy with either entecavir or tenofovir is the current preferred option in treatment-naive patients. Combination therapy is appropriate in those with drug-resistant HBV infection, where drug choice is guided by the viral drug-resistance genotype/phenotype. Although combination therapy has been advocated in other patient groups (e.g., those with decompensated cirrhosis and following liver transplantation), there are, as yet, no data to mandate the use of combination therapy in such patients and any perceived benefit must be weighed against increased cost and risk for toxicity.

Keywords: guidelines, interferon, nucleoside, resistance

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1. Introduction

Hepatitis B virus (HBV) infection is a significant global health problem, with > 400 million chronically infected individuals in the world. Although the majority never develop significant liver disease, around 25% of those with chronic HBV infection ultimately develop cirrhosis or hepatocellular carcinoma (HCC). The level of serum HBV DNA is a strong predictor of future HBV-related complications, and a large Asian cohort study has clearly shown that serum HBV DNA level at diagnosis is the best independent predictor of cirrhosis and HCC over a follow-up period of ≤ 12 years [1,2]. Importantly, HBV DNA levels as low as 2000 IU/ml are associated with an increased disease risk. These findings intimate that antiviral therapy achieving maximal suppression of serum HBV DNA might reduce the risk of complications [3,4].

Current antiviral therapies rarely eradicate HBV infection, but they can effectively suppress viral replication (**Figure 1**) and improve clinical outcome. Several drugs with two different modes of action are currently available for treatment of chronic HBV infection. Peginterferon alfa enhances the antiviral immune response and suppresses viral replication. Following a finite duration of therapy, peginterferon can induce

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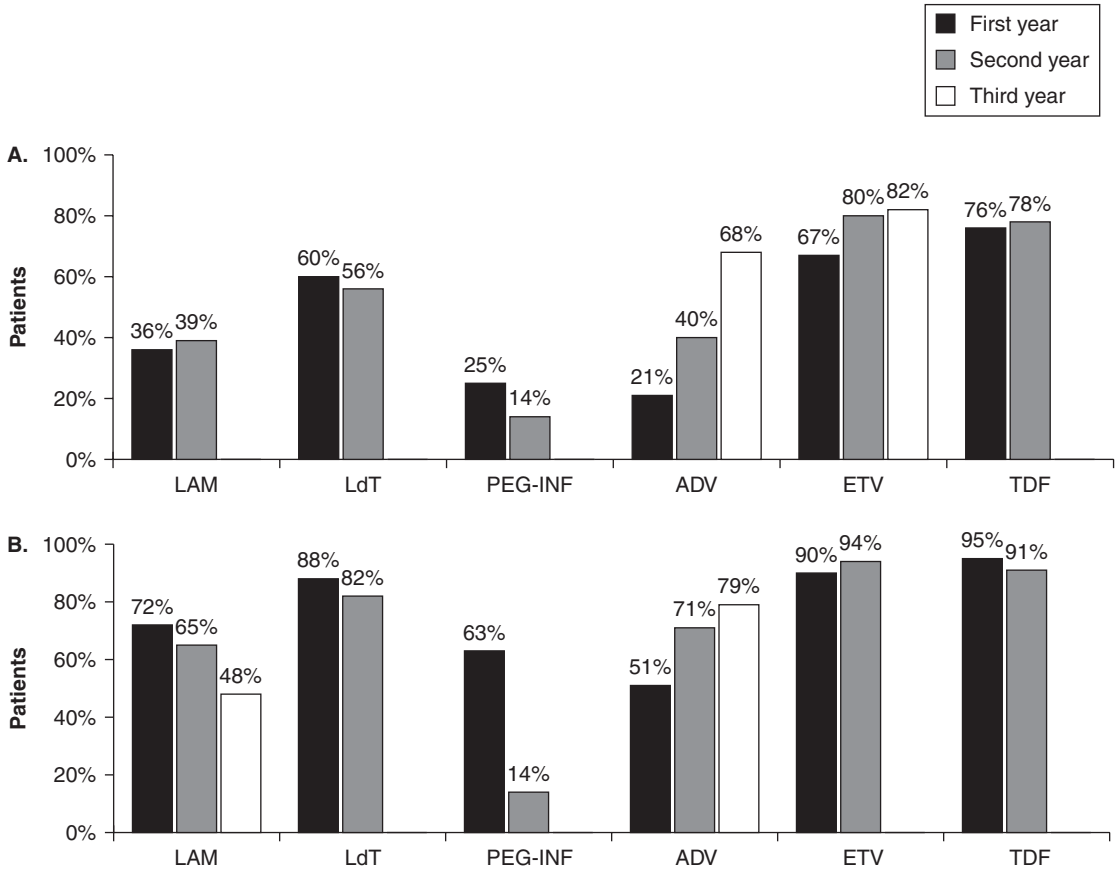

Figure 1. Response to antiviral drugs in patients with chronic Hepatitis B due to A) eAg-positive and B) eAg-negative disease. Rates of undetectable HBV DNA over time.
ADV: Adefovir; ETV: Entecavir; LAM: Lamivudine; LdT: Telbivudine; PEG-INF: Pegylated interferon; TDF: Tenofovir.

long-term viral suppression (after 48 weeks' treatment in patients with eAg-negative disease, 15.7% achieved HBV DNA < 400 copies/ml and 8% cleared HBsAg 3 years after treatment [5]) but interferon is associated with significant dose-dependent side effects. Nucleos(t)ide analogues inhibit the HBV polymerase and suppress viral replication, resulting in a reduction in serum HBV DNA levels (**Figure 1**). Although associated with few side effects [6], they usually need to be taken indefinitely. This article reviews the available therapeutic options for chronic HBV infection. In particular, we discuss the relative merits of single drug therapy compared to combination drug therapy.

2. Drugs used to treat chronic HBV infection

2.1 Interferon therapy

2.1.1 Standard interferon

When introduced as a treatment for chronic hepatitis B around 17 years ago, it was demonstrated that standard IFN-α was more likely to induce HBeAg loss and a sustained reduction of HBV DNA compared with no therapy [7-9]. IFN-α has a dual mechanism of action because it both suppresses HBV replication by inducing the expression and functional activation of a variety of cellular proteins [10], and stimulates a cell-mediated immune response against HBV [11,12]. Flares in aminotransferase levels occurring during treatment with IFN-α are thought to be due to the destruction of infected hepatocytes and are predictive of HBeAg loss and a sustained reduction of HBV DNA [13,14]. Although rates of HBsAg clearance were modest within the first year of follow-up [8,9], HBsAg seroconversion was found to occur at a steady rate, during long-term follow-up, especially in patients who had HBeAg seroconversion and undetectable serum HBV-DNA 48 weeks after treatment discontinuation [15]. After a mean follow-up of 6.2 years after therapy, 71% of responders were negative for HBsAg [9].

2.1.2 Peginterferon

Patients receiving pegIFN-α-2a have a more rapid decline in HBV DNA levels and a higher rate of HBeAg seroconversion compared to those treated with standard IFN-α-2a [16]. Phase III clinical trials [14,17,18] have identified both patient and viral parameters that are predictive of a sustained virologic response to pegIFN, including ALT at least twice the normal

limit, HBV DNA levels ≤ 2 x 10^8 IU/ml at baseline in HBeAg-positive patients and infection with either genotypes A or B [19,20]. The best predictor of response to pegIFN is still unclear, but quantitative measurements of serum HBsAg levels on therapy have utility because in a large multinational study of pegIFN-α-2a, the end-of-treatment HBsAg level correlated strongly with HBV DNA suppression to ≤ 400 copies/ml at 6 months post-treatment and a HBsAg level < 10 IU/ml at week 48, plus an on-treatment decline > 1 $\log_{10}$ IU/ml, were significantly associated with sustained HBsAg clearance 3 years after treatment [5]. Serial measurement of serum HBsAg concentration during treatment has shown that a decrease of 0.5 and 1 $\log_{10}$ IU/ml at weeks 12 and 24 of therapy, respectively, were highly predictive of achieving undetectable serum HBV DNA (< 70 copies/ml) at 6 months after treatment cessation (negative predictive value [NPV] 90%, positive predictive value [PPV] 89% for week 12; NPV 97%, PPV 92% for week 24) [21].

However, despite guidelines advocating pegIFN as a first-line therapy for both HBeAg-positive and HBeAg-negative chronic HBV infection [22] and the potential for a finite duration therapy with a durable off treatment response, pegIFN has a low market share in America, Europe and Asia [23].

2.2 Nucleos(t)ide analogues

The HBV genome encodes a polymerase enzyme that reversely transcribes the viral pregenomic RNA to generate the minus strand viral DNA and, subsequently, synthesizes the plus strand viral DNA. Nucleos(t)ide analogues inhibit this viral polymerase by competing with endogenous intracellular nucleotides for incorporation into the nascent viral DNA. Once incorporated, they can also terminate DNA synthesis by blocking inclusion of the next nucleotide in the viral DNA strand. Inhibition of the viral polymerase results in reduced production of new virions.

The HBV viral polymerase has poor proofreading ability, resulting in error-prone replication of new viral DNA. Mutations arising in the HBV polymerase gene region can lead to amino acid changes in the polypeptide, causing a conformational change in the protein structure. This in turn can result in reduced affinity to nucleos(t)ide analogues and resistance to the inhibitory effect of the drug [24]. In clinical practice, treatment failure is usually the first indication of the emergence of viral drug resistance, and in these cases genotypic assays to define the resistance pattern are required, assuming that non-HBV–related causes of failure such as noncompliance have been excluded [25]. Mutations within the HBV polymerase gene can be detected by direct sequencing and/or hybridisation line probe assay (INNO-LiPA) [26,27]. The results of resistance testing permit the clinician to make an informed decision about subsequent treatment, especially now that the pattern of viral drug resistance mutations is becoming more complex in patients who have received several courses of drug therapy. Knowledge of the HBV resistance mutations prevents the administration of a drug that exhibits cross-resistance (**Table 1**).

2.2.1 *Lamivudine*

Lamivudine is a nucleoside analogue and is an inhibitor of reverse transcriptase activity of the viral polymerase. It has an excellent safety profile and is an inexpensive drug. However, monotherapy is associated with a very high rate of viral drug resistance [28], around 70% after 5 years (**Figure 2**), leading to treatment failure [29]. Mutation in codon 204 of HBV polymerase (rtM204V/I) confers resistance to lamivudine [30] and most other nucleoside analogues [31]. These mutations also reduce HBV polymerase activity [32] but compensatory mutations in codons 80, 173 or 180 recover the replication fitness of HBV without influencing drug sensitivity. Unfortunately, lamivudine monotherapy can also select for HBV strains associated with resistance to entecavir [33] and adefovir [34-36].

Although approximately 20% of patients maintain viral suppression during long-term treatment with lamivudine, they are difficult to identify before treatment commences [37]. A HBV DNA level < 2000 IU/ml at treatment week 4 was found to be an accurate predictor (AUC 0.89 [95% CI, 0.82 – 0.97]; 100% PPV) of long-term response (HBV DNA < 400 IU/ml and absence of drug resistance mutation after 5 years) [38]. Although continuing with lamivudine monotherapy would be suitable for those with HBV DNA levels < 2000 IU/ml at treatment week 4, only 8% of the total population (35% of long-term responders) achieved this target and 92% of patients would require treatment modification at week 4 [38]. Consequently, current treatment guidelines no longer recommend lamivudine monotherapy as primary treatment for chronic hepatitis B [22,39-41]. Nevertheless, it may still have a role in the prevention of HBV reactivation in chronic carriers who receive immunosuppressive therapy or chemotherapy [42].

2.2.2 *Adefovir dipivoxil*

The nucleotide adefovir dipivoxil impedes the priming of reverse transcription, as well as elongation of viral minus strand DNA, but exhibits moderate antiviral potency. It reduced serum HBV DNA to undetectable levels (< 400 copies/ml) after 48 weeks in 21% of HBeAg-positive individuals (**Figure 1**) [43] and to < 1000 copies/ml after 144 weeks in 79% of HBeAg-negative individuals [44], but a high proportion of patients have a suboptimal response to therapy [43,45,46]. Since it is active against lamivudine-resistant virus carrying codon 204 mutations, it was used not only as a first-line therapy but also as a rescue therapy for patients with lamivudine resistance [47,48]. However, the development of mutations rtN236T or rtA181V/T confers resistance to adefovir [49,50] and, although viral resistance to adefovir develops at a slower rate than to lamivudine, these are detected in nearly 30% of patients with HBeAg-negative disease after 5 years of therapy (**Figure 2**), limiting the drug's clinical utility [51,52]. Resistance is more likely to develop when HBV DNA levels remain > 200 IU/ml after 48 weeks of treatment [51]. Adefovir-resistant viral strains carrying the mutation rtN236T are sensitive to lamivudine, telbivudine and entecavir, but viral strains carrying

Table 1. Cross-resistance profile of nucleos(t)ide analogues used to treat hepatitis B.

	Lamivudine	Telbivudine	Entecavir	Adefovir	Tenofovir
Wild-type	S	S	S	S	S
M204I	R	R	I	S	S
M204V + L180M	R	R	I	S	S
A181T/V/S	R	S	S	R	S
N236T	S	S	S	R	I
M204V/I ± L180M + T184G or S202I/G or M250V	R	R	R	S	S

I: Decreased *in vitro* activity; R: Resistant; S: Susceptible.

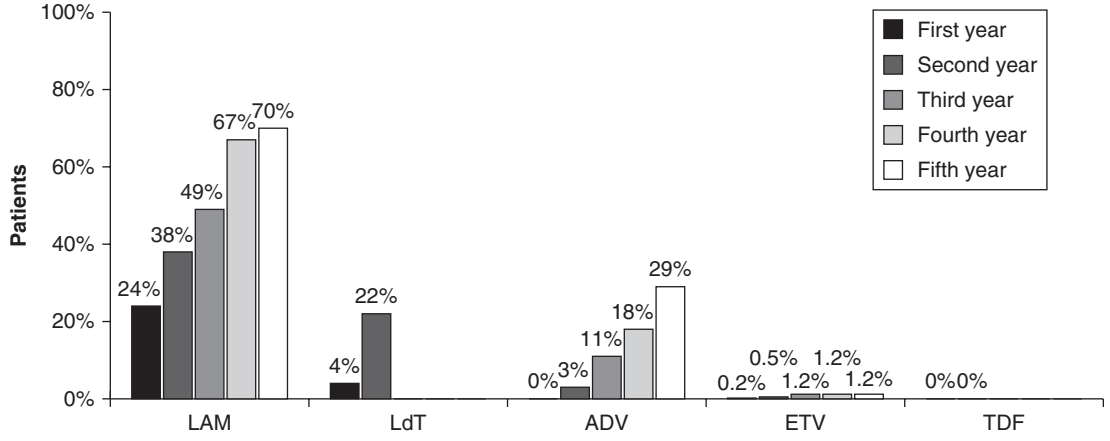

Figure 2. Cumulative probability of emergence of drug resistance to antiviral drugs.
ADV: Adefovir; ETV: Entecavir; LAM: Lamivudine; LdT: Telbivudine; TDF: Tenofovir.

codon 181 mutations also demonstrate reduced susceptibility to lamivudine [35,53].

2.2.3 *Entecavir*

Entecavir is a member of the cyclopentane group and is rapidly phosphorylated to the active intracellular 5′-triphosphate form that is a very potent inhibitor of viral polymerase activity by inhibiting both minus- and plus-strand DNA synthesis [54,55]. It induces a significant decline in viral load in both HBeAg-positive and -negative treatment-naive patients [56-59], leading to a faster and greater fall in HBV DNA compared with adefovir in nucleoside-naive HBeAg-positive patients [58]. Over time, entecavir suppresses serum HBV DNA to undetectable levels in an increasing proportion of patients, because 67, 80 and 82% of HBeAg positive patients were reported to achieve undetectable HBV DNA (< 300 copies/ml) after 1, 2 and 3 years, respectively, of therapy (**Figure 1**). In treatment-naive patients, the cumulative rate of emergence of entecavir-resistant strains is very low at 1.2% [60], even after 5 years of therapy (**Figure 2**) [61], because the development of resistance requires the selection of a primary resistance mutation at codon 204, with or without the compensatory mutation rtL180M, followed by the addition of secondary resistance mutations (at codons 184, 202, or 250) [62-65]. The antiviral potency of entecavir and the requirement for the virus to harbor multiple mutations in order to display resistance explain why it is a good first-line therapy in HBeAg-positive or -negative nucleoside-naive patients. HBV strains harboring the lamivudine resistance mutations, rtM204V/I, exhibit reduced susceptibility to entecavir *in vitro* but demonstrate sensitivity to entecavir administered at a higher dose (1.0 mg daily) *in vivo*. Despite this, entecavir administration in lamivudine-refractory patients results in a 5-year cumulative probability of genotypic entecavir resistance of 51% [61]. Patients with a suboptimal response to lamivudine but no evidence of viral drug resistance at the time of switch to entecavir still have a risk of developing entecavir resistance [66]. Patients with persistently high HBV DNA during adefovir treatment were found to have a slow reduction of viral load in response to a change to entecavir monotherapy, regardless of prior lamivudine exposure, and were unlikely to achieve undetectable levels of HBV DNA [67].

Although entecavir is an excellent therapy for treatment-naive patients, these data indicate that entecavir monotherapy is not the optimal treatment for patients with evidence of viral replication on lamivudine or adefovir and especially for those infected with lamivudine-resistant HBV.

2.2.4 *Telbivudine*

This nucleoside analogue has potent antiviral activity [68] and after 1 year of therapy, 60% of HBeAg-positive and 88% of HBeAg-negative patients achieved undetectable levels (< 300 copies/ml) of serum HBV DNA [69]. However, telbivudine is associated with a high rate of viral resistance (**Figure 2**); HBeAg-positive patients demonstrate resistance rates of 5 and 25% at 1 and 2 years, respectively, and rates of 2.3 and 11% at 1 and 2 years are seen in HBeAg-negative patients [69,70], especially in patients with persistent viremia at 24 weeks of treatment. Telbivudine mainly selects for the rtM204I mutation, which confers cross-resistance to other nucleosides but is associated with fewer compensatory mutations than the classical rtM204V lamivudine resistance mutation [71]. It is active against adefovir-resistant mutants. The high rate of development of drug resistance limits the drug's clinical utility as a monotherapy, but its role in combination with nucleotide analogues should be evaluated in clinical trials.

2.2.5 *Tenofovir*

Tenofovir is structurally very similar to the nucleotide analogue adefovir, but it exhibits more potent inhibitory activity against both wild-type and lamivudine-resistant strains [46,72,73]. Clinical trials have shown that tenofovir effectively controls HBV replication in patients with both HBeAg-positive and HBeAg-negative disease, with approximately 75 and 93%, respectively, achieving undetectable HBV DNA (< 400 copies/ml) by quantitative PCR after 1 year of therapy [74], and 78 [75] and 91%, respectively, after 2 years (**Figure 1**). It is effective in patients who have had only a partial virologic response to adefovir, but patients infected with viral strains resistant to adefovir are less likely to achieve complete viral suppression than those infected with wild-type virus [76]. A mutation rtA194T has been implicated as conferring tenofovir resistance [77] but, to date, no tenofovir resistance phenotype has been reported in patients treated for up to 2 years [74,75]. Tenofovir is a first-line therapy for both HBeAg-positive and -negative patients, whether naive to treatment or after first-line treatment failure. However, reported studies of tenofovir therapy in patients with documented nucleoside resistance are currently of limited duration and an add-on strategy or a switch to a combination of tenofovir plus emtricitabine might be recommended; long-term clinical studies are warranted in this setting. Tenofovir is associated with a dose-dependent but usually reversible proximal renal tubular toxicity [78] and reduced bone mineral density in patients with HIV infection. In a cohort of patients with HIV/HBV co-infection treated for 5 years with tenofovir, eGFR declined by 22.2 ml/min from a baseline of 96.8 ml/min [79]. In five patients, eGFR fell below 60 ml/min and all were classified as having CKD stage 3 disease; tenofovir was withdrawn in two patients due to renal dysfunction. Long-term, prospective studies in patients with HBV monoinfection are lacking [6], but 2-year follow-up results have shown no evidence of renal dysfunction [75,80].

3. Monotherapy or combination therapy?

3.1 Monotherapy

Lamivudine monotherapy is associated with a particularly high rate of viral drug resistance [29], and both telbivudine [69,70] and adefovir monotherapy [52] are associated with high levels of drug resistance. Sequential monotherapy with these agents clearly exposes a patient to the risk of selection of multi-drug–resistant viral strains and studies have demonstrated that patients with established lamivudine resistance are more likely to develop dual resistance if adefovir is substituted for [81], rather than added to, lamivudine [53,82,83]. Furthermore, sequential entecavir therapy in patients with lamivudine resistance results in a 5-year cumulative probability of genotypic entecavir resistance of 51% [61], even when it is used at a higher dose [84,85]. In both of these situations, multi-drug resistance occurs by the sequential addition of mutations on the same viral genome leading to resistance to both drugs [62,86], although lamivudine monotherapy can preselect for HBV variants associated with resistance to entecavir [33] and adefovir [34-36]. The selection of multi-drug–resistant strains is more frequent when the second agent does not induce complete viral suppression – either due to low potency of the drug, as in the case of adefovir, or reduced susceptibility of the virus to the second drug in the presence of one or more mutations, in the case of entecavir.

The new-generation HBV polymerase inhibitors, entecavir and tenofovir, demonstrate very low rates of resistance in nucleoside-naive patients when given as monotherapy, 1.2% for entecavir during the first 5 years of therapy [61] and no cases to date for tenofovir during the first 2 years of therapy [74]. It is clear that the choice of first-line treatment is critical in preventing the emergence of multi-drug resistance [22].

3.2 Add-on or *de novo* combination nucleos(t)ide analogue therapy?

The role of drug combinations is well established in the treatment of HIV infection, where the use of antiretroviral drugs belonging to different classes of compounds, which target distinct steps of the viral life cycle, achieves an additive effect on viral load suppression. Short-term clinical trials have demonstrated the added value of combination therapy in terms of viral load decline, prevention of drug resistance and decrease in mortality rate.

All of the nucleos(t)ide analogues licensed to treat HBV inhibit the viral polymerase and combinations of these drugs reduce viremia to the same degree as the most potent antiviral in the combination. Nevertheless, the emergence of drug-resistant

HBV strains during treatment with the early generation polymerase inhibitors has driven the concept of combination therapy for chronic hepatitis B.

Several studies have shown that the addition of adefovir after development of virological breakthrough due to lamivudine resistance leads to effective viral suppression in most cases [53,87-90]; also patients receiving add-on adefovir have a lower risk of developing genotypic resistance to adefovir compared with those given sequential adefovir monotherapy [53,81,82,87,88,91,92]. Adefovir should be added early, at the time of viral breakthrough, rather than waiting for an increase in aminotransferase levels associated with high viremia, in order to control viral replication and prevent clinical deterioration [53]. Although the early addition of adefovir is an effective strategy in the majority of cases because adefovir is active against lamivudine-resistant virus carrying codon 204 mutations, substitutions at codon 181 have been described in patients taking lamivudine; these individuals fail to respond to add-on adefovir [53,89-91,93] and can experience significant viral rebound and fatal hepatic decompensation [49]. The prevalence of codon 181 mutations is low, being found in < 4% of patients with resistance to lamivudine, but this observation highlights the importance of ensuring that the drugs used in combination therapy have no cross-resistance. Indeed, treating patients with combinations of drugs that have a genotypic drug-resistance mutation pattern in common, such as lamivudine and telbivudine, is ineffective at preventing resistance development, even when one of the drugs in the combination has potent antiviral activity [68].

It is established that combination therapy achieves better long-term control of viral replication compared with sequential monotherapy, once viral drug resistance has developed. So why, then, is *de novo* combination therapy for HBV not the standard of care? The answer is that treatment guidelines are based on published results and very few controlled trials have compared *de novo* combination therapy with monotherapy or an add-on strategy. In a small study, adefovir plus emtricitabine induced more potent viral suppression than adefovir plus placebo, but neither treatment group developed viral drug resistance over 96 weeks of therapy [94]. Unfortunately, this study did not include an emtricitabine control group, and the greater antiviral potency of the combination therapy is likely to have been due to the effect of the emtricitabine rather than due to synergistic activity of the drug combination. In another report, nucleoside-naive patients with HBeAg-positive disease receiving lamivudine monotherapy for 2 years had more virological breakthrough compared to those taking lamivudine and adefovir combination therapy (44 vs 19%) [95]. However, rates of HBeAg seroconversion were similar (20% in the monotherapy vs 13% in the combination therapy patients). This study shows clear benefit in favour of *de novo* lamivudine and adefovir combination therapy over lamivudine monotherapy in terms of control of viral replication, but the rate of virological breakthrough in the combination group was substantially higher than has been observed in studies of entecavir [61] or tenofovir monotherapy [75] over a similar time period.

Patients with long-standing infection, high viremia levels and a pre-existing HBV polymerase mutation pattern conferring resistance to the early generation nucleos(t)ide analogues are generally considered at risk of developing further drug-resistance mutations. Such patients are the most likely to benefit from combination drug therapy using potent antiviral agents. Other groups of patients who should be considered candidates for *de novo* combination therapy because of the risk of clinical deterioration if they develop recurrent viremia due to antiviral drug resistance are patients with liver cirrhosis and those who have received a liver graft for HBV-related cirrhosis. However, there are as yet no data to support a role of combination therapy in these patient populations and any perceived benefit must be weighed against increased cost, risk for toxicity, and the potential for drug–drug interactions.

The potential for an increased risk of toxicity must always be considered when giving drugs in combination. Although 8.7% of patients receiving long-term adefovir had a documented increase in creatinine, > 0.5 mg/dl [96], 16% of patients taking lamivudine and adefovir combination therapy developed renal impairment and those with baseline GFR < 89 ml/min were at higher risk, 45% [97]. These findings highlight the importance of studying the effects of drug combinations long-term.

Partial virologic response is encountered with all nucleos(t)ide therapies. Patients on treatment with adefovir or telbivudine who are found to have a partial virologic response, at week 24, should either change to a more potent drug (entecavir or tenofovir) or have a more potent drug added to their therapy that does not share cross-resistance with the existing drug (i.e., add tenofovir to telbivudine, or add entecavir to adefovir), in order to reduce the risk of development of viral drug resistance [22]. However, viral drug resistance to lamivudine develops in 5% of patients by week 24 [98] and the decision to adapt therapy as a consequence of inadequate viral suppression needs to be taken earlier, either at week 4 or week 16 time points [38]. Switching therapy to the combination of tenofovir and emtricitabine in a small number of subjects with partial virologic response to adefovir achieved undetectable HBV DNA in all patients [99]. However, on the basis of 1-year follow-up data, there is no evidence that a combination strategy is more effective than tenofovir monotherapy in those with an inadequate response to adefovir [100,101].

Since entecavir demonstrates very low rates of resistance in nucleoside-naive patients when given as monotherapy, 1.2% during the first 5 years of therapy [61], and no cases to date for tenofovir during the first 2 years of therapy [74], even in those with a partial virologic response, treatment modification is not yet mandatory for patients receiving entecavir or tenofovir who have partial virologic response at week 48, although some experts suggest adding the other drug, in order to prevent resistance in the long term [22]. Rescue therapy with combination entecavir and tenofovir in HBV

monoinfected patients harboring complex viral resistance patterns or showing only partial antiviral response to existing antiviral therapy was effective, safe, and well tolerated, and 14 out of 20 patients reduced serum HBV DNA below 400 copies/ml [102]. However, more data are required about combination entecavir and tenofovir in terms of their long-term safety and efficacy, as well as their ability to prevent emergence of viral drug resistance mutations, especially in heavily pretreated patient populations. Trials comparing entecavir or tenofovir monotherapy against the strategy of adding the other drug where there is partial virologic response should be evaluated as soon as possible, although large studies of 5 – 10 years' duration will be required. Prospective trials comparing entecavir monotherapy with entecavir plus tenofovir *de novo* combination therapy in treatment-naive patients with HBeAg-positive or -negative disease and entecavir plus adefovir to lamivudine plus adefovir in lamivudine-resistant disease are recruiting, but the outcomes will not be known for 1 – 2 years.

3.3 Combination pegIFN and nucleos(t)ide analogue therapy

PegIFN-α-2b given in a dose of 100 µg weekly for 32 weeks followed by 50 µg weekly, until completion of 52 weeks of treatment, in combination with lamivudine 100 mg daily, showed a greater decline in HBV DNA compared with pegIFN alone (approximately 5 $\log_{10}$ vs 2 $\log_{10}$ decline), as well as a higher rate of HBeAg loss (44 vs 29%) by the end of treatment [17]. However, these differences were not sustained following a 26-week follow-up period and both groups showed similar rates of HBsAg loss (7% in the combination therapy group vs 5% in the pegIFN monotherapy group). A major finding of this study was that the response to treatment was dependent on HBV genotype, with those infected with genotype A or B having higher rates of HBeAg loss (47 and 44%, respectively) compared to those with genotype C or D (28 and 25%, respectively). Similarly, the rate of HBsAg clearance was also closely linked to viral genotype, ranging from 14% in those with genotype A to 2% for genotype D.

In Phase III trials of pegIFN-α-2a, given at a dose of 180 µg weekly for 48 weeks, in either HBeAg-positive [14] or HBeAg-negative patients [18], combination of lamivudine and pegIFN induced a greater end-of-treatment decline in HBV DNA than pegIFN alone, or lamivudine monotherapy (HBeAg positive, 7.2, 4.5, and 5.8 log decline, and HBeAg-negative, 5.0, 4.1, and 4.2 log decline, respectively). However, at the end of a 24-week off-treatment follow-up period, the rates of sustained virologic response were similar in pegIFN monotherapy and combination therapy groups. These studies found lower rates of resistance to lamivudine when it was administered in combination with pegIFN, presumably as a consequence of the greater degree of viral suppression achieved. When patients in the HBeAg-negative study were re-evaluated, 1 year after completion of treatment, those infected with genotypes B or C had a significantly greater chance of a sustained biochemical and virologic response compared to patients with genotype D. Five-year post-treatment follow-up of patients in the HBeAg-negative study showed that in those receiving pegIFN, with or without lamivudine, 21% maintained HBV DNA < 10,000 copies/ml and 17% had < 400 copies/ml [103]. HBsAg clearance increased with time, and at 5 years post-treatment 12.2% of patients treated with pegIFN, with or without lamivudine, had cleared HBsAg compared with 3.5% of those treated with lamivudine alone. Among those with suppression of HBV DNA < 400 copies/ml, 72% lost HBsAg.

These trials demonstrate that the sustained response to pegIFN is not enhanced by combining therapy with lamivudine, but this drug has lower potency compared with the newer nucleos(t)ide analogues. A small study suggested better efficacy when pegIFN was used for 48 weeks in combination with adefovir because the rate of HBeAg loss (58%) and HBsAg seroconversion (15%) were higher compared with historical cohorts [104]. Although these findings could be interpreted to indicate that the two drugs work synergistically to promote greater elimination of covalently closed circular DNA (cccDNA), the study had no control group and the observed rate of HBsAg clearance was surprisingly high. Especially as a study of HIV/HBV-co-infected patients who were HBeAg-positive and had documented lamivudine-resistant HBV, showed no loss of HBeAg after 48 weeks' therapy with adefovir 10 mg daily and pegIFN-α-2a 180 µg weekly [105]. Further trials of pegIFN in combination with more potent nucleos(t)ide analogues, which have a higher genetic barrier to resistance such as tenofovir or entecavir, are required.

It has been suggested that therapeutic efficacy is enhanced when a nucleoside analogue is used to lower HBV DNA levels before commencing pegIFN [106]. Additional studies are needed to determine whether the staggered introduction of an immunomodulatory agent rather than simultaneous commencement of combination nucleos(t)ide and pegIFN therapy might be a more effective strategy to achieve sustained suppression of viral replication.

Unexpected drug toxicity can be encountered when drugs are given in combination and a study of pegIFN plus telbivudine had to be prematurely terminated due to a higher-than-expected incidence of peripheral neuropathy [107]. Although this side effect has been reported uncommonly in patients receiving telbivudine alone [108], this higher risk was not predicted based on the side-effect profiles of the individual drugs, and emphasizes the importance of studying drug combinations in trials in order to establish safety and efficacy prior to their introduction in clinical practice.

4. Conclusions

Several drugs are now available to inhibit viral replication and can suppress HBV DNA in serum to levels undetectable by sensitive PCR-based assays in the majority of patients with either eAg-positive or -negative disease. Achieving optimal

suppression of viral replication is associated with a reduction in serum aminotransferase levels, improvements in histological necro-inflammatory activity and fibrosis levels, a reduced chance of developing cirrhosis and HCC [4], and improved survival [3]. However, mutations within the viral polymerase gene permit the selection of drug-resistant viral strains and monotherapy with lamivudine [29], telbivudine or adefovir has been associated with a high risk of viral drug resistance. Furthermore, sequential monotherapy using these agents has led to the emergence of multi-drug–resistant viral strains. In contrast, the latest nucleos(t)ide analogues, entecavir and tenofovir, effectively suppress viral replication in the majority of patients, and in nucleoside-naive patients are associated with very low rates of virologic resistance [22]. PegIFN-α-2a is approved as initial therapy for chronic hepatitis B [22] and offers the potential for a finite-duration therapy with a durable off-treatment response.

5. Expert opinion

Should the management of chronic hepatitis B follow the HIV model, where the use of combination therapy enhances the therapeutic response and diminishes the rate of emergence of viral drug resistance? When only lamivudine and adefovir were available to treat chronic hepatitis B, their combination had theoretical advantages, and the limited clinical studies supported this therapeutic approach. Although combining these drugs did not enhance antiviral potency and added to the short-term cost, it reduced the risk of viral breakthrough due to emergence of drug-resistant virus. Following the addition of entecavir and tenofovir to the arsenal of medications, it is difficult to envisage a role for combination nucleos(t)ide therapy in the majority of uncomplicated, treatment-naive patients because these drugs have high antiviral potency and the former has demonstrated a high genotypic barrier to resistance. Current European guidelines recommend first-line therapy with either of these two agents [22]. Nevertheless, *de novo* combination therapy is currently advisable in patients who already harbor drug-resistant mutants and could be justified in patients at risk of rapid clinical deterioration following the development of viral drug resistance, for example, cirrhotic patients with high-level viremia or those who have undergone liver transplantation for HBV-related disease.

Nucleos(t)ide analogues suppress the generation of new virions but, in the short term, they only slowly deplete the hepatocyte pool of HBV cccDNA [109]. Studies have shown that cccDNA has a long half-life and the fall in cccDNA levels during nucleos(t)ide administration is associated with both hepatocyte turnover and block of new cccDNA synthesis [110]. It is not known how long effective suppression of HBV replication with nucleos(t)ide analogues will need to be maintained in order to reduce cccDNA to levels where the adaptive and innate anti-HBV immune responses can clear the infection. But a recent report suggests that indefinite therapy may not be required because complete suppression of viral replication by adefovir for 4 or 5 years was sufficient to induce long-term control of hepatitis B infection off treatment in 55% of patients, and 50% of them achieved HBsAg loss [111]. This observation needs to be confirmed by other studies.

Currently, pegIFN is the only licensed drug for treating HBV with a different mode of action to the nucleos(t)ide analogues. Patients treated with pegIFN have an increased probability of losing HBsAg, which is as close to a cure for HBV infection that can be achieved at present. Although the combination of lamivudine with pegIFN did not enhance the long-term response to pegIFN alone, more studies are required to investigate its combination with entecavir or tenofovir to see if their greater antiviral potency results in higher rates of HBsAg loss. The identification of new agents that target different steps in the viral life cycle is a priority, because the inhibition of HBV replication at multiple steps might provide an effective means to circumvent the antiviral resistance of nucleos(t)ide analogues. Nitazoxanide, a thiazolide active against anaerobic bacteria and protozoa, has shown preliminary evidence of efficacy in the treatment of chronic hepatitis B. *In vitro* studies show that it potently inhibits replication of wild-type, lamivudine and adefovir -resistant HBV mutants [112]. The antiviral mechanism of action is not fully characterized, but it appears to activate protein kinase activated by double-stranded RNA (PKR), an interferon-induced gene, which in turn activates eukaryotic initiation factor 2 alpha (eIF2-α) [113]. In a small clinical study over 1 year, nitazoxanide decreased serum HBV DNA and patients showed an unexpectedly high rate of HBsAg loss [114]. These preliminary studies suggest that nitazoxanide, either as monotherapy or in combination therapy with nucleos(t)ide analogues, has the potential to increase HBsAg loss and offer another finite-duration treatment for HBV.

Declaration of interest

PM Harrison has acted as consultant for Bristol-Myers Squibb, Gilead and Schering Plough. I Carey states no conflict of interest. The authors have received no payment in preparation of this manuscript.

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