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Natural Course, Therapeutic Options and Economic Evaluation of Therapies for Chronic Hepatitis B

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Abstract

Chronic hepatitis B virus infection afflicts 400 million people worldwide and untreated will progress to cirrhosis in 15–40% of individuals, with an associated increased risk for the development of hepatocellular carcinoma. The ‘inactive carrier state’ carries a benign prognosis with a very low risk of cirrhosis or hepatocellular carcinoma. However, the hepatitis B e antigen (HBeAg)-positive chronic hepatitis state is an active disease state with increased risk for progressing

to cirrhosis and hepatocellular carcinoma. The HBeAg-negative mutant variety of chronic hepatitis B has been associated with a higher incidence of cirrhosis at initial presentation and more frequent progression to hepatocellular carcinoma compared with the wild-type hepatitis B.

Five medications are currently approved by the US FDA for the treatment of chronic hepatitis B: interferon-α, lamivudine, adefovir dipivoxil, entecavir and peginterferon-α-2a. Interferon-α therapy has been shown to increase the rate of HBeAg and hepatitis B DNA loss with a small chance of hepatitis B surface antigen loss, but has significant adverse effects and is ineffective against the HBeAg-negative mutant. Lamivudine is a safely used, orally administered drug with good efficacy, but is associated with the development of a lamivudine-resistant (Lam-R) mutant in a large proportion of patients after long-term therapy. High relapse rates after lamivudine therapy make this medication less effective in the HBeAg-negative mutant also. Adefovir dipivoxil is a safely used, orally administered drug, which is effective against the Lam-R mutant. Adefovir dipivoxil is effective against the wild-type and HBeAg-negative hepatitis B and has a very low incidence of resistance development. Entecavir is a highly potent and selective new oral drug against hepatitis B. It has demonstrated no resistance development in treatment-naive patients, but a low incidence of resistance in patients infected with prior Lam-R mutants. Peginterferon-α-2a is administered once weekly and has improved efficacy compared with standard interferon-α and lamivudine. However, it has a similar adverse-effect profile to standard interferon-α.

Pharmacoeconomic studies have demonstrated a cost benefit in treating chronic hepatitis B patients compared with no therapy. However, results have been conflicting, with earlier studies showing a cost advantage of lamivudine over interferon-α and a more recent, comprehensive study favouring interferon-α monotherapy in HBeAg-negative patients and adefovir dipivoxil 'salvage' after lamivudine resistance development in HBeAg-positive patients.

1. Hepatitis B Virus (HBV) Infection

Hepatitis B virus (HBV) infection and its complications are global health problems. Approximately 400 million people are chronic HBV carriers worldwide.[1] The spectrum of chronic HBV infection ranges from an asymptomatic hepatitis B surface antigen (HBsAg) carrier state to chronic hepatitis with progression to cirrhosis and end-stage liver disease.[2,3] It is estimated that 15–40% of people with chronic HBV infection will progress to cirrhosis.[4]

In endemic regions of the world such as Southeast Asia, Africa and the Pacific Islands, vertical transmission from infected mothers and perinatal transmission from infected family members are the predominant routes of HBV passage. In less endemic Western countries, HBV transmission occurs as a consequence of high-risk sexual practices or injection drug use.[5]

Chronic HBV infection is characterised by distinct phases of viral replication (marked by high levels of serum HBV DNA or circulating hepatitis B

e antigen [HBeAg]) and nonreplication (or low replication), which are based on host immune-virus interactions. An 'immunotolerant' phase exists characterised by no clinical symptoms, normal serum ALT levels, and minimal histological activity despite circulating hepatitis B surface antigen (HBsAg), HBeAg and high levels of serum HBV DNA. This phase is likely to result from an absent or weak immune response to HBV-infected hepatocytes and studies in mice have suggested that the presence of HBeAg confers a state of immunological tolerance.[6] The patient may then enter an 'immunoactive' phase characterised by increasing serum ALT levels and histological activity in conjunction with decreased serum HBV DNA levels, felt to represent immune-mediated lysis of HBV infected hepatocytes. The triggering event is not clearly understood. Finally, the patient may enter a low or nonreplicative phase marked by undetectable serum HBV DNA, normalisation of serum ALT levels, resolution of histological activity and seroconversion of HBeAg to antibody against HBeAg (anti-HBe). This phase is frequently termed the 'inactive HBsAg carrier state'.[2,3] The inactive HBsAg carrier state may persist for life, but a proportion of patients will experience 'reactivation' of HBV marked by reappearance of high levels of serum HBV DNA and elevation of serum ALT levels.[2] Reactivation of HBV may be spontaneous or triggered by active immunosuppression.

1.1 Inactive Hepatitis B Surface Antigen Carrier State

This disease state carries a benign prognosis with long-term follow-up studies indicating very low risk for developing cirrhosis or hepatocellular carcinoma (HCC).[7,8] Indeed, the inactive HBsAg carrier state following HBeAg seroconversion to anti-HBe is associated with marked reduction of serum HBV replication, biochemical normalisation and histological inflammatory remission in most patients.[7,9-12] Regression of fibrosis has been shown to occur following sustained HBeAg seroconversion.[13] However, 20–30% of inactive HBV carriers may develop spontaneous episodes of reactivation, which if sustained or recurrent can eventually progress to decompensated liver disease.[7,9,14,15]

1.2 Hepatitis B e Antigen (HBeAg)-Positive Chronic HBV Infection

This active disease state of chronic HBV infection usually manifests in the third or fourth decade of life of patients. At presentation, liver damage usually ranges from mild to severe chronic hepatitis (24–63%) or, less frequently, established cirrhosis (10–24%).[10,11,16-18] This phase of chronic HBV infection is characterised by varying degrees of active viral replication depending on whether the patient is in a state of 'immune tolerance' or 'immune clearance (or activity)'. During 'immune tolerance', a relatively weak immune response theoretically permits normal serum ALT levels and absent or low histological inflammation despite high serum HBV DNA levels. The 'immune clearance' phase heralds a heightened immune attack on HBV-infected hepatocytes, marked by high serum ALT spikes and histological inflammation with decreasing serum HBV DNA levels. These periods of exacerbation may last 2–4 months.[15] If HBeAg seroconversion to anti-HBe occurs following this flare, then the patient enters the 'inactive HBsAg carrier state'. In some patients, HBeAg seroconversion does not occur and the patient remains in the active HBeAg-positive state. Accordingly, the patient may continue to experience fluctuating levels of viral replication with recurrent disease flares and remissions, which over time, are believed to contribute to progression of liver disease.

1.3 HBeAg-Negative Chronic HBV Infection

This disease state is seen in patients with chronic HBV infection with circulating HBsAg, undetect-

able HBeAg, the presence of anti-HBe, ongoing viral replication confirmed by detectable serum HBV DNA (>10 000 copies/mL), elevated serum ALT levels (>2 times the upper limit of normal), absence of other chronic liver diseases and moderate-to-severe histological necroinflammatory activity.[2] This HBV variant results from mutations in the HBV genome including the precore region (termed the 'precore mutant'), which prevents the production of HBeAg,[19] and the core promoter region (termed the 'basal core promoter mutant'), which results in down-regulation of HBeAg.[20] HBeAg-negative chronic HBV infection is believed to represent a late phase in the natural course of chronic HBV infection, as long-term studies have noted an increasing cumulative incidence of the HBeAg-negative mutants after spontaneous HBeAg seroconversion in patients with chronic HBV.[7] HBeAg-negative chronic HBV infection is more aggressive than wild-type HBeAg-positive chronic HBV infection with advanced histological disease evident in >50% of patients at initial presentation.[16] Indeed, several large studies[16,18] have shown 29–38% of HBeAg-negative chronic HBV patients had cirrhosis at initial presentation. This type of chronic hepatitis B is also more aggressive with frequent development of HCC.[19] Therefore, treatment of this variant of chronic HBV infection is particularly important.

Goals of treatment with the HBeAg-negative mutant are different than with HBeAg-positive chronic HBV infection, as HBeAg seroconversion is not feasible by definition. Thus, virological and biochemical response are monitored when treating HBeAg-negative chronic HBV.[2,21] Indeed, induction of a sustained ALT normalisation, even in the presence of low HBV DNA levels, should be the main therapeutic goal.[21] Virological response using quantitative polymerase chain reaction (PCR) assays is arbitrarily defined as <10 000 copies/mL.[2,3] Finally, on-treatment response with the HBeAg-negative mutant is frequently not durable; hence, efficacy assessments should still be made ≥12 months after therapy has been discontinued.[2,21] Life-long, maintenance antiviral therapy may be warranted in patients with HBeAg-negative chronic HBV infection.

1.4 Progression to Cirrhosis and Hepatocellular Carcinoma

Longitudinal studies have indicated the incidence of developing cirrhosis ranges from 2 to 5 per 100 person-years for untreated patients with HBeAg-positive chronic HBV infection[17,22-24] and from 8 to 10 per 100 person-years for untreated patients with HBeAg-negative chronic HBV infection.[25] Active HBV replication with persistent or intermittent detection of HBV DNA is also a risk factor for cirrhosis.[17,22,24] The 5-year cumulative incidence of developing decompensated cirrhosis was 16% in a European study,[26] manifesting as ascites development, variceal bleeding or increasing jaundice. In an Asian study, the 5-year cumulative incidence of cirrhotic decompensation was 20%.[27]

Chronic HBV infection and established cirrhosis are known risk factors for the development of HCC. In a study of 161 patients with compensated HBV-cirrhosis, the 5-year cumulative incidence of HCC was 9% with an incidence per 100 person-years of 2.2.[26] In endemic regions such as Asia, the incidence of HCC per 100 person-years increases when comparing asymptomatic HBsAg-positive carriers to patients with chronic HBV infection without cirrhosis to untreated patients with compensated HBV cirrhosis (0.1, 1.0 and 3–8, respectively).[27-30]

1.5 HBV Genotypes

HBV can be classified into seven different genotypes (A–G), based on intergroup divergence in nucleotide sequence. The distribution of HBV genotypes favours geographic regions of the world: genotype A (northwest Europe, North America and central Africa), genotypes B and C (Southeast Asia,

China and Japan), genotype D (Mediterranean countries, India and the Middle East), genotype E (Africa), genotype F (American natives, Polynesia, and Central and South America), and genotype G (US and France).[31] Studies have shown that specific HBV genotypes are associated with higher response rates to antiviral therapy or spontaneous HBeAg seroconversion. Genotype C is associated with a lower response rate to interferon-α than genotype B.[32] Chu et al.[33] found that HBV genotype B is associated with lower prevalence of HBeAg at presentation and higher rates of HBeAg seroconversion than HBV genotype C. The precore mutant is most prevalent with HBV genotypes B and D, and early childhood acquisition.[2,3,19,21] As our understanding of HBV genotypes increases, it is likely that differing genotypes may account for the heterogeneity in disease manifestations seen in patients with chronic HBV infection.

1.6 Summary

Chronic HBV infection poses significant worldwide health issues, afflicting hundreds of millions of individuals. Untreated chronic HBV infection can lead to decompensated cirrhosis and HCC, both of which significantly impact on the cost of healthcare in terms of dollars spent for acute hospitalisations, chronic medical management and ultimately liver transplantation where available. Our understanding of the natural course and prognosis of the various stages of chronic HBV infection should allow us to intervene with antiviral therapy to decrease the risk of liver progression and reduce the financial impact of this worldwide disease.

2. Antiviral Therapy

The ultimate goal of antiviral therapy in chronic HBV infection is to prevent progression to cirrhosis and development of HCC. However, such endpoints are difficult to assess given the prolonged natural course of chronic HBV infection. Thus, most clinical studies of antiviral therapy in chronic HBV infection have relied on short-term surrogate markers of treatment response including serum HBV DNA levels, HBeAg loss or seroconversion to anti-HBe and histological improvement. Whether these surrogate markers of treatment response translate to long-term benefit in regards to cirrhosis progression or HCC development awaits the test of time.

Currently, five drugs are approved by the US FDA for the treatment of chronic hepatitis B: standard interferon-α, lamivudine, adefovir dipivoxil, entecavir and, most recently, peginterferon-α-2a (see table I and table II for a comparison of these medications).

2.1 Interferon-α

Interferon-α is a naturally occurring protein with antiviral, antiproliferative and immunomodulatory effects. *In vivo*, it is a potent stimulator of natural killer (NK) and dendritic cells.[36]

Table I. Currently approved medications for the treatment of chronic hepatitis B virus (HBV) infection

Generic name	Trade name[a]	Manufacturer	Date approved for hepatitis B[b]	Total average monthly cost ($US)[c]
Interferon-α-2b	Intron® A	Schering Corporation	1992	2166.08
Lamivudine	Epivir-HBV®	GlaxoSmithKline	1998	202.38
Adefovir dipivoxil	HepSera™	Gilead Sciences	2002	524.39
Entecavir	Baraclude™	Bristol-Myers Squibb	29 March 2005	629.15
Peginterferon-α-2a	Pegasys®	Hoffman La-Roche	13 May 2005	1614.13

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

b Date approved by the US FDA.

c Total average monthly cost = the cost of all strengths and forms of the medication, divided by the number of claims processed for it during the past 8 weeks. Information obtained from 'RxPrice Guide'.[34]

Table II. Comparison of clinical data for approved treatments for chronic hepatitis B (CHB)[35] a

Parameter	Interferon-α	Lamivudine	Adefovir dipivoxil	Entecavir	Peginterferon-α-2a
HBeAg+ CHB (HBeAg seroconversion)b	~18	16–18	12	21	27
HBeAg− CHB (HBV DNA loss)	60–70	50–70	51	90	63
Duration of therapy					
HBeAg+ CHB	4–6 months	>1 year	>1 year	>1 year	1 year
HBeAg− CHB	12 months	Indefinite	Indefinite	Indefinite	1 year
Durability of response (%)					
HBeAg+ CHB	80–90	50–80	91	82	~80
HBeAg− CHB	~20	<10	<10	NA	~30
Route of administration	Subcutaneous	Oral	Oral	Oral	Subcutaneous
Adverse effects	Many	Negligible	Negligible	Negligible	Many
Contraindications	++	–	–	–	++
Drug resistance (%)	None	~20 at year 1 ~70 at year 5	0 at year 1 ~18 at year 4	0 at year 1 7 in Lam-R	None

a Response in year 1 (%)

b Seroconversion from HBeAg+ to HBeAg−/HBeAg+.

HBeAg = hepatitis B e antigen negative; HBV = hepatitis B virus; **Lam-R** = lamivudine-resistant mutant; **NA** = not applicable; **–** indicates none; **++** indicates many contraindications.

In 1993, Wong et al.[37] performed a meta-analysis of 25 quality studies evaluating the short-term efficacy of interferon-α in patients with HBeAg-positive chronic HBV infection. The treatment endpoints were loss of detectable serum HBV DNA, HBeAg and HBsAg. These authors found statistically significant differences in the three endpoints between interferon-treated patients and placebo-treated patients (loss of HBV DNA in 37% vs 17%, loss of HBeAg in 33% vs 12%, and loss of HBsAg in 7.8% vs 1.8%, respectively). In patients who lost serum HBeAg, seroconversion to anti-HBe occurred during or shortly after cessation of therapy. Their analysis did not find a difference in response between patients treated for 3, 4 or 6 months with interferon. In addition, a dose administration schedule of 5MU daily was equally efficacious as 10MU thrice weekly. In patients who ultimately responded to interferon-α, a biochemical flare in serum ALT was observed to coincide with a fall in serum HBV DNA near the end of treatment.

Long-term outcomes and durability of response after interferon-α therapy have been studied by several investigators, but the results have not been consistent. Lin et al.[38] performed an 11-year follow-up study in Taiwan of 67 interferon-treated patients regardless of treatment response compared with 34 untreated control patients. A significant improvement in overall survival ($p = 0.018$) and a decrease in the incidence of HCC development ($p = 0.013$) was noted in the interferon-treated patients. However, a subsequent study by Yuen et al.[39] showed conflicting results. In this 20-year follow-up study in Hong Kong, 208 interferon-treated patients were compared with 203 untreated control patients, and the investigators did not find a long-term benefit in survival or the development of HCC.

In 1997, Lau et al.[40] reported on the 10-year follow-up of 103 patients with chronic hepatitis B treated with interferon-α at the National Institutes of Health (NIH). They noted an overall 30% end-of-treatment response rate with loss of serum HBeAg and undetectable HBV DNA, and at 10-year follow-up, 94% of responders remained HBeAg negative compared with 40% of nonresponders ($p < 0.001$). Interestingly, in patients with established pretreatment cirrhosis who lost serum HBeAg, a significant

survival advantage was found; however, no such benefit was found in patients with mild pretreatment histological disease. Fattovich et al.[41] reported a similar survival benefit in patients with compensated HBV cirrhosis who responded virologically and biochemically to interferon-α therapy compared with untreated control patients. However, Niederau et al.[42] reported improved survival in patients who lost HBeAg after interferon-α therapy regardless of baseline histological disease.

Several investigators have studied predictors of response to interferon-α therapy in patients with chronic HBV infection. Lok et al.[43] noted that elevated baseline serum ALT level was a good predictor of response, defined as seroconversion to anti-HBe, to interferon-α therapy, regardless of ethnicity (Asians vs Caucasians). However, delayed clearance of serum HBsAg was not seen in any patients who developed HBeAg seroconversion. Brook et al.[44] subsequently reported that high baseline Histological Activity Index (HAI) and low serum HBV DNA levels were predictors of response to interferon-α therapy. More recent studies have focused on the importance of HBV genotypes in predicting response to antiviral therapy.[32,33] Indeed, HBV genotype B has been shown to be more responsive to interferon-α therapy, as well as being associated with a greater rate of spontaneous HBeAg seroconversion.

Several investigators have explored different ways to potentially increase response rates to interferon-α therapy. Perrillo et al.[45] studied response rates (clearance of HBeAg and serum HBV DNA) to interferon-α (5 MU/day) following a 6-week prednisone 'priming' taper, but found no significant improvement in response rates between prednisone-primed patients and controls. Furthermore, severe hepatitis flares occasionally followed corticosteroid withdrawal leading to hepatic decompensation. Longer courses of interferon-α therapy have been studied as a means to increase response rates. Janssen et al.[46] noted a significant increase in HBeAg loss and undetectable serum HBV DNA in patients following a 32-week prolonged course of interferon-α (10MU thrice weekly) compared with those receiving a standard 16-week course (28% vs 12%; $p = 0.04$). Carreno et al.[47] studied the effect of an additional 6-month retreatment course of interferon-α (9MU thrice weekly) in patients whose previous interferon-α therapy was unsuccessful and who found a significant increase in HBeAg and serum HBV DNA loss in the re-treated patients compared with untreated patients (33.3% vs 10%; $p = 0.031$).

There have been several smaller trials studying the efficacy of interferon-α in patients with HBeAg-negative chronic HBV infection.[48-52] In these studies, the end-of-treatment biochemical and virological response rates were impressive, ranging from 60% to 90%. However, following treatment, relapses rates were substantial, resulting in overall sustained response rates ranging from only 10% to 15%. It has been suggested that longer treatment courses with interferon-α may improve overall sustained response rates, ranging from 20% to 25%.[3] In a larger study[53] of 216 patients with HBeAg-negative chronic HBV infection, sustained response rates of 11% after a 6-month course of interferon-α and 22% after a 12-month course of interferon-α were reported. Consequently, it is now recommended that for the treatment of patients with HBeAg-negative chronic HBV infection, at least a 12-month course of interferon-α with doses of 3–6MU thrice weekly is considered.[2,21]

A limiting factor in the use of interferon-α therapy is several associated adverse effects. Typical adverse effects include influenza-like symptoms including headaches, fevers, chills, myalgias and malaise associated with interferon-α administration. Irritability and depression are frequent adverse effects. In fact, interferon-α therapy can sometimes exacerbate underlying psychiatric disorders, thus limiting its use in patients with uncontrolled or

significant psychiatric illness. Interferon-α therapy is absolutely contraindicated in patients with uncontrolled seizure disorder, autoimmune disorders, cardiopulmonary disorders or decompensated cirrhosis. Indeed, treatment of decompensated cirrhosis with interferon-α has been associated with the development of septicaemia.

2.2 Lamivudine

Lamivudine, the (−)enantiomer of 2′-deoxy-3′-thiacytidine (3TC), is an oral dideoxynucleoside inhibitor of DNA synthesis which blocks DNA viral replication by terminating the nascent proviral DNA chain. Lamivudine has a good safety profile with no known mitochondrial DNA effects. Lamivudine 100 mg/day has been shown to be effective in suppressing viral replication in chronic HBV infection. Hence, lamivudine appears to be an excellent medication for chronic HBV infection with potent inhibition of HBV, oral administration, low cost and excellent safety profile.[54,55]

The short-term efficacy of a 1-year course of lamivudine therapy in patients with chronic HBV infection has been studied in three published phase III trials.[56-58] The primary outcome measure was histological improvement, and in two of the trials, end-of-treatment histology showed a significant decrease in inflammation and fibrosis by the Knodell HAI score (defined as a ≥2 point decrease in the inflammatory score).[56,57] In the Asian study,[57] improvement in necroinflammation was greatest with the 100mg dose (67%), less with the 25mg dose (59%) and least with placebo (30%); however, improvement in fibrosis was seen only with a dose of lamivudine 100mg. Serum HBV DNA levels decreased in all patients taking lamivudine, although HBV DNA became undetectable at end-of-treatment in 96% taking the 100mg dose, 73% taking the 25mg dose and only 23% taking placebo. HBeAg seroconversion was greatest with the 100mg dose (16%), less with the 25mg dose (13%) and only 4% in the placebo group. The overall HBeAg seroconversion rate in the North American study was similar at 17%.[56] Interestingly, HBsAg loss occurred in 2% of the responders in the North American study compared with no patients in the Asian study.[56,57]

Longer treatment courses have been evaluated in two Asian studies. Liaw et al.[59] noted incremental increases in HBeAg seroconversion rates when extending lamivudine treatment from 52 weeks to 104 weeks. Given a 25mg dose, HBeAg seroconversion rates increased from 18% (week 52) to 25% (week 104) and with a 100mg dose, from 17% (week 52) to 27% (week 104). Leung et al.[60] described a cumulative increase in HBeAg seroconversion up to 40% after 3 years of lamivudine therapy and histological improvement was sustained if there was no emergence of viral resistance to lamivudine.

Predictors of response with lamivudine therapy in chronic HBV are similar to interferon-α and include high baseline ALT levels and low baseline serum HBV DNA levels, although HBV DNA levels are not as important a predictor with lamivudine as with interferon-α.[61] Chien et al.[62] found that the baseline ALT level is highly predictive of response to lamivudine therapy, but additionally, is highly predictive of spontaneous HBeAg seroconversion.

Most notably, the ‘Achilles’ heel’ of lamivudine is the relatively high rate of emergence of viral resistance to lamivudine with long-term therapy. This lamivudine-resistant (Lam-R) variant contains a mutation in the tyrosine-methionine-aspartate-aspartate (YMDD) motif of the HBV polymerase and is selected out by antiviral therapy. This mutation is an amino acid substitution (isoleucine or valine replacing methionine at codon 204 or methionine replacing leucine at codon 180) in the HBV polymerase. This so-called ‘YMDD mutant’ has been identified as early as 2–6 months after initiating lamivudine therapy in patients.[63] After 1 year of lamivudine therapy, the incidence of genotypic de-

velopment of the Lam-R mutant increases, reportedly ranging from 14% to 32%.[64] Although genotypic resistance may be detected as early as 49 days after initiating lamivudine therapy, phenotypic expression of the Lam-R mutant (specifically, a marked rise in the serum ALT level) seldom occurs before 6 months.[65] This recurrent hepatitis flare is likely related to an increase in replication of the mutant HBV.[66]

The clinical significance of the Lam-R mutant remains unclear, as this mutant is less replication competent than the wild-type HBV virus in immunocompetent patients. Indeed, the Lam-R mutant may not cause significant clinical disease in the early stages in immunocompetent patients. However, significant hepatic decompensation and even death have been reported in immunosuppressed patients such as those with HIV infection or cirrhosis.[67] Other less severe complications of Lam-R mutant development in immunosuppressed patients include exacerbation of hepatitis, decreased rate of HBeAg seroconversion, rapid allograft reinfection with rapid disease progression in liver transplant recipients and possible transmission of drug resistance. Furthermore, second-generation mutations in patients with established Lam-R mutant disease continuing with long-term lamivudine therapy could be responsible for the recurrent acute flares of hepatitis seen in this cohort.[68] Finally, submassive hepatic necrosis has been described after development of the Lam-R mutant in patients continuing with long-term lamivudine therapy.[69] Therefore, it is likely to be unwise to ignore development of the Lam-R mutant and additional antiviral medications should be considered.

Lamivudine treatment of HBeAg-negative chronic HBV infection, similar to interferon-α, achieves very high end-of-treatment biochemical and virological response rates, ranging from 70% to 90% after 12 months of therapy.[70-73] However, relapse rates are again substantial, resulting in low overall sustained response rates. Unfortunately, long-term or life-long therapy with lamivudine is not feasible because of the high rate of emergence of the Lam-R mutant.[70,74] Development of the Lam-R mutant in this patient population is associated with an increase in serum HBV DNA levels, ALT elevations and adverse effects on histology. The optimal duration of therapy is undefined and the long-term outcome in sustained responders is unknown.

Lamivudine therapy has been studied in patients with decompensated HBV infection in whom liver transplantation was not an option.[75] In a study of 75 patients with decompensated HBV infection, Hann et al.[75] showed that lamivudine therapy for a median duration of 12.7 months resulted in undetectable HBV DNA (by the bDNA assay) in 64%, ALT normalisation in 48% and median Child-Pugh score improvement from ten to eight overall. Although virological breakthrough occurred in 18%, biochemical tests of liver function at last follow-up were not significantly different between patients with and without virological breakthrough.

Lamivudine has also been studied in patients after liver transplant who have established recurrence of HBV infection.[76] In this study of 33 post-liver transplant patients with active HBV infection, Fontana et al.[76] showed at a median duration of therapy of 85 weeks, median HBV DNA levels became undetectable within 16 weeks and biochemical tests of liver function significantly improved in patients with abnormal values at study entry. Virological breakthrough caused by YMDD mutations occurred in 13 patients at a median of 61 weeks of lamivudine therapy; however, none of the patients developed worsening clinical parameters at last follow-up as compared with patients without virological breakthrough.

2.3 Adefovir Dipivoxil

Adefovir dipivoxil is an oral nucleotide analogue with *in vitro* and *in vivo* activity against HBV. It was

FDA approved in September 2002 for the treatment of chronic HBV infection and is also now approved in Europe and many other countries worldwide. In a large international study of 515 HBeAg-positive patients with chronic HBV infection, adefovir dipivoxil 10 mg/day for 1 year resulted in significantly higher HBeAg seroconversion rates than placebo (12% vs 6%; $p < 0.05$).[77] Significant histological improvements were also seen in necroinflammatory and fibrosis scores after 1 year of therapy. In a dose-dependent manner, adefovir dipivoxil-treated patients compared with controls showed greater rates of serum ALT normalisation (55% receiving 30 mg/day and 48% receiving 10 mg/day vs 16% receiving placebo) and undetectable HBV DNA levels to ≤400 copies/mL (39% receiving 30 mg/day and 21% receiving 10 mg/day vs 0% receiving placebo). Adverse events leading to study drug discontinuation were seen in only 3% receiving 30 mg/day, 2% receiving 10 mg/day and <1% of placebo recipients. Adverse events included transaminase elevations, weight loss and rash in the 10 mg/day group, and gastrointestinal complaints, headache and a Fanconi-like syndrome in the 30 mg/day group.

Adefovir dipivoxil has been studied in patients with HBeAg-negative chronic HBV infection in a large, international study.[78] After 48 weeks of therapy, significant differences were found between 123 adefovir-treated patients and 61 placebo-controls with regards to serum ALT normalisation (72% vs 29%; $p < 0.001$) and undetectable HBV DNA by quantitative PCR (51% vs 0%; $p < 0.001$). Histological improvement was also significantly improved in the adefovir dipivoxil-treated group (64% vs 33%; $p < 0.001$). At 48 weeks therapy, no resistance to adefovir emerged. However, subsequent follow-up at 96 weeks identified one patient who developed an adefovir-resistant mutation after developing viral breakthrough.[79] This patient responded to subsequent lamivudine therapy with normalisation of serum ALT and decrease in serum HBV DNA. The optimal duration of therapy with adefovir dipivoxil remains undefined.

Adefovir dipivoxil has been shown to be effective against the Lam-R mutant HBV.[80-82] Adefovir dipivoxil has also been shown to be effective against the Lam-R mutant in patients on active immunosuppression in the post-liver transplant setting.[80,83] This is a clear advance in treatment of a resistant mutant for which there was previously no effective therapy.

A major advantage of adefovir dipivoxil is its relatively low incidence of development of a drug-resistant viral mutant with long-term therapy. Previously, investigators reported no emergence of drug-resistant mutants after 48–60 weeks of therapy in patients with chronic HBV infection enrolled in clinical trials.[84,85] However, a novel mutation was identified in one patient after viral breakthrough was observed at 96 weeks of adefovir dipivoxil therapy.[79] This mutation, an asparagine to threonine substitution at position 236 in the D domain of the HBV polymerase (termed the N236T mutation), confers resistance to adefovir dipivoxil. This patient remained susceptible to subsequent therapy with lamivudine, which resulted in normalisation of serum ALT and a decrease in serum HBV DNA levels.

More recently, data on continued adefovir dipivoxil therapy to 144 weeks in patients with HBeAg-negative chronic HBV was published.[86] With longer duration of adefovir dipivoxil therapy, median HBV DNA suppression decreased from 3.47 $\log_{10}$ at week 96 to 3.63 $\log_{10}$ at week 144, and HBV DNA became undetectable (<1000 copies/mL) in 71% at week 96 to 79% at week 144. The adverse effects observed at week 144 were not significantly worse than at week 96. More importantly, resistance mutations (N236T and the more recently discovered A181V) were identified in 5.9% of the patients by week 144.

Adefovir dipivoxil has been studied in patients with Lam-R HBV-related cirrhosis awaiting liver

transplantation and in post-liver transplant patients with established recurrence of HBV infection.[87] After 48 weeks of adefovir dipivoxil therapy, 81% of pre-liver transplant patients and 34% of post-liver transplant patients achieved undetectable HBV DNA (<400 copies/mL by the Roche Amplicor assay) with improvement in Child-Pugh-Turcotte scores in 90% in both cohorts. No patient in either cohort developed resistance to adefovir dipivoxil at 48 weeks of therapy and the medication was fairly well tolerated.

2.4 Entecavir

Entecavir is an oral guanosine nucleoside analogue with potent and selective inhibitory activity against HBV replication. It was recently approved by the FDA for treatment of chronic HBV in adults and is now approved in Europe and many countries worldwide. Data from three international phase III studies in patients with HBeAg-positive, HBeAg-negative and Lam-R chronic HBV infection demonstrated significantly better improvement in the primary endpoint of histological inflammation (defined as ≥2-point decrease in Knodell necroinflammatory score) with entecavir compared with lamivudine in all three patient populations at 48 weeks of therapy. In the HBeAg-positive (AI463-022) study,[88] significantly more patients in the entecavir-treated group (n = 354) demonstrated improvement in histological necroinflammation compared with the lamivudine-treated group (n = 355) [72% vs 62%; p = 0.0085]. Entecavir was also significantly better than lamivudine in the secondary endpoint measures of viral load suppression (<300 copies/mL by PCR assay) [67% vs 36%; p < 0.0001] and ALT normalisation (68% vs 60%; p = 0.02). However, HBeAg seroconversion at 48 weeks was not significantly better with entecavir than with lamivudine (21% vs 18%). In the HBeAg-negative (AI463-027) study,[89] the entecavir-treated group (n = 325) again demonstrated significantly better improvement in histological necroinflammation than the lamivudine-treatment group (n = 313) [70% vs 61%; p = 0.0143]. Entecavir was again significantly better than lamivudine in the secondary endpoint measures of viral load suppression (90% vs 72%; p < 0.0001) and ALT normalisation (78% vs 71%; p = 0.0451). Finally, in the Lam-R (AI463-026) study,[90] significantly more patients in the entecavir-treatment group (n = 141) showed improvement in histological necroinflammation compared with the continued lamivudine-treatment group (n = 145) [55% vs 28%; p > 0.0001]. Entecavir also was significantly better than continuing lamivudine in the secondary endpoints of improvement in fibrosis (defined as ≥1-point decrease in Ishak fibrosis score) [34% vs 16%; p = 0.0019], viral load suppression (19% vs 1%; p < 0.0001), and ALT normalisation (61% vs 15%; p < 0.0001). However, HBeAg seroconversion was not significantly different between entecavir and lamivudine at 48 weeks (8% vs 3%).

Viral resistance testing in the nucleoside-naive patient groups demonstrated no genotypic changes in the HBV polymerase associated with phenotypic resistance to entecavir at week 48 in any of the HBeAg-positive or HBeAg-negative patients. On the other hand, in patients with pre-existing chronic Lam-R HBV infection, genotypic analysis of all patients with detectable HBV DNA at week 48 revealed the presence of entecavir-associated resistance mutations (rtI169, rtS202 and/or rtM250) in 13 of 189 (7%) patients, although virological rebound due to resistance was observed in only 3 of 189 (1.6%) at week 48 of therapy. Thus, it appears that Lam-R mutations are a prerequisite for the emergence of entecavir resistance.

2.5 Peginterferon-α-2a

Polyethylene glycol is an inert, water soluble molecule of varying size, which when attached to standard interferon to form pegylated interferon theoretically decreases the clearance and antigenicity

of interferon, thus extending and sustaining its activity *in vivo* allowing for once weekly administration. The proof of concept was a 24-week study in patients with HBeAg-positive chronic HBV infection comparing standard interferon-α-2a (4.5 MU thrice weekly) to three doses of peginterferon-α-2a (90, 180 or 270 μg/week), in which Cooksley et al.[91] found the composite response of HBeAg loss, HBV DNA suppression and ALT normalisation was significantly higher in all peginterferon-α-2a dosages combined than with standard interferon (24% vs 12%; p = 0.036).

Peginterferon-α-2a (40kD) was subsequently approved by the FDA for chronic HBV infection based on the results of two large international studies comparing peginterferon-α-2a with lamivudine monotherapy and lamivudine plus peginterferon-α-2a combination therapy in patients with HBeAg-positive and HBeAg-negative chronic HBV infection.[92,93] After randomisation to one of three treatment arms, patients were treated for 48 weeks and followed for an additional 24 weeks in both studies. In the HBeAg-positive study, significantly more patients receiving peginterferon-α-2a or combination therapy compared with lamivudine monotherapy developed HBeAg seroconversion (32% and 27% vs 19%; p < 0.001 and p = 0.02, respectively) or HBV DNA suppression below 100 000 copies/mL (32% and 34% vs 22%; p = 0.01 and p = 0.003, respectively). In the HBeAg-negative study, significantly more patients receiving peginterferon-α-2a or combination therapy compared with lamivudine monotherapy developed ALT normalisation (59% and 60% vs 44%; p = 0.004 and p = 0.003, respectively) and HBV DNA suppression below 20 000 copies/mL (43% and 44% vs 29%; p = 0.007 and p = 0.003, respectively). However, in both the HBeAg-positive and HBeAg-negative studies, the addition of lamivudine to peginterferon-α-2a did not improve efficacy, as there was no significant difference in study endpoints between the peginterferon-α-2a monotherapy and lamivudine plus peginterferon-α-2a combination arms.

2.6 Combination Therapy

Several investigators have studied combination antiviral therapy with interferon-α and lamivudine with varied results. Schalm et al.[58] found no significant difference in HBeAg seroconversion between patients with chronic HBV infection treated with lamivudine monotherapy for 52 weeks (18% HBeAg seroconversion), interferon-α monotherapy 10MU thrice weekly for 16 weeks (19% HBeAg seroconversion), or combination lamivudine pretreatment for 8 weeks followed by interferon-α 10MU thrice weekly for 16 weeks (29% HBeAg seroconversion). However, a subsequent 'per protocol analysis' yielded different findings, noting a significantly higher HBeAg seroconversion rate in the combination therapy group compared with the monotherapy group (36% vs 19%; p = 0.02). No Lam-R mutant emergence was seen in the group receiving combination interferon-α plus lamivudine; however, 31% in the lamivudine monotherapy arm developed the Lam-R mutant.

Barbaro et al.[94] studied 150 Italian patients with chronic HBV infection, comparing combination interferon-α 9MU thrice weekly plus lamivudine 100 mg/day for 24 weeks versus lamivudine monotherapy for 52 weeks. At 48 weeks post-treatment, they found a significantly higher rate of HBeAg seroconversion and serum HBV DNA loss in the combination group compared with the monotherapy group (33% vs 15%; p = 0.014). Barbaro et al.[94] also noted a significant improvement in histological inflammation, defined as ≥2-point reduction in HAI score (46% vs 27%; p = 0.021) and fibrosis (42% vs 24%) in the combination group compared with the monotherapy group.

Yalcin et al.[95] compared response rates (defined as HBeAg seroconversion and serum HBV DNA

loss) between 33 HBeAg-positive chronic HBV patients treated with combination interferon-α 10MU thrice weekly plus lamivudine 100 mg/day for 12 months and 16 patients treated with interferon-α 10MU thrice weekly for 12 months. They found no significant difference in response rates between the group receiving combination therapy and the group receiving interferon-α monotherapy (45% vs 19%; $p = 0.133$).

Studies evaluating combination therapy with lamivudine plus adefovir dipivoxil have been restricted to patients with prior Lam-R mutations of HBV. Perrillo et al.[96] showed that in patients with compensated and decompensated HBV infection with prior Lam-R mutations, the addition of adefovir dipivoxil to ongoing lamivudine resulted in significant viral load suppression (<100 000 copies/mL or >2 $\log_{10}$ reduction from baseline) and ALT normalisation compared with ongoing lamivudine monotherapy during 52 weeks of therapy. Peters et al.[97] showed that in patients with compensated HBV infection with prior Lam-R mutations, the addition of adefovir dipivoxil to ongoing lamivudine or conversion to adefovir dipivoxil monotherapy resulted in significantly better viral load suppression from baseline and ALT normalisation compared with ongoing lamivudine monotherapy at 48 weeks of therapy; however, combination adefovir dipivoxil plus lamivudine did not appear to be significantly better than adefovir dipivoxil monotherapy. Nonetheless, in both studies, combination therapy was well tolerated without significant adverse effects.

To date, there have not been any published studies evaluating the efficacy of combining interferon-α plus adefovir dipivoxil, interferon-α plus entecavir or adefovir dipivoxil plus entecavir for the treatment of chronic HBV infection. Given that previous studies suggested a potential benefit of combination therapy in regards to response rates and emergence of viral resistance, future studies utilising combinations of nucleoside and nucleotide analogues are needed.

2.7 Post-Treatment Follow-Up

Continued follow-up in patients with an end-of-treatment response to antiviral therapy is recommended because of the chance of viral reactivation. HBV reactivation following spontaneous HBeAg seroconversion occurs at a rate of about 4.2% at a median of 8.6 years (range 1–18) of follow-up[7] and is associated with an increased risk of progression to cirrhosis or HCC. HBV reactivation following interferon-α therapy is even more likely, occurring at a rate of up to 24% at ≥6 month follow-up.[43] However, in patients sustaining HBeAg loss following interferon-α therapy, long-term follow-up indicates a halt in fibrosis progression.[98] HBV reactivation following lamivudine therapy can be as high as 50%.[99] However, even in the absence of HBeAg seroconversion, histological inflammation and fibrosis may be reduced in patients treated with lamivudine, although these benefits may not be maintained following cessation of therapy.[100] There are no data suggesting optimal duration of therapy with lamivudine or entecavir following HBeAg seroconversion. Unpublished data suggest that 12 additional months of therapy with adefovir dipivoxil following HBeAg seroconversion may result in a durable response in 91% of patients following cessation of therapy.[101]

3. Pharmacoeconomic Analysis

Pharmacoeconomic analysis determines the relationship between costs and outcomes (in regards to clinical, economic and quality of life measures) of an intervention.[102] For investigating therapies for chronic HBV infection, 'cost-utility analysis' is frequently employed, which measures costs in dollars and outcomes in quality-adjusted life-years (QALYs).[103] A QALY is calculated by multiplying the quantity of life gained by the quality of life

during that time. Results of a cost-utility analysis of two competing strategies are reported as "incremental of marginal cost-effectiveness ratios" and aim to determine the additional cost per additional QALY gained of one treatment strategy compared with another.[103]

Most pharmacoeconomic analyses of chronic HBV treatments have used a computer decision analytic model called a 'Markov model'. This model simulates the effect of a treatment on a population of chronic HBV patients progressing through different disease states over time. These disease states might include chronic hepatitis, compensated cirrhosis, decompensated cirrhosis, HCC, liver transplantation or death. The probability of moving from one disease state to another and the costs of each disease state are programmed into the model, and the model can track accumulated costs and QALYs. At the end of the model, cost and outcome for a treatment strategy can be calculated.

3.1 Interferon-α

In 1995, Wong et al.[104] performed a meta-analysis and cost-effectiveness analysis of nine randomised studies of interferon-α therapy in patients with HBeAg-positive chronic HBV infection. In total, they analysed 552 with HBeAg-positive chronic HBV infection and compared two treatment strategies: interferon-α 10MU thrice weekly versus 'standard-of-care' (symptomatic) therapy. A Markov decision analytic model was employed. Outcomes assessments were lifetime incidence of cirrhosis and HCC, life expectancy, QALY, and costs and marginal cost-effectiveness ratios from a societal standpoint. They found that interferon-α treatment increased the chance of clearing HBeAg from 9.1% to 45.6% in the first year of therapy. The cost-utility analysis demonstrated that interferon-α therapy yielded 3.4 additional QALYs, increased life expectancy 3.1 years and decreased projected lifetime costs for a hypothetical 35-year-old patient with chronic HBV infection when compared with 'standard-of-care'. Thus, interferon-α was considered the cost-effective, dominant strategy in this cohort of patients.

Dusheiko and Roberts[105] performed an economic analysis of 1000 hypothetical patients with chronic HBV infection treated with interferon-α 10MU thrice weekly for 16 weeks versus no treatment. They utilised a transitional probability model to estimate disease progression over 30 years. Costs were estimated for antiviral therapy, monitoring, symptomatic treatment of disease and liver transplantation. Their analysis also took into account indirect costs to the patients. Overall, mortality was lower in the treated group, ranging from 18 to 31 lives saved with interferon-α therapy. Fewer patients in the treated group progressed to cirrhosis or decompensated cirrhosis, requiring liver transplantation. The model estimated a discounted cost of $US1535 per QALY gained for hepatitis B treatment. The cost-benefit analysis indicated excess benefits over costs, and the authors concluded that interferon-α therapy was cost-effective in this patient population.

3.2 Lamivudine

Several investigators have studied the cost-effectiveness of lamivudine treatment for chronic HBV infection.[106-108]

Crowley et al.[107] performed a cost-utility analysis on a hypothetical population of patients with chronic HBV infection to assess the long-term cost effectiveness of lamivudine versus interferon-α therapy versus no treatment. Their hypothetical patient population was representative of patients with chronic HBV infection who would have been candidates for antiviral therapy in Australia and was modelled into either scenario A (treatment with lamivudine 100 mg/day for 52 weeks or interferon-α 10MU thrice weekly for 4 months versus no treatment based on predicted medication availability

and choice of therapy based on predicted clinical parameters), scenario B (treatment with interferon-α versus no treatment predicting situations where only interferon-α therapy is available) or scenario C (no treatment), thus modelling the natural progression of chronic HBV infection. They used a two-step modelling analysis. First, a 1-year model, based on data from three clinical trials, was used to estimate costs and outcomes of treatment with lamivudine or interferon-α versus no treatment. Then, these results were extrapolated to 70 years using a Markov model. The Markov model consisted of six health states: HBeAg seroconversion, chronic HBV infection, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma and death. The patients entered the Markov model in the health state they were in at the time of completion of the 1-year model. In the 1-year analysis, lamivudine therapy resulted in more HBeAg seroconversion compared with interferon-α therapy or no therapy. The incremental cost-effectiveness ratio associated with lamivudine was $A3341 per additional HBeAg seroconversion and $A5272 per additional case of cirrhosis avoided, which were substantially lower than the incremental cost-effectiveness ratios associated with interferon-α therapy or no therapy at all. In the long-term Markov analysis, lamivudine increased life expectancy by 3.9 years or 3.2 QALYs compared with interferon-α therapy and 4.6 years or 3.8 QALYs compared with no treatment. Lifetime risk of developing compensated cirrhosis, decompensated cirrhosis and hepatocellular carcinoma decreased 5%, 11% and 11%, respectively, with lamivudine therapy. Thus, the authors concluded that lamivudine delays the progression of chronic HBV infection, increases life expectancy, and improves quality of life for patients and is cost-effective compared with interferon-α therapy or no therapy.

Brooks et al.[106] performed an economic analysis comparing lamivudine therapy versus interferon-α given a fixed drug budget of $US558 910 (an amount assumed to treat 100 patients with interferon-α). A Markov decision-tree analysis was used to predict 1-year outcomes. Clinical data from randomised, controlled trials were programmed into the model. Outcomes measurements included HBeAg seroconversion and progression to cirrhosis. Their analysis showed that on the fixed budget, 353 patients could be treated with lamivudine with 62 predicted HBeAg seroconversions and six patients progressing to cirrhosis, compared with 100 patients treated with interferon-α with 32 predicted HBeAg seroconversions and 28 patients progressing to cirrhosis. The cost per additional HBeAg seroconversion compared with no treatment was $US12 703 for lamivudine and $US39 922 for interferon-α. In addition, assuming an average cost per hospitalisation of $US14 063 for a patient with HBV cirrhosis, the 22 fewer patients progressing to cirrhosis with lamivudine therapy compared with interferon-α therapy translates to a substantial $US309 386 hospital cost savings with the use of lamivudine. Thus, the authors concluded that from a third-party payor perspective with a fixed budget, lamivudine is a more cost-effective treatment than interferon-α in patients with chronic HBV infection.

In 2001, Crowley et al.[108] performed another analysis, utilising a two-step modelling approach, similar to their previous analysis in 2000. Whereas the previous study had utilised clinical trial data on lamivudine therapy up to 3 years duration, the present study utilised data on lamivudine therapy up to 4 years duration. They again found that the introduction of lamivudine increased the number of patients eligible for and receiving antiviral therapy; hence, scenario A (eligibility to receive lamivudine or interferon-α) doubled the HBeAg seroconversion rates compared with interferon-α alone and no therapy. The incremental cost-effectiveness ratio with lamivudine remained at $A3341 per additional HBeAg seroconversion. One-year progression to

cirrhosis was 5.1% for scenario A, 12.2% for scenario B and 12.7% for scenario C. In the long-term analysis, lamivudine therapy was predicted to increase life expectancy and reduce lifetime risk of compensated cirrhosis, decompensated cirrhosis and hepatocellular carcinoma even further than previously reported (reduced lifetime risk of 6%, 12% and 12%, respectively). Additionally, lamivudine therapy was noted to decrease lifetime costs by $A548. The authors concluded that lamivudine therapy in patients with chronic HBV infection allowed more patients to be treated, increased HBeAg seroconversion rates, delayed disease progression and further extended life expectancy when compared with interferon-α therapy.

3.3 Adefovir Dipivoxil

Recently, a comprehensive cost-effectiveness analysis comparing interferon-α, lamivudine and adefovir dipivoxil in the treatment of patients with HBeAg-positive and HBeAg-negative compensated chronic HBV infection was published.[109] In this study, Kanwal et al.[109] stratified the analysis according to HBeAg status. A Markov model was used to simulate five different treatment strategies over a lifetime horizon: (i) no pharmacological intervention ('do nothing'); (ii) interferon-α monotherapy; (iii) lamivudine monotherapy, (iv) adefovir dipivoxil monotherapy; and (v) lamivudine with crossover to adefovir dipivoxil upon development of viral resistance to lamivudine ('adefovir salvage'). Model assumptions were derived from published data in the literature including survival assumptions, antiviral resistance rates, treatment efficacy rates and natural course of HBV infection with regards to development of cirrhosis, HCC and liver transplantation. Outcomes were measured as incremental cost of QALY gained. In both HBeAg-positive and HBeAg-negative cohorts, the 'do nothing' strategy, although the least expensive, was the least effective approach. In HBeAg-negative patients, the most cost-effective strategy was interferon-α monotherapy, costing $US2280 per QALY gained. In HBeAg-positive patients, the most cost-effective strategy was the 'adefovir salvage' strategy, which dominated over all other strategies. In both cohorts, lamivudine monotherapy and adefovir dipivoxil monotherapy were much more expensive, yet less effective, and were therefore dominated by other competing strategies as less cost effective.

3.4 Entecavir

To date, there are no published studies evaluating the cost effectiveness of entecavir in chronic HBV infection.

3.5 Peginterferon-α-2a

To date, there are no published studies evaluating the cost-effectiveness of peginterferon in chronic HBV infection.

4. Conclusions

Chronic HBV infection remains a worldwide problem, afflicting hundreds of millions of people. Its economic impact on the healthcare system is substantial, both in direct and indirect costs. The vast proportion of these costs is a result of hospitalisations for the treatment of chronic hepatitis or complications of end-stage cirrhosis, including management of portal hypertension, HCC or liver transplantation. Hence, abortion of progression of chronic HBV infection to decompensated liver disease is paramount and likely to have the most long-term economic impact, as shown in pharmacoeconomic models. In this regard, effective antiviral therapy is crucial.

Our increasing understanding of the different phases of chronic HBV infection, the existence of specific mutant variants of chronic HBV, and the worldwide distribution of HBV genotypes is important to choosing effective antiviral medications to

suppress HBV replication and halt disease progression. Interferon-α held initial promise and, in a subset of eligible patients, could effect HBeAg seroconversion and potentially induce clearance of HBsAg. However, interferon-α was limited in its efficacy by significant adverse effects, preventing its use in a large proportion of patients with chronic HBV infection, and was not effective in the increasing number of patients infected with the HBeAg-negative mutant.

With the advent of lamivudine into the hepatologist's armamentarium, a new low-cost, orally administered medication with an excellent safety profile heralded a major step forward in the treatment of chronic HBV infection. Indeed, response rates were comparable, if not slightly better, than interferon-α, but without the potential harmful side effects. Hence, a greater proportion of patients with chronic HBV infection were now eligible for antiviral therapy, and earlier pharmacoeconomic modelling suggested this had a large potential impact on the cost effectiveness of treating patients with chronic HBV infection. Unfortunately, with greater widespread use of lamivudine, the emergence of Lam-R mutants developed, limiting the long-term use of this medication. Furthermore, lamivudine was not an effective treatment for the HBeAg-negative mutant HBV, which potentially requires life-long antiviral suppression owing to its high relapse rate following cessation of antiviral therapy.

Adefovir dipivoxil shares an excellent safety profile and oral administration with lamivudine. In large clinical trials, adefovir dipivoxil was comparable with lamivudine in producing viral suppression. However, it has a major advantage over lamivudine and interferon-α in its ability to effectively suppress the HBeAg-negative mutant. This advantage is likely to be a result of the more favourable resistance profile of adefovir dipivoxil compared with lamivudine, allowing more confident long-term use of this drug. More recent follow-up data with adefovir dipivoxil confirm sustained efficacy with longer duration of treatment. Finally, in addition to effectively suppressing the HBeAg-negative mutant, adefovir dipivoxil effectively suppresses the Lam-R mutant, as it is a nucleotide analogue and does not share cross resistance with lamivudine and other nucleoside analogues.

The recently approved entecavir adds a third oral drug with highly specific and potent activity against HBV. The early data have been very promising with regard to resistance, and have shown no resistance development to date in previously nucleoside-naive patients treated for 48 weeks with entecavir. However, a low incidence of entecavir resistance has emerged in patients with prior Lam-R mutations, suggesting that caution must be exercised in the use of entecavir with this cohort of patients.

Peginterferon-α-2a is the most recently approved therapy for chronic HBV and is most likely to supplant standard interferon-α as the treatment for chronic HBV infection when considering interferon. Peginterferon-α-2a therapy offers the advantages of a defined duration of therapy and no known resistance to therapy. However, administration of peginterferon-α-2a is still accompanied by significant adverse effects and a higher cost compared with the oral antiviral drugs. Nonetheless, in a subgroup of patients with low HBV viral load, moderate ALT elevations and favourable HBV genotype, peginterferon-α-2a may still be a viable option.

Cost-effectiveness analyses of treatments for chronic HBV infection have been conflicting when comparing earlier studies with more recent publications. In part, these differences may just reflect the inherent inconsistencies associated with mathematical models based on assumptions and estimates extrapolated from real-life scenarios, many of which are highly variable in and of themselves. On the other hand, the discrepancies among different studies may be related to the evolving diagnostic and treatment landscape of chronic hepatitis B itself. As

understanding of the natural course of HBV infection is changing as better diagnostic technologies are developed for measuring HBV DNA levels, for example, assumptions and estimates which are incorporated into cost-effectiveness models are changing. Similarly, as the treatment armamentarium evolves with newer, competing antiviral drugs, so will the cost figures, indications for treatment, and combinations and permutations of different antiviral drug therapies change in cost-effectiveness models.

Treatment of chronic HBV infection is rapidly evolving. Newer antiviral medications with great promise are currently in phase II and III clinical trials. In the future, combination therapy with different nucleoside and nucleotide analogues is likely to be favoured for efficacy and prevention of drug resistance.

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