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TOPIC HIGHLIGHT

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Future prospectives for the management of chronic hepatitis B

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Abstract

Chronic hepatitis B virus infection affects about 400 million people around the globe and causes approximately one million deaths a year. Since the discovery of interferon-α as a therapeutic option the treatment of hepatitis B has evolved fast and management has become increasingly complicated. The amount of viral replication reflected in the viral load (HBV-DNA) plays an important role in the development of cirrhosis and hepatocellular carcinoma. The current treatment modalities for chronic hepatitis B are immunomodulatory (interferons) and antiviral suppressants (nucleoside and nucleotide analogues) all with their own advantages and limitations. An overview of the treatment efficacy for both immunomodulatory as antiviral compounds is provided in order to provide the clinician insight into the factors influencing treatment outcome. With nucleoside or nucleotide analogues suppression of viral replication by 5-7 $\log_{10}$ is feasible, but not all patients respond to therapy. Known factors influencing treatment outcome are viral load, ALT levels and compliance. Many other factors which might influence treatment are scarcely investigated. Identifying the factors associated with response might result in stopping rules, so treatment could be adapted in an early stage to provide adequate treatment and avoid the development of resistance. The efficacy of compounds for the treatment of mutant virus and the cross-resistance is largely unknown. However, genotypic and phenotypic testing as well as small clinical trials provided some data on efficacy in this population. Discontinuation of nucleoside or nucleotide analogues frequently results in viral relapse; however, some patients have a sustained response. Data on the risk factors for relapse are necessary in order to determine when treatment can be discontinued safely. In conclusion: chronic hepatitis B has become a treatable disease; however, much research is needed to tailor therapy to an individual patient, to predict the sustainability of response and determine the best treatment for those failing treatment.

Key words: Hepatitis B virus; Cirrhosis; Treatment; Interferon; Nucleoside analogues; Nucleotide analogues; Lamivudine; Adefovir; Entecavir; Telbivudine; Tenofovir; Resistance; Genotype

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INTRODUCTION

Treatment of chronic hepatitis B remains an important clinical objective. Estimates are that 2 billion people have been infected worldwide and chronic hepatitis B currently affects about 400 million people, particularly in developing countries[1]. Chronic hepatitis B is responsible 500 000 to 1.2 million deaths annually from liver cirrhosis and hepatocellular carcinoma (HCC)[2]. It is one of the most common infectious diseases and among the world's leading causes of death. There are two strategies to decrease these numbers, prevention of new infections and treatment of those already chronically infected. Treatment options consist of immunomodulatory and viral suppressant drugs. In this review the current standard of care and the future developments in the field of chronic hepatitis B are discussed.

WHAT IS THE OPTIONAL TREATMENT

Naïve patients

The ideal treatment for hepatitis B is an effective cheap treatment, resulting in HBsAg loss and formation of anti-HBs, with finite treatment duration and little side effects. Currently none of the HBV treatments fulfill these conditions. With interferon based therapy HBsAg loss occurs in 3%-10% of the patients within one year of start of therapy and increases in sustained responders to 11%-32%[3-9]. HBsAg loss is rare (< 2% after one year of treatment) in patients treated with nucleos(t)ide analogues, which is about the rate observed in the natural history of the disease[10-16]. However, in a small cohort treated with tenofovir, HBsAg loss was observed in 14% of 35

Table 1 Baseline factors influencing likelihood of response to antiviral therapy

Treatment	Increased likelihood of response	Decreased likelihood of response
(PEG) interferon	Baseline ALT > 2 ULN[28,145,146]	Baseline ALAT < 2 ULN[28,145,146]
	Baseline HBV DNA < 10^9 c/mL[4,28]	Baseline HBV DNA > 10^9 c/mL[4,28]
	Genotype A or B	Genotype C or D
	Longer treatment duration[33-35,147]	
Nucleoside/nucleotide analogues	Baseline serum aminotransferases > 2 ULN[148, 149]	Baseline serum aminotransferases < 2[148,149]
	Baseline HBV DNA < 10^9 c/mL[148]	Baseline HBV DNA > 10^9 c/mL[148]

ULN: Upper limit of normal; c/p = copies/mL.

patients[17]. More large size trials have to be conducted to investigate the rate of HBsAg loss for the newer nucleos(t)ide analogues or their combinations. Treatment with Interferon-α or PEG-interferon-α treatment is of finite duration and response is often durable off-treatment. However, this treatment has side effects and only a minority responds. Nucleosides/nucleotides are well tolerated and most patients respond to therapy but treatment is hampered by the selection of drug resistant mutants leading to loss of efficacy and frequent relapse after discontinuation. As none of the current registered therapies for chronic HBV is ideal, none of the drugs is regarded as the standard first-line therapy for HBV. Strategies have particularly aimed at selecting host and virus characteristics either before or during therapy to increase treatment efficacy and also withdraw ineffective treatments. The argument about the poor tolerability of interferon has been weakened by the introduction of PEG-interferon-α, which only has to be administered once a week. Furthermore it is believed PEG-interferon-α is more potent than the conventional interferons; however good comparative studies have not been performed[18]. Based on treatment outcomes, the preferable treatment shifts to interferon based therapy or nucleoside/nucleotide analogue therapy for different patient groups. In Table 1 the known predictors for response are given for both interferon-α based therapies or nucleos(t)ide analogues.

Recent studies found a strong correlation between HBV DNA level and the development of liver cirrhosis and HCC. However, as none of the studies concerning natural history separately analysed the outcome in patients with prolonged normal aminotransferases the exact influence of the viral load is not known[19-21]. Interferon based therapies are generally ineffective in patients with low pre-treatment serum aminotransferase levels, and for these patients nucleoside/nucleotide treatment would be indicated. Low pre-treatment serum aminotransferases and high HBV DNA levels also decrease the likelihood of response for these agents; however, this confers to HBeAg loss/seroconversion. In theory nucleoside/nucleotide analogues are effective in lowering the viral load and thereby decreasing the risk for development of cirrhosis and HCC[22]. However, the benefit of this approach on survival is not supported by clinical trials.

For therapy of treatment naïve patients with elevated ALT levels, consensus guidelines have no preference for interferon or nucleoside/nucleotide therapy. Treatment outcomes for different therapies are provided in Table 2. Genotype proved to be an important predictor for the response to interferon-α or PEG-interferon-α therapy, especially in HBeAg positive patients. Genotype A and B show superior end of treatment responses as well as off treatment responses compared to genotypes C and D[3,4,18,23-25]. HBeAg loss occurred in 34%-36% of patients. In addition HBsAg seroconversion was observed in 13%-22% of patients with genotype A[18,26,27]. Therefore, a 48 wk course of PEG-interferon-α should be considered as first-line therapy for HBeAg positive patients with genotype A or B.

For HBeAg negative patients the distinctions are less clear. Genotype D responds less to PEG-interferon-α compared to genotypes A, B or C. Sustained ALT normalisation and a viral load < 20 000 copies/mL was observed in 27%, 44%, 52% and 16%, for genotype A, B, C and D, respectively. Sustained response occurred significantly more frequently in genotypes B and C compared to genotype D. The difference in sustained response between genotype A and D was not significant, probably due to the small number of genotype A infected patients[28]. However, only patients with genotype A, treated with PEG-interferon-α for 48 wk, had a considerable chance (18%) to develop HBsAg seroconversion[27]. The long-term follow-up is not known for PEG-interferon-α. Two years of follow-up showed a decrease in response (HBV DNA < 2.0×10^4 copies/mL) from 43% after 24 wk of follow-up to 29%[29]. However, long-term follow-up studies with conventional interferon showed high relapse rates[2,5,30]. Nucleos(t)ide analogues are effective across all genotypes in both HBeAg positive and HBeAg negative patients and have proven to be a good treatment option for chronic active hepatitis B[31,32].

Retreatment of non-responders

Treatment of non-responders to previous treatment is little studied and most studies are of small size. Studies show that retreatment with conventional interferon can induce HBV DNA loss and HBeAg seroconversion; however the overall results are not conclusive (Table 3). Most of the results are difficult to interpret as the initial schedule of interferon therapy differs as well as the time to retreatment. The retreatment schedules often differ from the initial schedule, and treatment duration is often prolonged influencing treatment outcome positively[33-35]. The real benefit of interferon retreatment, especially with pegylated interferon is unclear. Nucleos(t)ide analogues appear to be effective in interferon failures, although

Table 2 Treatment outcomes after 1 year of treatment for different antiviral drugs for the management of chronic hepatitis B

	Author; Journal; Year	HBeAg loss (%)	HBeAg seroconversion (%)	HBsAg loss (%)	Decline viral load (log_{10} copies/mL)	HBV DNA negativity (%)	ALT normalisation (%)	Histological improvement (%)	Resistance (%)
HBeAg pos									
PEG-IFN-α 2a	Cooksley; J. Viral Hepatitis; 2003[18]	35	33			39[9]	35		
PEG-IFN-α 2a	Lau: NEJM; 2005[4]	34	32	3[12]	2.4	14[4]	41	49	
PEG-IFN-α 2b	Janssen; Lancet; 2005[3]	36	29	7	2.3	7[4]	32	53[10]	
Lamivudine	Chang; NEJM; 2006[13]	20	18	1	5.4	36[2]	60	62	13
Lamivudine	Alexander; BMC Gastroenter; 2005[150]	42	28				56		10
Lamivudine	Chan; Ann Intern Med; 2005[151]	28	28	0	2.74	10[1]	78	59[11]	40
Lamivudine	Yao; Hepatobil Pancr Dis Int; 2004[152]	10	8			36	72		12
Lamivudine	Jonas; NEJM; 2002[153]	26		2		61[6]	55		19
Lamivudine	Mazur; Med Sci Monit; 2002[154]	49	44	5		37[8]	56		
Lamivudine	Barbaro; J Hepatol: 2001[155]		19	0			23	27[10]	16
Lamivudine	Dienstag; NEJM 1999[47]	32	17	2		44[7]	41	52[10]	32
Lamivudine	Gane; J Hepatol; 2006[63]	23	21		5.5	40[2]	75	56	8
Adefovir	Marcelin; NEJM; 2003[16]	24	12		3.6	21[4]	48	53	0
Adefovir	Lee; Hepatology; 2006[102]	14			4.0	29[5]	79		0
Adefovir[15]	Zheng; Hepatology; 2006[124]	13	8	0	4.5	28[2]	79		0
Adefovir	Bzowej; Hepatology; 2006[65]	20	18		5.7	39[2]	81		2
Entecavir	Chang; NEJM; 2006[13]	22	21	2	6.9	67[2]	68	72	0
Telbivudine	Gane; J Hepatol; 2006[63]	26	22		6.5	60[2]	77	65	3
Telbivudine	Bzowej; Hepatology; 2006[65]	31	27		6.6	58[2]	77		4
HBeAg neg									
PEG-IFN-α 2a	Marcellin; NEJM; 2004[5]			4	2.3	19[4]	59	59	
Lamivudine	Marcellin; NEJM; 2004[5]			0	4.2	73[4]	73	58[14]	41
Lamivudine	Lai; NEJM; 2006[15]			0	4.5	72[2]	71	61	6
Lamivudine	Lai; NEJM; 1999		16	0			72	56[10]	14
Adefovir	Hadzyannis; NEJM; 2003[14]				3.9	51[4]	72	64	0
Entecavir	Lai; NEJM; 2006[15]			0	5.0	90[2]	78	70	0
Mixed									
Lamivudine	Ooga; J Gastroenterology; 2004[156]					78[5]	78		16
Lamivudine	Suzuki; Intervirology; 2003[108]	42	28	0		88[6]	86		
Lamivudine	Yao; J Hepatology; 2006[64]		18		4.3	43[2]	78		
Entecavir	Yao; J Hepatology; 2006[64]		15		5.9	76[2]	90		

Although conventional interferon-α is widely used for the treatment of HBV it is not listed as this treatment will be replaced by PEG-interferon-α in the near future. Efficacy measures for PEG-interferon presented are off-treatment responses after 24 wk of follow-up. Studies are organised by HBeAg status and the mixed studies included both HBeAg positive as HBeAg negative patients. [1]LLD 200 copies/mL; [2]LLD 300 copies/mL; [3]LLD 366 copies/mL; [4]400 copies/mL; [5]5.0 × 10^3 copies/mL; [6]7.0 × 10^5 copies/mL; [7]1.0 × 10^6 copies/mL; [8]1.4 × 10^6 copies/mL; [9]5.0 × 10^6 copies/mL; [10]only improvement of ⩾ 2 points in necroinflammation according to Ishak, [11]only improvement of ⩾ 2 points in necroinflammation according to Knodell, [12]HBsAg seroconversion, [13]treatment duration 24 wk, [14]After 24 wk of follow-up, Lamivudine study performed in children, [15]Includes some lamivudine resistant patients.

Table 3 Response to interferon-α or PEG-interferon-α after having failed a prior course of interferon or response to interferon-α or PEG-interferon-α after having failed a prior course of lamivudine

Author; Journal; Year	Treatment regimen	Pretreatment HBeAg status (*n*)	HBeAg loss	HBeAg seroconversion (%)	HBV DNA loss (%)	ALT normalisation (%)
Janssen; J Hepatology; 1993[157]	IFN 1.5 MU daily for 4 wk followed by 3 MU daily for 8 wk and then 5 MU daily for 4 wk	Positive (18)		11	17	
Carreno; Hepatology; 1999[158]	IFN 9 MU thrice weekly for 24 wk	Positive (27)	41	22	44[5]	22
Munoz; J Hepatology; 2002[159]	IFN 6 MU 5 times weekly for 24 wk	Positive (11)		18	18[1]	18
Munoz; J Hepatology; 2002[159]	IFN 6 MU 5 times weekly for 24 wk	Negative (18)			22[1]	44
Ballauff; Eur J Pediatr;[160]	IFN 5-9 MU/m^2 thrice weekly for 16-24 wk	Positive (15)		33	33[4]	
Teuber; Z Gastroenterol; 1995[161]		Positive (27)		30	59	
Flink; Hepatology; 2004[162]	PEG-IFN-α 2b 100 μg/wk for 32 wk followed by 50 μg/wk for 20 wk	Positive (18)	28		0[2]	22
Lau; J Hepatology; 2005[163]	PEG-IFN-α 2a for 48 wk	Positive (30)		43		
Prev lamivudine						
Flink; Hepatology; 2004[162]	PEG-IFN-α 2b 100 μg/wk for 32 wk followed by 50 μg/wk for 20 wk	Positive (8)	50		0[2]	47
Lau; J Hepatology; 2005[163]	PEG-IFN-α 2a 180 μg/wk for 48 wk	Positive (31)		32		
Marcellin; J Hepatology; 2006[164]	PEG-IFN-α 2a 90-180 μg/wk for median 48 wk	Positive (71)	37[6]	32[6]	47[3,6]	51
Marcellin; J Hepatology; 2006[164]	PEG-IFN-α 2a 90-180 μg/wk for median 48 wk	Negative (36)			67[3,6]	52

[1]LLD 200 copies/mL; [2]LLD 400 copies/mL; [3]LLD 1.0 × 10^4 copies/mL; [4]LLD 4.25 × 10^5 copies/mL; [5]LLD 4.81 × 10^5 copies/mL; [6]on-treatment responses.

efficacy may be different and data are limited[36]. A clinical trial using adefovir dipivoxil included 123 HBeAg positive and 48 HBeAg negative patients failing prior interferon therapy. HBeAg seroconversion rates were similar for interferon naïve and experienced patients[37]. The efficacy of the use of interferon for lamivudine failures is unclear (Tables 3 and 4). It appears interferon is effective in patients who received lamivudine, but did not develop resistance. Interferon-α therapy probably has a low efficacy in lamivudine resistant patients, but the numbers published are small[38,39].

Cirrhotic patients

The life expectancy of patients with cirrhosis, if untreated, is greatly diminished with a 5-year survival of 84% for compensated and 14%-35% for decompensated cirrhosis[40-42]. Interferon has to be used with caution in cirrhotic patients and its use is limited to Child A cirrhosis. Interferon may be effective in compensated cirrhotics in which treatment outcomes do not differ from those without cirrhosis[6,33,35,43,44]. Adverse events, dose reductions and early discontinuation occur more frequently in cirrhotic patients[45,46]. Nucleos(t)ide analogues appear to be as effective in cirrhotics as in those without cirrhosis regardless of HBeAg status[47-49]. Lamivudine treatment in patients with advanced fibrosis or compensated cirrhosis reduced the progression of liver disease. Loss of efficacy due to resistance resulted in an increase of disease progression[50]. Entecavir treatment resulted in undetectable HBV DNA loss (LLD 300 copies/mL) in > 90%, ALT normalisation in over 60% and histological improvement in > 70% of patients with compensated cirrhosis[51].

Decompensated cirrhotic patients should be treated with nucleoside analogues as interferon-α is contra-indicated[52,53]. The timing of the initiation of therapy is essential. If the bilirubin level has risen above 3.5 mg/dL the 3 mo survival is poor and probably cannot be influenced by nucleos(t)ide analogue therapy. Several studies have confirmed the efficacy of lamivudine therapy in patients with HBV related decompensated cirrhosis. Therapy resulted in a significant improvement in virological, biochemical and markers of disease status[54-58].

Treatment of lamivudine refractory patients, who waited for liver transplantation, with adefovir for 48 wk resulted in a 4.1 $\log_{10}$ copy decline in viral load. Liver functions improved significantly and the Child Pugh-Turcotte score (CPT) improved or remained stable in 92% of the patients[59]. Adefovir therapy initiated in pre-transplant patients resulted in undetectable serum HBV DNA in 76% and normal ALT in 84% of the patients after 96 wk of treatment. Markers of synthetic liver function improved in most patients, the Child-Pugh scores improved, or remained the same and survival was over 80% after two years[60]. Another study in lamivudine refractory patients with decompensated cirrhosis showed a HBV DNA response ($\leqslant 10^5$ copies/mL or $\geqslant$ 2 log decrease from baseline) in 92%, over half of the patients had ALT normalisation and there was improvement of liver synthesis function and Child-Pugh scores after one year of treatment[61]. Although it is possible to inhibit viral replication and prevent clinical decompensation, the occurrence of HCC is not prevented. After 5 years of continuous lamivudine therapy or add-on therapy with adefovir in lamivudine resistant cases in HBeAg negative cirrhotic patients, 16% of patients had died, or had a liver transplantation. However, 24% was diagnosed with HCC[62]. The moment of initiation of nucleos(t)ide analogues to prevent the occurrence of HCC has yet to be determined. In cirrhotic patients there seems to be no benefit, but a study including patients with advanced liver fibrosis or cirrhosis showed a reduction in HCC in lamivudine treated patients compared to placebo. Patients with lower fibrosis and Child-Pugh scores were less prone to disease progression[50]. The data suggest nucleos(t)ide analogue therapy has to be initiated before the development of cirrhosis to prevent HCC and has to be continued indefinitely[50,62].

TREATMENT WITH NUCLEOSIDE/ NUCLEOTIDE ANALOGUES

Four oral nucleoside or nucleotide analogues, lamivudine, adefovir, entecavir and telbivudine, are currently marketed and approved as a first line of therapy for the treatment of chronic hepatitis B. All therapies result in reduction of viral load, ALT levels and improvement of liver histology (Table 2). It is difficult to point out one compound which should be the first nucleoside or nucleotide used for the treatment of chronic hepatitis B. At least two major points at least have to be taken into account: (1) efficacy of the treatment on the short and long term, including the development of resistance and (2) the costs. Comparing the efficacy of treatment is difficult; however, some comparative studies have been performed. Both entecavir and telbivudine proved superior efficacy over lamivudine after 1 year of treatment[13,15,63,64]. Direct comparison of telbivudine or adefovir for 52 wk showed superior efficacy on viral and biochemical parameters for telbivudine, but resistance was not assessed[65]. Adefovir has not directly been compared to lamivudine. Direct comparison of entecavir and adefovir for a duration of 24 wk showed a decline of HBV DNA of 6.97 $\log_{10}$ copies/mL for entecavir and 4.84 $\log_{10}$ copies/mL for adefovir. PCR undetectability (HBV < 300 copies/mL) was reached in 45% of entecavir treated patients *vs* 13% of those receiving adefovir[66]. Tenofovir looks a promising new drug, but is only used in small series in lamivudine or adefovir treatment failures. The long term outcomes are only known for lamivudine and adefovir. Another problem with interpretation and positioning of the outcomes of clinical studies is the lack of standardisation of outcome measures.

The development of resistance is the most important factor for loss of efficacy. Lamivudine has a high rate of resistance of 18%-27% after 1 year and this increases over time, being 44% at year 2, 60% at year 3, and after 4 years of treatment almost 70% has developed resistance[5,67-73]. Adefovir showed no resistance after 1 year, but rates increased to 1%-3%, 11%, 18% and 28% at year 2, 3, 4 and 5[14,16,74]. Entecavir showed no resistance up to 2 years of treatment; however, complete non-responders did not receive treatment in year 2[75]. Telbivudine had a resistance

Table 4 Treatment outcomes after 1 year of treatment for different antiviral drugs for the management of lamivudine resistant chronic hepatitis B for both HBeAg positive and HBeAg negative patients

	n	Author; Journal; Yr	HBeAg loss (%)	HBeAg serocon-version (%)	HBsAg loss (%)	Decline viral load (log_{10} copies/mL)	HBV DNA negativity (%)	ALT normalisation (%)	Histological improvement (%)	Resistance (%)
HBeAg pos										
PEG-IFN-α 2b	16	Leemans; J Hepatology; 2006[38]	13	13	6	0.6	6[4]	19		
Adefovir	45	Buti; Hepatology; 2004[165]		13	0		33[7]	51		
Adefovir	19	Peters; Gastroenterology; 2004[118]	16	11		4.0	26[5]	47		0
HBeAg neg										
PEG-IFN-α 2b	20	Vassiliadis; WJG; 2006[39]					5[4]	10		
Adefovir	75	Buti; Hepatology; 2004[165]			0		51[7]	63		
Adefovir	20	Manilakopoulos; Hepatology; 2005[119]				3.3		72		5
Adefovir + lamivudine	44	Manilakopoulos; Hepatol; 2005[119]				3.3		87		0
Adefovir	26	Koskinas; J Hepatology; 2005[166]				2.5		92		4
Adefovir + lamivudine	74	Lampertico; Hepatology; 2005[167]					78[6]	82		0
Adefovir + lamivudine	23	Koskinas; J Hepatology; 2006[166]				2.8		87		0
Adefovir + lamivudine	49	Vassiliadis; AP&T; 2005[168]			0	6.5	57[4]	75		
Mixed										
Adefovir	18	van Bömmel; Hepatology; 2004[17]	19		0	2.8	44[4]			
Adefovir + lamivudine	20	Peters; Gastroenterology; 2004[118]	17	6		3.6	35[5]	53		0
Adefovir	57	Lee; Hepatology; 2006[102]	20			2.4	19[3]	60		18
Adefovir + lamivudine	46	Perrillo; Gastroenterology; 2004[61]	15	8	0	4.6	20[1]	30		
Adefovir ± lamivudine[11]	126	Schiff; Hepatology; 2003[59]				4.1	81[4]	76		0
Adefovir + lamivudine	34	Moriconi; J Hepatology; 2006[169]					68[1]			
Adefovir ± lamivudine	65	Hann; J Hepatology; 2006[132]	7[10]			2.4	21[5]			
Entecavir	42	Chang; Gastroenterology; 2005[170]	11	4		5.6	26[4]	68		0
Entecavir	141	Sherman; Gastroenterology; 2006[129]	10	11		5.1	27[2]	61	55	7
Entecavir	42	Karino; J Hepatology; 2006[171]		15		3.8	60[4]	78	60	0
Entecavir	116	Yao; J Hepatology; 2006[172]	8	6		5.8	27[2]	85		
Tenofovir ± lamivudine[9]	35	van Bömmel; Hepatology; 2004[17]				5.5	100[4]			0
Tenofovir ± lamivudine	44	Hann; J Hepatology; 2006[132]	4[10]			5.0	86[5]			
Tenofovir + lamivudine[9]	11	Van der Eijk; J Viral Hepatitis; 2005[173]	10	0	0	5.0		91		
Tenofovir[9]	10	Dore; J Infect Dis; 2004[174]	20	10		4.9		25		
Tenofovir[9]	12	Núñez; Aids; 2002[175]		11	8	3.8	58[1]			
Tenofovir[9]	20	Nelson; Aids; 2003[176]		25		4.0				
Tenofovir[9]	12	Benhamou; NEJM; 2003[177]	0	0	0	3.8				

Efficacy measures presented are off-treatment responses for PEG-interferon and on-treatment responses for nucleos(t)ide analogues. [1]LLD 200 copies/mL; [2]LLD 300 copies/mL; [3]LLD 366 copies/mL; [4]LLD 400 copies/mL; [5]LLD 1.0×10^3 copies/mL; [6]LLD 2.0×10^3 copies/mL ; [7]LLD 1.0×10^5 copies/mL; [8]results after 24 wk of treatment; [9]including HIV/HBV co-infected patients ± some patients with, some patients without combination therapy; [10]after 24 mo of treatment; [11]patients with decompensated cirrhosis.

rate of 2%-4% after 1 year of treatment[63,65].

With long-term lamivudine treatment HBeAg seroconversion increases to 27%, 40%, 47% and 50% at year 2, 3, 4 and 5, respectively, despite the development of resistance[67,71,73,76]. Prolonged therapy with adefovir in HBeAg positive subjects resulted in viral load below 10^3 copies/mL in 28% at year 1, 45% and 56% at year 2 and 3. ALT levels became normal in 48%, 71% and 81% after 1, 2 and 3 years of treatment. Rates of HBeAg-loss increased to 42% and 52% and HBeAg seroconversion rates increased to 29% and 43% at year 2 and 3[77]. A study with continued treatment up to 2 years showed an increase in viral reduction from -4.5 to -5.0 $\log_{10}$ copies/mL, increased in PCR-negativity (lower limit of detection 300 copies/mL) from 28% to 42%, but the percentage of ALT normalisation remained unchanged (79% to 78%). The percentage HBeAg-loss increased from 13% to 19% and the percentage of patients with HBeAg seroconversion increased to 15%[78]. In HBeAg negative subjects prolonged adefovir therapy of 2 years, showed little additional decline in viral load, but consolidated the response to adefovir as 71%-75% of the patients had a viral load below 10^3 copies/mL and ALT normalisation in 73%-79%. Long term treatment up to 5 years resulted in a viral load below 10^3 copies/ml in 78%-79% at year 3, 65%-68% at year 4 and 67% after 5 years of continuous treatment. ALT levels were normal in 69%-78% at 3 years, 70%-75% at 4 years and 69% after 5 years[74]. Also entecavir showed a continuous viral decline in patients with detectable HBV DNA beyond wk 48 and HBeAg seroconversion rates increased[79,80]. Another aspect which is little studied is the sustainability of response after discontinuation of therapy. In HBeAg positive subjects who seroconverted during therapy, response is durable in over half of the subjects[13,81-84]. In HBeAg positive patients treated with lamivudine who discontinued after achieving a complete response (HBeAg loss, undetectable HBV DNA and normal ALT) had a sustained response of 78%, 72%, 70%, 67% and 64% after 1, 2, 3, 4 and 5 years of follow-up, respectively[85]. In HBeAg positive subjects with HBeAg seroconversion during adefovir therapy the response was sustained in 91%[84]. In entecavir treated HBeAg positive subjects for 48 wk the sustained response (HBeAg loss and HBV DNA $< 7.0 \times 10^5$ copies/mL) was 82% after a 24 wk follow-up[86]. The durability can be increased by continuing treatment for several months after HBeAg seroconversion. Therefore, it is recommended to continue treatment for at least 3-4 mo[82,83]. As many clinical trials had a predetermined endpoint, sustainability could be a bit higher if treatment was continued for a longer period in those patients who underwent HBeAg seroconversion within 3 mo before discontinuation. In HBeAg negative subjects the durability of response is often poor. Patients treated for two years with lamivudine who had undetectable HBV DNA levels (LLD 200 copies/mL) discontinued treatment. After 12 mo of follow-up the virological relapse rate was 50%[87]. The viral load at discontinuation and duration of treatment do not accurately predict sustainability of response in HBeAg negative patients.

Other parameters such as intrahepatic total HBV DNA and intrahepatic cccDNA and HBcore expression and the level of hepatitis B virus core related antigen appear to be superior in prediction of sustained response compared to viral load at the end of therapy. The studies were, however, small and the results have not been confirmed by others[88,89].

MANAGEMENT OF TREATMENT FAILURES TO NUCLEOS(T)IDE ANALOGUES

A distinction can be made for patients failing therapy: due to resistance or other reasons. Many patients do not achieve complete suppression of HBV DNA during treatment. Several factors may contribute such as non-compliance, inefficient conversion from the prodrug to its active metabolite, inadequate phosphorylation within the hepatocytes or underdosing of the drug. Some patients failing to respond initially to treatment may already harbour a resistant mutant prior to the start of therapy[90,91]. Underdosing is particularly an issue with adefovir treatment as the 10 mg dose was chosen for safety reasons. The 30 mg dose was more effective, but also more nephrotoxic[16].

Little is known why some patients have suboptimal viral suppression. The known baseline predictors for response provide information on the likelihood of response, but outcome cannot be predicted (Table 1). A high baseline viral load is probably one of the reasons why more HBeAg-positive patients have a suboptimal response compared to HBeAg-negative patients[13-16]. Recently, genotypic dependent polymorphisms have been described associated with primary treatment failure and more might be detected[91,92]. As viral factors, as well as host factors play an import role in response, it is difficult to assess the optimal treatment for sub-optimal responders. Presuming study randomisation led to an equal distribution of both viral and host factors, it is to be expected that more potent drugs are able to suppress viral replication in subjects with suboptimal suppression. Entecavir and telbivudine proved their superior potency over lamivudine in a head to head comparison and for telbivudine this observation also has been made in comparison with adefovir[13,15,63-65]. In adefovir treatment failures the more potent drug tenofovir showed good viral suppression[93]. Patients responding to tenofovir and switched to adefovir showed viral relapse, while no mutants could be detected[94]. Another strategy could be adding a second drug to the failing compound. *In vitro* testing demonstrated that combining adefovir with an L-nucleoside (lamivudine, telbivudine, emtricitabine) exerted additive antiviral effects[95]. Clinically the combination of adefovir and emtricitabine resulted in stronger viral suppression[96]. In patients failing adefovir switching therapy to tenofovir and either emtricitabine or lamivudine resulted in decrease in viral load in most patients[97].

PREVENTION OF RESISTANCE

For nucleoside/nucleotide analogue treatment, a number of risk factors for resistance have been identified. For lamivudine this includes: prior course of lamivudine,

duration of lamivudine therapy, high body weight and body mass index, male sex and high baseline HBV DNA, insufficient HBV DNA suppression at month three, and elevated ALT levels during treatment[98-100]. For adefovir the following risk factors for resistance have been reported: lamivudine resistance at start of treatment, high baseline viral load, < 1 mo continuation of lamivudine after the start of adefovir therapy in case of lamivudine resistance, insufficient HBV DNA suppression during treatment[101-103]. For entecavir, lamivudine resistance and suboptimal suppression of HBV DNA on treatment were found as risk factors[75]. A key factor in the development of resistance is the persistence of viral replication. Several studies found a relation between ongoing viral replication and the development of resistance. Patients with a serum HBV DNA > 10^3 copies/mL after 6 mo of lamivudine treatment had a 63% chance for developing resistance[100]. Another study in 24 patients, found that none of the subjects with excellent viral suppression (nadir HBV DNA < 50 copies/mL), two out of 5 patients with a nadir viral load between 50-300 copies/mL and all 11 patients with a nadir viral load > 300 copies/mL developed resistance[99]. For adefovir, a load of over 10^5 copies/mL after 48 wk of treatment is a risk factor for resistance[103]. In a study in which patients were treated with either telbivudine, or lamivudine, a viral load > 10^3 copies/mL after 24 wk of treatment was associated with an increased risk for resistance.

The role of genotypes is controversial as some have reported influence of the genotype on the development of resistance, while others do not find this association[101,100-111]. Genotype might influence the mutational pattern. When genotype A and D in lamivudine resistant patients were compared, the rate of M204V mutants and rates of mutations at position rtL180 was higher in genotype A. The rate of M204I mutations was higher in genotype D. The median time of shift from M204I to M204V was shorter in genotype A. Additional resistance associated mutations were only detected in patients infected with genotype D[112]. In genotype C patients HBV DNA was significantly higher compared to genotype B after the development of YMDD mutants[104]. Studies are often hampered by their small size. For compounds with a low rate of resistance it is hard to determine the role of the genotype as large numbers have to be treated often for a prolonged period.

The current strategy of continuous monotherapy is insufficient to completely suppress viral replication in a large number of patients. *In vitro* testing has to be done in order to find promising combinations of drugs. These combinations of drugs then have be to investigated in long-term large scale trials with clinical response and resistance as outcome measures[95].

It is important to detect resistance as early as possible during treatment with nucleoside or nucleotide analogues. In case of virological breakthrough, which is generally agreed to be a 1 $\log_{10}$ increase in viral load in either copies/ml or IU/L after an initial response in compliant patients[113-115]. Sensitive quantitative HBV DNA assays are therefore advised for monitoring as a viral rebound can be detected earlier. Virological breakthrough mostly precedes biochemical breakthrough and the time lapse may vary from weeks to months[116]. Genotypic testing provides information on the type of mutation which arises during treatment and if there might be decreased drug sensitivity. Knowledge of the specific mutation will be increasingly important in the future as different mutations may have a distinct influence on treatment efficacy of other compounds. Newly detected mutations should be investigated by phenotypic assays to determine their replication fitness and susceptibility to other compounds[117].

MANAGEMENT OF RESISTANCE

Lamivudine resistance

Adefovir has proven to be effective for lamivudine resistant mutants. Adefovir monotherapy is able to suppress viral load by 2.4-4.0 $\log_{10}$ copies/mL[102,118]. The data of adefovir and lamivudine combination therapy by adding adefovir to ongoing lamivudine is controversial. A randomised study found no difference in viral decline[118]. Another study did not find a difference in viral suppression after one year of treatment, but at month 18 adefovir and lamivudine showed a stronger viral decline (4.3 $\log_{10}$ copies/mL) *vs* adefovir monotherapy (3.4 $\log_{10}$ copies/mL)[119]. A study comparing combination therapy to monotherapy in lamivudine resistant patients showed significantly higher rates of PCR-negativity (81% *vs* 40%) in patients with a baseline viral load $\geqslant$ 5 $\log_{10}$ copies/mL[120].

Although adefovir is effective for the treatment of lamivudine refractory patients there seems to be some degree of cross-resistance as *in vitro* testing shows a 2.8-16 fold increase in IC_{50} values for adefovir for lamivudine resistant strains[121-123]. Clinically mutations also associated with lamivudine resistance appear to influence treatment outcomes. Viral decline and ALT normalisation might be less in lamivudine resistant patients compared to treatment naïve patients, but other studies do no report such difference[102,124,125]. The rate of resistance is increased in patients with lamivudine resistance switched to adefovir monotherapy compared to the large phase III trials and to patients switched to adefovir and lamivudine combination therapy[14,16,101,102,120]. Considering the mounting evidence of more potent antiviral effect and a lower rate of resistance adding adefovir to the ongoing lamivudine therapy is to be preferred above switching to adefovir monotherapy. If chosen to switch to adefovir monotherapy lamivudine has to be continued for at least 2-3 mo as this overlap may prevent the emergence of adefovir resistance[101,126].

Lamivudine resistance shows some cross-resistance with entecavir in cell culture, but lamivudine resistant strains remain sensitive to entecavir[127,128]. Although very effective, treatment outcomes with 1 mg entecavir in lamivudine were less compared to 0.5 mg entecavir in treatment naïve patients as viral decline (6.9 $\log_{10}$ copies/mL *vs* 5.1 $\log_{10}$ copies/mL) and rates of PCR-negativity (67% *vs* 19%) were lower after 48 wk of treatment (Table 4)[13,129]. Entecavir has a high barrier to resistance as multiple mutations are necessary for the virus to be resistant. Lamivudine refractory patients already harbour some of these mutations and entecavir resistance occurs,

therefore, more frequently in lamivudine resistant patients. After 1 year 1.4% of patients became resistant increasing up to 9% after two years and 15%-19% after 3 years of treatment[75,129,130].

Tenofovir disoproxil fumarate possesses potent activity against lamivudine resistant hepatitis B (Table 4)[17,93,131,132]. Lamivudine resistant mutants lead to a slight 1.8-5.7 fold increase in IC_{50} values. The known mutants however, remain sensitive to tenofovir and the mutation pattern of tenofovir has no overlap with the mutational pattern of lamivudine[121,123,133]. Most studies add tenofovir to lamivudine, though tenofovir mono therapy seems to be equally effective[134]. Tenofovir is thought to be a more potent viral suppressing agent for lamivudine resistant HBV compared to adefovir, but its efficacy is only investigated in relatively small groups of patients. Many of them including HIV-HBV co-infected patients[17,132]. Being a very promising drug, more studies have to be conducted to determine the exact role or the combination with other compounds for the treatment of lamivudine resistant hepatitis B.

Adefovir resistance

Adefovir resistant strains are susceptible to lamivudine and lamivudine can thus be used for rescue therapy[135]. Indeed clinically lamivudine is able to reduce the viral load in adefovir resistant patients[136,137]. The effect of adefovir associated mutations on long-term treatment is unknown. It is likely that lamivudine resistant strains severely limit the use of lamivudine. *In vitro* a strain conferring resistance to both adefovir and lamivudine is viable and has reduced sensitivity to all common drugs used for hepatitis B, although tenofovir and entecavir are likely to be able to suppress HBV DNA[135]. Adefovir resistant strains are susceptible to entecavir and tenofovir *in vitro*[135,138]. In very small series tenofovir and entecavir proved effective against adefovir resistant HBV[101,139].

Entecavir resistance

Entecavir resistance is highly cross-resistant with lamivudine as entecavir resistance requires lamivudine resistance[127]. This mutant strain is sensitive *in vitro* to adefovir and clinical treatment with adefovir resulted in decline of the viral load[127,140].

Future directions for the management of resistance

The development of resistance is the largest limiting factor for long-term treatment with nucleoside or nucleotide analogues and should therefore be studied in detail. Lamivudine as well as many other L-nucleosides have high rates of resistance caused by a single mutation. Due to the high resistance rate and being the only oral drug available for a long time it gave the opportunity to study the mechanisms and outcomes of resistance. The large number of patients treated with lamivudine with subsequent development of resistance made it possible to study the effect of salvage therapy. Entecavir and adefovir proved their efficacy in large populations. But despite all these opportunities we still do not know the exact incidence of adefovir resistance in lamivudine resistant patients. Although the balance tips to lamivudine and adefovir combination therapy over adefovir monotherapy, the definite answers have not been provided, especially the question whether monotherapy comes with higher rates of resistance. Tenofovir looks very promising, although studies are small and little is known on the effect of tenofovir monotherapy on lamivudine resistant strains. Very little data is available on the occurrence and management of adefovir and entecavir as well as newer drugs. Studying resistance for compounds with low rates is difficult as large numbers have to be treated. Large scale initiatives are necessary to study the effectiveness and resistance. Insight in the mutational patterns is very important as each pattern has its own influence on replication fitness and cross-resistance. *In vitro* studies and molecular modelling have to provide these answers to design optimal treatment regimens. This approach is needed as many drugs have been developed and it is not feasible to test all drugs or combinations for all mutational patterns.

CONCLUSION

The knowledge and therapeutic options have come a long way since the discovery of the hepatitis B virus. Today chronic hepatitis B virus infection is a treatable disease. However, much remains unknown and treatment options are far from perfect. The natural history is only partially understood and only recently the importance of viral load has been revealed[19-21]. Further studies have to identify the factors involved in progression of disease in order to be able to identify those patients in need of treatment. Treatment options are diverse and have limitations in tolerability and efficacy. More data are needed to be able to predict treatment outcome in patients. This is especially important for treatment with interferon, which is costly and is associated with considerable side effects and an overall success rate between 30%-40%. However, this treatment has proven to be able to inactivate the disease for long periods in responders, which might result in HBsAg-seroconversion. Research to identify those patients likely to respond before start of therapy or within a few weeks after start of treatment is urgently needed. Nucleoside or nucleotide analogue therapy is the alternative for interferon based treatments and the response rates on treatment are higher compared to interferon. However, relapse is frequent after discontinuation, while identifying those relapsing is not possible. This has resulted in long-term treatment, although it is known that response can be sustained off-treatment. By identifying the factors responsible for sustained response it might be possible to accurately predict sustainability. In theory this could result in nucleos(t)ide analogue therapy of limited duration. This is especially important in young adults who often have a desire for pregnancy, whilst the antiviral drugs have not been investigated on safety for the unborn child or long term in patients themselves.

Data on treatment efficacy in treatment experienced patients is limited. Therefore, large cohorts of patients have to be studied. Especially the rate of resistance and the mutational patterns are hard to assess. For some therapies resistance rates are low or mutational patterns are diverse.

Genotypic and phenotypic testing and molecular modelling are helpful to determine the level of cross-resistance with other compounds. Promising rescue therapies should be studied clinically in order to determine their efficacy. The data on resistance (mutational patterns, replication fitness, molecular modelling and cross resistance) is scattered, and therefore, it is almost impossible to look up the implications of a specific mutational pattern. A large central database combining all the data on resistance could provide this information and would be of great value for everyone interpreting mutational patterns. This database could also provide clinicians advice on treatment for an individual resistant patient. More specific knowledge on resistance calls for the development of new techniques that are sensitive, able to detect new variants, able to determine if multiple variants are located on the same genome, easy to perform and interpret, cheap and suitable for mass screening.

As none of the current treatments for chronic hepatitis B is optimal, prevention of infection should be one of the cornerstones of management of chronic hepatitis B. Safe and well tolerated vaccines for hepatitis B have been developed and their effectiveness have been proved. There have been some concerns about the luxation of autoimmune phenomena[141]. Three WHO large scale evaluations revealed no increased risk for the development of autoimmune diseases[142-144].

In conclusion: The management of chronic hepatitis B has evolved fast and currently hepatitis B is a treatable disease. More research on the factors involved in response to treatment or treatment failure is needed to tailor treatment to the individual patient. Much attention should be paid to universal worldwide vaccination as this may significantly change the burden of disease.

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