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Therapies for Chronic Hepatitis B: Review of Indications, Outcomes and New Tools for Tailoring Treatments to Patients

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Abstract

Chronic Hepatitis B is a major cause worldwide of liver cirrhosis, hepatocellular carcinoma and liver related mortality. The ultimate goals of treatment are to reduce the risk of these complications and the endpoints used in clinical practice are viral suppression, ALT normalisation and histological regression of fibrosis as well as HBeAg seroconversion in patients who are HBeAg positive. The indications for treatment differ slightly in different regions however may still be conceptualised in terms of the phase of chronic hepatitis B Treatment options include a finite course of Peg IFN which has immunomodulatory as well as antiviral effects although its use may be limited by troublesome side effects and low efficacy in some patients. Recent advances in the use of quantitative HBsAg and HBeAg levels during Peg IFN treatment has provided some predictors of response and therefore the ability to individualise treatment courses to a degree, avoiding unnecessary prolongation of treatment where it is likely to be futile. The oral nucleoside/nucleotide analogues now available have high potency and very low rates of resistance however must be continued indefinitely in HBeAg negative patients and most HBeAg positive patients. Lifelong treatment raises issues of side effects such as renal and bone disease, compliance, and management during pregnancy. Research aimed at novel targets in the HBV life cycle or host immune response is ongoing. The ultimate goal of therapies for CHB remains HBsAg clearance which at present still occurs only in a minority of cases.

Keywords: Chronic Hepatitis B; HBeAg; liver cirrhosis; HBV infection

Management of HBV Infection

Goals of treatment

Chronic Hepatitis B remains a major global problem with approximately 240 million people chronically infected and an estimated 600,000 people dying each year from the disease [1]. Reduction of the complications of chronic HBV infection, namely cirrhosis, decompensated liver disease, hepatocellular carcinoma and liver related death are the main goals of treatment of HBV. Sustained viral suppression is a necessary step in achieving reduction in the risks of complications in CHB even though a cure of the disease is currently not possible due to the persistence of cccDNA in the nucleus of infected liver cells and integration of the viral genome into that of the host. Important levels of CHB treatment response include: biochemical, defined as ALT normalisation; virological, HBV DNA undetectability histological, regression of liver fibrosis; serological response, HBeAg seroconversion in HBeAg positive patients; and ultimately HBsAg clearance with development of anti-HBs. There are 2 major categories of therapeutic agents available; immunodulatory agents ie Interferon and anti-viral agents which include a number of oral nucleos(t)ide analogues.

Indications for treatment

The indications for and timing of therapy depend on a number of clinical features, including the phase of disease, the degree of ALT and HBV DNA elevation and the degree of hepatic inflammation and/or fibrosis present.

There are different treatment guidelines set out by the 3 international societies for the study of liver disease AASLD, APASL and EASL which are largely concordant [2-4]. Table 1 sets out treatment indications according to phase of disease as defined in 2007 by Thomas [5] although the guidelines do not all set them out in this way.

Choice of treatment

The choice of therapy is determined by the likelihood of sustained response, patient tolerability to certain side effects and in certain parts of the world, cost and availability of different medications.

There have been significant advances in the available treatments for CHB over the past 3 decades with the advent of pegylated interferon (Peg IFN) which also now has useful on treatment predictors of response (quantitative HBsAg) and high efficacy in certain populations (eg genotype A patients), including the possibility of HBsAg clearance. Oral nucleos(t)ide analogues now available including entecavir and tenofovir have high potency and very low rates of resistance. The main drawback to using them being the need for indefinite therapy as viral rebound commonly occurs with cessation. There are no current recommendations made by any of the international societies about the choice of therapy to be used initially and this is largely left up to individual clinicians, however clinical guidelines published in the National Health Service in Britain recommend offering Peg IFN initially to patients with compensated liver disease for both HBeAg positive and negative patients [6,7].

Peg IFN for HBeAg positive CHB

Peg IFN is available for use as a once weekly injection and has

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	AASLD 2009	APASL 2012	EASL 2012
Immune tolerant	HBeAg positive, ALT ≤ 2 X ULN Observe. Consider tx when ALT becomes elevated (degree of elevation not mentioned). Consider biopsy in >40 yrs/ ALT high normal/ FHx HCC. Consider tx if HBV DNA >20,000 and biopsy significant inflammation/fibrosis	HBeAg Positive, ALT normal (regardless of HBV DNA) – monitor HBV DNA/ALT/HBeAg 3-6 monthly HBeAg positive, HBV DNA ≥ 20,000IU/ml, ALT 1-2 x ULN → No tx. Monitor and consider liver biopsy or fibroscan if >40 yrs and tx if moderate/severe inflammation/fibrosis.	HBeAg Positive, PNALT and high HBV DNA. If <30 yrs and no FHX of HCC or evidence of liver disease – 3 monthly followup. No tx required. Consider liver biopsy if >30yrs and/or FHx HCC/cirrhosis.
Immune clearance	HBeAg positive HBV DNA >20,000 IU/ml ALT > 1-2 X ULN. →Observe for 3-6 months. If no spontaneous HBeAg loss, HBV DNA≥20,000 IU/ml and ALT >2x ULN – treat. . If HBV DNA>20,000. ALT <2xULN or >40 years→Consider liver biopsy and treat if mod/ severe inflammation/fibrosis.	HBV DNA ≥ 20,000: and ALT 2-5 x ULN - Treat if persistent over 3-6 months or if concerns about decompensation. Or ALT > 5 X ULN . Treat, although if HBV DNA < 2 x 10^5 may choose to observe for 3 months for spontaneous seroconversion, if no risk of decompensation.	Obviously active CHB (HBeAg positive, ALT >2xULN and HBV DNA>20,000) - start tx (no liver biopsy required but fibroscan useful). Any patient with elevated HBV DNA>2000, ALT >ULN and mod-severe fibrosis can be considered for treatment.
	AASLD 2009	**APASL 2012**	**EASL 2012**
Immune control	HBeAg negative, HBV DNA ≤2000 IU/ml, ALT ≤ ULN → Observe.	HBV DNA <2000 IU/ml and ALT normal → Observe with ALT/DNA 6-12 monthly.	HBeAg negative, PNALT, HBV DNA<2000 – no tx. 3/12ly ALT and HBV DNA 6-12 monthly for at least 3 years
Immune Escape	HBeAg negative, HBV DNA >2000 IU/ml, ALT > 2 x ULN → Treat. HBeAg negative, HBV DNA >2000 IU/ml and ALT 1-2 X ULN → Consider liver biopsy and treat if moderate/severe inflammation or fibrosis.	HBV DNA ≥ 2000 IU/ml and ALT <2 X ULN → No tx. If age >40 yrs liver biopsy or fibroscan and tx if moderate/severe inflammation. HBV DNA ≥ 2000 IU/ml and ALT > 2 X ULN → treat if persistent for 3-6 months or concern re decompensation.	Obviously active CHB (HBeAg positive, ALT >2xULN and HBV DNA>20,000) - start tx (no liver biopsy required but fibroscan useful). Any patient with elevated HBV DNA>2000, ALT >ULN and mod-severe fibrosis can be considered for treatment.
Cirrhosis – compensated	HBV DNA > 2000 IU/ml → treat. HBV DNA <2000 IU/ml consider tx if ALT elevated.	HBV DNA <2000 IU/ml → No tx. MonitorALT/HBeAg or HBV DNA 3 monthly. HBV DNA ≥ 2000 IU/ml and ALT elevated →treat. Can consider IFN only if ALT not ≥ 5 X ULN.	Consider starting tx if detectable HBV DNA even if ALT normal.
Cirrhosis - decompensated	If HBV DNA detectable coordinate tx with NA with transplant centre.	Urgent treatment with NAs. (HBV DNA level not mentioned).	Urgent commencement of NA treatment if any detectable HBV DNA. Consider transplant

Table 1: Recommendations for initiation of treatment by international societies.

modest antiviral effect but also has an immunomodulatory effect. A large trial of 814 patients with 3 arms (Peg IFN α-2a monotherapy, lamivudine monotherapy and Peg IFN/lamivudine combination therapy for 48 weeks) showed that the combined response rate of HBeAg seroconversion, normalisation of ALT and HBV DNA<100,000 copies/ml was 10% at end of treatment and rose to 23% 24 weeks post end of treatment. These patients were predominantly Asian (87%) and genotype C (60%). At the end of follow-up (week72), 29% of patients had achieved HBeAg seroconversion (compared to 19% receiving lamivudine alone), 41% had ALT normalisation, 32% had HBV DNA<10^5 Copies/ml and 14% had HBV DNA <400 copies/ml [8]. The optimal dose and duration of Peg IFN α-2a is 180 mcg weekly for 48 weeks [9]. In a European trial of 52 weeks of Peg IFN α-2b in HBeAg positive patients (n=307), HBeAg seroconversion rates 26 weeks post therapy were 36% overall [10]. HBeAg loss varied with genotype, being 47% in genotype A, 44% in Genotype B, 28% in genotype C and 25% in D [10]. The HBsAg loss rate at 6 months post end of therapy was 3-5% in these studies. HBeAg seroconversion, especially if achieved during treatment or early post treatment is durable in the majority (83%), as is HBV DNA suppression and ALT normalisation [11]. Overall sustained HBeAg and HBsAg loss at 3 years following Peg IFN treatment has been reported in 37% and 11 % respectively of the European cohort [12]. However in patients with HBeAg loss before 32 weeks of therapy, the rates of HBV DNA suppression <400 copies/ml and HBsAg loss were 47% and 36% at 3 years [13]. The use of Peg IFN α-2b in HBeAg positive CHB patients with advanced fibrosis and well compensated cirrhosis has been shown to be safe and effective in a study by Buster et al which included 70 patients with advanced fibrosis (including 24 cirrhotic patients), compared with 169 patients without advanced fibrosis. They in fact reported higher response rates (HBeAg seroconversion and HBV DNA < 10,000 copies/ml at week 78) in those with advanced fibrosis compared to those without (25% v/s 12%), however genotype A was more prevalent in the former groups than the latter (57% vs 24%) [14].

Buster et al analysed the pooled data of the 2 largest global trials of Peg IFN in HBeAg positive patients (n=712) and reported on predictors of sustained response (defined as HBeAg loss and HBV-DNA level less than 2.0 x 10^3 IU/mL 6 months after treatment). They report that HBV genotype, ALT ≥ 2 x ULN, HBV DNA <2 x 10^8 IU/ml, female sex, older patients (average age of those with response was 34 compared to 32 in non-response) and lack of previous IFN exposure were associated with a higher chance of sustained response. They chose a predicted response rate of 30% or greater on which to base recommendations for use of Peg Interferon and recommend it be used in all genotype A patients, in genotype B and C patients with a high ALT and a low HBV DNA (levels as defined above and in Table 2) and not at all in genotype D patients [15]. They also include useful monograms in genotypes A-D to predict % chance of SVR based on individual patient characteristics. The responsiveness of Interferon overall has also been compared in other studies and is considered to be better in genotype A than D and better in B than C [16]. In addition some host genetic variants, including single nucleotide polymorphisms may play a role in the response to Peg IFN treatment. IL28B does not appear to predict responsiveness to IFN unlike the situation in Hepatitis C, however this data was in a study of largely Asian patients, the majority of whom had the good response (CC) IL28 B genotype [17]. There are a few studies which have looked at host IFN pathway genes, or certain HLA locus genes which have shown a possible improvement in response in patients with certain polymorphisms [18,19], although there is not enough evidence to include these factors in clinical decision making at present. Quantitative HBsAg and HBeAg levels in Peg IFN therapy for HBeAg positive CHB.

Quantitation of HBsAg using automated assays has recently been developed and serum HBsAg levels have been shown to be a marker

	HBeAg positive	HBeAg negative
qHBsAg	• qHBsAg level of <1500 IU/ml at week 12 • qHBsAg decrease of >1 log 10 and qHBsAg <300 IU/ml at week 24 of treatment	• HBsAg decline of >1 $\log_{10}$ IU/ml and HBsAg <10 IU/ml at week 48 (53% HBsAg loss at 3 years post tx). • 0.5 $\log_{10}$ decrease in qHBsAg at week 12 (89% PPV of sustained response). • 1 $\log_{10}$ decrease in qHBsAg at week 24 (92 % PPV of sustained response)
qHBeAg	• qHBeAg level of <10 PEIU/ml at week 24 (associated with HBeAg seroconversion in over 50%)	

Table 2: On treatment predictors of response to Peg IFN treatment.

of the transcriptional activity of cccDNA [20]. HBsAg levels at weeks 12 and 24 of Peg IFN therapy may be used to identify HBeAg positive patients with a low chance of response. In genotype A and D, absence of any decline in qHBsAg at week 12 has a negative predictive value (NPV) of 97-100% for poor response and in genotypes B and C, week 12 qHBsAg levels of >20,000 IU/ml has a high NPV. Week 24 HBsg levels of >20,000 IU/ml have a NPV for response of 99% and therefore may be considered a stopping rule for all genotypes (A-D) [21]. qHBsAg level of <1500 IU/ml at week 12 on the other hand is associated with a good response with 17% of patients achieving HBsAg clearance at 24 weeks post treatment [21]. Chan et al have also shown that a >1 log reduction in qHBsAg at month 6 combined with qHBsAg ≤ 300 IU/ml at this point had a positive predictive value of 75% for sustained response (defined as HBeAg seroconversion and HBV DNA <10 000 copies/mL until 12 months post-treatment) [22].

Quantitative HBeAg levels may also be of use in response guided therapy for peg IFN. A qHBeAg level of ≥ 100 PEIU/ml at week 24 is a predictor of poor response with only 4% of patients with this level of qHBeAg achieving HBeAg seroconversion 6 months post therapy while in contrast a qHBeAg level of <10 PEIU/ml at week 24 is associated with HBeAg seroconversion in over 50% of Peg IFN treated patients [23].

Peg interferon for HBeAg negative CHB

Peg IFN α in the treatment of HBeAg negative CHB was evaluated in over 500 patients by Marcellin et al who compared 48 weeks Peg-IFN alone, to Peg-IFN + Lamivudine and to Lamviduine alone [24]. Six months post therapy, normalisation of ALT was seen in 59%, HBV DNA < 20,000 copies/ml in 43% and HBV DNA <400 copies/ml in 19% of Peg IFN monotherapy patients. These rates were significantly higher than in the lamivudine group [24]. Combined biochemical and virological response was seen in 36% of patients but this dropped to 25% at 3 years post follow up [25]. HBsAg clearance was in 6% of the Peg IFN group (compared to 0% in the Lamivudine group) at 24 weeks post treatment and this increased to 8.7% at 3 years.

Similar to the case in HBeAg positive CHB, predictors of response to Peg IFN (defined as ALT normalisation and HBV DNA <20,000 copies/ml 24 weeks post treatment) include high baseline ALT, lower HBV DNA at baseline and female gender [26]. Younger age and genotype (B and C did better than D) were also significant predictors. There have been conflicting reports on the effect of IL28 B genotype on Interferon treatment responsiveness. In a study of predominantly genotype D patients (92%), Lampertico reported higher sustained response rates (31% vs 13%) and higher HBsAg clearance rates (29% vs. 13%), in those with the IL28 B genotype CC (at position rs12979860) compared to non CC patients [27]. However other studies have not shown any difference [28]. A number of the large studies in HBeAg negative chronic hepatitis B have been done in cohorts of largely genotype D patients and because of the overall poorer response, strategies to improve response rates have been tried, e.g extension of Peg IFN treatment to 96 weeks from 48 weeks. This results in viral suppression rates (HBV DNA <2000 IU/ml) at 6 months post treatment, of 28.8% compared to 11.8% in the 48 week treatment group [29]. Trials of combination Peg IFN with Tenofovir/entecavir are currently ongoing and the optimal way to use a combination of nucleotide analogues and Peg IFN, whether at the same time, or after a "lead in" of several weeks of nucleotide analogues are still the subject of debate and study. Quantitative HBsAg levels in Peg IFN therapy for HBeAg negative CHB.

Early decrease in HBsAg levels in HBeAg negative patients treated with Peg IFN has been shown to predict sustained virological response. Moucari et al showed that decrease of 0.5 $\log_{10}$ at week 12 and a 1 $\log_{10}$ at week 24 had a high positive predictive value (89% and 92% respectively) for sustained response (defined as undetectable serum HBV DNA <70 copies/ml 24 weeks post treatment cessation) [30]. Changes in HBsAg levels during Peg IFN were shown to be genotype specific in a study of 230 HBeAg negative CHB patients. The authors suggest different end of treatment cut off values for genotypes A-D to predict long term virological response (defined as HBV DNA <10,000 copies/ml at 5 years post treatment). They reported that Positive predictive values of 75%, 47%, 71% and 75% could be obtained using end of treatment cut off values of <400 IU/ml (genotype A), <50 IU/ml (genotype B), <75 IU/ml (genotype C) and <1000 IU/ml (genotype D) [31]. End of treatment HBsAg levels also correlate with HBV DNA suppression to ≤400 copies/ml 6 months post treatment. Furthermore, long term HBsAg clearance (at 3 years) has been shown to be strongly predicted by a HBsAg decline of >1 $\log_{10}$ IU/ml together with HBsAg <10 IU/ml at week 48 however the numbers of patients in which this is achieved is small [32]. Stopping rules in genotype D HBeAg negative CHB based on no decline in HBsAg and <2 $\log_{10}$ drop in HBV DNA at week 12 of therapy has also become part of recent guidelines [2] based on a very high NPV for sustained response [33,34].

Nucleoside/Nucleotide analogues (NA's) for CHB

There are 5 oral drugs, all belonging to the class of HBV Polymerase inhibitors that have been used for the treatment of CHB. Lamivudine, entecavir and Telbivudine are nucleoside analogues and Adefovir dipivoxil and Tenofovir disoproxil fumarate (TDF) are nucleotide analogues. Due to the significant issues with resistance encountered with lamivudine, adefovir and telbivudine, only the 3rd generation NA's, entecavir and TDF are recommended as first line choices for CHB. For patients with prior resistance to lamivudine, adefovir or telbivudine a nucleos(t)ide analogue without cross resistance should be chosen [4]. The main advantages of NA's over Peg IFN are their oral administration, tolerability and safety and the high rates of virological suppression achieved.

Entecavir

Entecavir is a cyclopentyl guanosine analogue which selectively inhibits the HBV polymerase in its DNA synthesis and reverses transcription functions. It has a high genetic barrier of resistance,

requiring at least 3 codon substitutions for resistance. Entecavir resistance in treatment naïve patients is very rare (1.2% after 5 years of treatment). However in patients with prior Lamivudine resistance, the presence of the rtL180M and rtM2041I/V codon substitutions means that only one further substitution is required and the development of genotypic resistance is 51% at 5 years [35]. In the initial phase 3 trial of entecavir versus lamivudine in 715 HBeAg positive patients, at 48 week, the rates of undetectable HBV DNA were 67%, ALT normalisation 68%, and histologic improvement 72% all of which were significantly better than in the lamviduine group. HBeAg seroconversion occurred in 21% of the entecavir group compared to 18% lamivudine group [36].

In HBeAg negative patients cohort of 648 patients, at 48 weeks 90% had undetectable HBV DNA, 78% normalisation of ALT and 70% had histologic improvement, again all rates were higher than in Lamivudine treated patients [37].

There is a progressive increase in HBV DNA undetectability with entecavir treatment over time and 5 year followup of the HBeAg positive group (n=183) treated with 1mg entecavir found that 94% had HBV DNA <300 copies/ml, 80% had normal ALT and a further 23% (in addition to those achieving it is the 1st year) achieved HBeAg seroconversion [38]. Numerous other studies have also shown high rates of HBV DNA suppression and ALT normalisation in HBeAg negative patients with progressive increases with increased duration of therapy although it is interesting to note that ALT normalisation rates are usually about 10% lower than rates of HBV DNA undetectability, In Yuen's Hong Kong study 98% had undetectable HBV DNA and 86% normal ALT at 3 years [39] and in a Japanese study 100% had undetectable HBV DNA and 91% normalised ALT after 4 years of entecavir [40].

Histologic improvement with reduction in necroinflammation was seen in 96% of patients and regression of fibrosis by ≥ 1 point was seen in 88% of patients treated with entecavir for at least 3 years [41].

HBsAg loss is uncommon occurring in 5% of HBeAg positive patients after 96 weeks of treatment and a further 1.4% after 5 years of entecavir treatment [38]. In HBeAg negative patients the rates are lower being approximately 0.3% after 48 weeks of entecavir [37].

Tenofovir

Tenofovir is an acyclic adenine nucleotide analogue used in the treatment of both HBV and HIV. Tenofovir at a daily dose of 300 mg daily for 48 weeks resulted in viral suppression (<69 IU/ml) in 76% of HBeAg positive and 93% of HBeAg negative patients (both significantly more than in adefovir treated patients) [42].

ALT normalisation was seen in 68% and loss of HBsAg in 3%. At 3 year follow up, HBeAg seroconversion was seen in 26% of HBeAg positive patients and HBsAg clearance in 8% of HBeAg positive patients but no HBeAg negative patients in a European cohort [43]. At 5 year followup, sustained viral suppression was seen in 97% of patients and there were no cases of resistance. Furthermore regression of cirrhosis was seen in 74% of patients who had biopsy proven cirrhosis at the outset of treatment [44]. HBsAg loss in tenofovir treatment is 3.2% at week 48 [42] and 6% following 96 weeks of therapy [45] although the rates in HBeAg negative patients are lower than in HBeAg positive patients.

HCC risk and treatment with NA's

Recent attention has been focused on whether the risk of HCC is reduced in CHB patients treated with entecavir or Tenofovir. A Japanese study showed that compared to a historical cohort of untreated patients, entecavir treatment reduced the HCC risk but this was only in cirrhotic patients (7% vs 39% p<0.001) [46]. Similarly, in a study by Wong comparing entecavir treated patients to historical untreated controls, although no difference overall in hepatic events (defined as complications of cirrhosis, HCC or liver related mortality) was seen between the 2 groups, there was a reduction in all these outcomes in the cirrhotic subgroup [47]. The reason for these studies fails to demonstrate HCC risk reduction in non-cirrhotic patients may relate to the low baseline risk in these patients [48]. A recent paper which was a retrospective nationwide cohort study of over 20,000 CHB patients treated for at least 90 days with Nucleoside analogue therapy showed a reduced risk of HCC in this group compared to a cohort of similar size given "hepatoprotective" therapy alone, (which included Silymarin, liver hydrolyste and choline bitartrate) [49]. Nevertheless, since HCC risk is not eliminated in patients on long term treatment with NA's, ongoing surveillance is required.

Safety/tolerability of nucleot(s)ide analogue

Entecavir has been shown to have a very good safety profile with a long term study (184 weeks) showing that the most common side effects (seen in ≥ 10%) were upper respiratory tract infections, headache, nasopharyngitis, cough and fatigue [50] however discontinuation is uncommon. Lactic acidosis has also been reported in patients with decompensated cirrhosis on entecavir [51] although other reports have not confirmed this [52].

Tenofovir has been associated with adverse effects of renal dysfunction and Phosphate wasting as well as decrease in bone mineral density and osteomalacia however most initial reports of these were from HIV patients receiving TDF containing regimens. In 6 year followup data of initial TDF registration trials the rates of renal events (defined as ≥ 0.5 mg/dl increase in serum creatinine from baseline) or eGFR <50 ml/min or phosphorus <2 mg/dl were ≤ 1.5% overall. Dose reduction may be required in patients who have some underlying renal impairment but TDF has been shown to be relatively safe even in elderly populations and those with decompensated liver disease [53]. Monitoring of eGFR and serum phosphate is recommended for those receiving TDF every 3 months for 1 year and 6 monthly thereafter [2].

Partial virological response to NA's

Detectable HBV DNA after 48 weeks of NA therapy is considered a partial virological response. Higher proportions of HBeAg negative patients achieve full virological response. For example in the VIRGIL study group, virological response to entecavir, defined as HBV DNA <80 IU/ml was seen in 48%, 76% and 90% of HBeAg positive and 89%, 98% and 99% of HBeAg negative patients at weeks 48,96 and 144 respectively [54]. The recommended management of partial virological response is debated, however if the level of virus is ≤ 1000 IU/ml or there is a continuous decrease in levels, the same NA may be continued. However in patients with viral loads >1000 IU/ml with no ongoing reduction or with underlying cirrhosis, switch to a non-cross resistant NA is recommended [54].

Cessation of NA's

Current recommendations from the international societies is that in HBeAg positive patients, NA therapy may be stopped following the loss of HBeAg, development of HBeAb and undetectable HBV DNA for 12 months (EASL and APASL) [2,55] or 6 months (AASLD) [3]. Cessation of NA therapy is not recommended in HBeAg negative patients according to EASL or AASLD guidelines except for situations

where HBsAg is cleared. APASL suggests that following a minimum of 2 years with HBV DNA undetectable on at least 3 occasions, NA treatment may be stopped in HBeAg negative patients. However in a study of 95 HBeAg negative patients who met this criteria, 45% of patients experienced a recurrence of their disease (ALT>2x ULN and HBV DNA >2000 IU/ml) within 1 year of discontinuation of entecavir [56].

Quantitative HBsAg during NA therapy

In comparison to IFN based therapy, the changes in HBsAg levels during NA treatment of CHB are slower and less pronounced [32,57]. Significant changes in HBsAg levels were noted in HBeAg positive patients treated with entecavir who had an elevated baseline ALT and who subsequently went on to lose HBeAg but no significant change was seen at all in HBeAg negative patients treated with entecavir [58]. Some studies have suggested that HBsAg loss may be predicted by a steep decline in HBsAg levels; especially early in the course of NA treatment however other studies have produced conflicting results [20]. Use of end of treatment HBsAg levels to predict long term viral suppression have also been studied but further, longer term and larger studies are required to further elucidate the role of quantitative HBsAg in NA therapy. Major interest also centres on whether qHBsAg can predict which patients can stop NA therapy long term and remain in remission [59].

Future directions

New targets for CHB therapies are the subject of ongoing research with multiple steps in the HBV replication cycle being investigated as potential targets including viral entry, cccDNA – both its formation and regulation by epigenetic mechanisms, nucleocapsid assembly and the RNAse H activity of HBV polymerase, The identification recently of the entry receptor for hepatitis B (and Hepatitis D), sodium taurocholate co-transporting polypeptide (NTCP) has been a particularly exciting advance [60]. Inhibition of viral entry into cultured hepatocytes has been shown to occur with Cyclosporin A and this represents an exciting avenue for future drug research into novel therapies for hepatitis B [61]. Small molecules targeting de novo synthesis of cccDNA have also recently been identified [62] and there has also been some in vitro evidence that IFN-α can inhibit established cccDNA [63]. Other compounds that can interfere with RNA encapsulation have also been studied with some early promise [64]. In addition, targets in the innate and adaptive immune system have been studied, for example there has been evidence of interferon stimulated gene expression and reduction in viral load in chimpanzees treated with an agonist of Toll-like receptor 7 [65]. Interest has also been focused on antivirals that target HBsAg levels since it seems intuitive that with a rapid reduction in HBsAg an excess of free anti-HBs may be able to contribute to humoral control of the virus [66]. The trends in research are towards finite treatments that will clear cccDNA and HBsAg and restore immune control [67]. Proposed definitions of "cure" have also been put forward, with a "functional cure" being a combination of undetectable viral load, HBsAg and cccDNA off treatment, with or without HBsAb, although it is recognised that the risk of death from liver disease may only be brought down to that of a person with naturally resolved infection, as opposed to one who has never been infected [68].

Conclusions

Therapeutic options for chronic hepatitis B have evolved over the past decade. The oral nucleoside analogue agents, Entecavir and Tenofovir, have high potency, very low rates of resistance and are well tolerated. They result in virological suppression and regression of fibrosis and reduce HCC in cirrhotic patients. They have a good safety profile however long term therapy is required in the majority of cases, especially in HBeAg negative CHB and monitoring of certain parameters eg renal function in Tenofovir remains necessary. Peg IFN is an alternative to oral NA's and although it has a more significant side effect profile, and requires more intensive monitoring, its advantages are the finite duration of therapy and potential immunomodulatory effects. This makes it particularly suitable for women of childbearing age. Tailoring treatment to those with the best chance of response based on pre-treatment variables as well as on treatment measurement of quantitative HBsAg levels can further improve the utility of a course of Peg IFN and reduce unnecessary prolongation of treatment in those with very low chance of response. Future research will focus on identifying patients who can successfully stop NA therapy as well as on novel therapies or combinations of therapies that can target the HBV at various levels. Reliable and early HBsAg and cccDNA clearance and normalisation of the risks of cirrhosis and HCC remains the ultimate endpoint to which all therapies for CHB must strive.

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