Hepatitis B virus treatment beyond the guidelines: special populations and consideration of treatment withdrawal

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***Abstract*:** The goal of chronic hepatitis B (CHB) treatment is to improve survival by preventing disease progression to decompensated cirrhosis and hepatocellular carcinoma which is the cause of over 1 million deaths annually. The risk of disease progression is reduced when a sustained reduction of hepatitis B virus (HBV) DNA to undetectable levels and suppression of HBV replication are obtained which can result in regression of liver fibrosis and may even reverse cirrhosis. However, even if HBsAg loss occurs, HBV is not completely eradicated by treatment, and long-term therapy is required in patients who are $HBeAg^-$ and $HBeAg^+$ who do not maintain off-treatment virological suppression and in those with advanced liver disease. The recently updated European Association of the Study of the Liver (EASL) clinical practical guidelines for HBV have clarified, first, how to treat HBV (interferon or the most potent oral drugs with optimal resistance profiles, i.e. entecavir and tenofovir disoproxil fumarate, should be used as first-line monotherapies); second, who should be treated (CHB in patients with significant liver disease but also patients who are $HBsAg^+$ and are receiving immunosuppressive treatment, patients coinfected with HBV and human immunodeficiency virus, mothers who are $HBsAg^+$ with high viral load in late pregnancy associated with sero vaccination to reduce the risk of vertical transmission of HBV; and third, when to stop antiviral therapies. The aim of this review was to clarify how to treat HBV and who should be treated, as well as when to stop treatment. Although the answer to these questions is clear for pegylated interferon, it is more debatable for nucleos(t)ide analogues (anti-HBe seroconversion, HBsAg loss or anti-HBs seroconversion with undetectable HBV DNA are clear indications to discontinue treatment but sustained undetectable HBV DNA in patients who are $anti\text{-}HBe^+$ without significant fibrosis might be another indication).

Keywords: chronic hepatitis, hepatitis B virus, hepatitis B virus related cirrhosis, hepatitis B virus therapies, hepatocellular carcinoma, nucleos(t)ide analogues, pegylated interferon

Introduction

Approximately 350–400 million people are infected with chronic hepatitis B (CHB) worldwide, resulting in 0.5–1 million deaths annually from end-stage liver disease and hepatocellular carcinoma (HCC) [Lok and McMahon, 2007, 2009; Liaw *et al.* 2012; EASL, 2012].

The risk of disease progression is reduced when sustained reduction of hepatitis B virus (HBV) DNA to undetectable levels and suppression of HBV replication is obtained, which can prevent the progression of fibrosis to cirrhosis, decompensated cirrhosis, end-stage liver disease, HCC and death, and even result in the regression of fibrosis and cirrhosis [Marcellin *et al.* 2013]. Furthermore, maintaining undetectable levels of HBV DNA also increases the rate of HBeAg and HBsAg seroconversion, which are the desired endpoints of CHB therapy. However, current therapeutic options do not eradicate HBV infection, since HBV remains either integrated in the host genome or in the nuclei of hepatocytes as covalently closed circular DNA, which may favour

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oncogenesis, the development of HCC and explain HBV reactivation.

International guidelines of the scientific associations for the study of the liver disease [European Association for the Study of the Liver (EASL), American Association for the Study of Liver Diseases, Asian Pacific Association for the Study of the Liver] have been published on who, how and when to treat patients with HBV infection [Lok and McMahon, 2007, 2009; Liaw *et al*. 2012; EASL, 2012]. The aim of this review was to summarize recent trends beyond the guidelines on who should be treated and when to stop HBV treatment.

Who should be treated?

How to treat

There are two different treatment strategies for CHB which each has its advantages and disadvantages. Pegylated interferon α has a finite duration, no resistance and higher rates of anti-HBe and anti-HBs seroconversion after 12 months of therapy, but a moderate antiviral effect, poor tolerance and is administered by subcutaneous injections with adverse events (including flu-like symptoms, neurocognitive disturbances and haematological toxicity). Interferon therapy is effective in one-third of cases, but only in a few and selected patients. Nucleos(t)ide analogues (Nucs) have a potent antiviral effect, good tolerability and oral administration but must usually be taken indefinitely, have a risk of resistance (low when Nucs with a high barrier to resistance are used) and unknown long-term safety.

Entecavir and tenofovir disoproxil fumarate are potent Nucs that are the recommended first-line monotherapies for CHB. Phase III trials and long-term clinical studies [Lok and McMahon, 2007, 2009; Liaw *et al*. 2012; EASL, 2012; Marcellin *et al*. 2008, 2013; Chang *et al*. 2006; Lai *et al*. 2007; Ono *et al*. 2012] as well as 'real-life' studies [Pol and Lampertico, 2012], including a wide range of patients with different morbidities, comorbidities and lifestyles, have shown that both drugs result in virological response rates of around 95%, with very low rates of resistance and good safety profiles. Thus, it is now easy to know how to treat patients even if HBV is not completely eradicated by treatment and if HBsAg loss occurs. Long-term therapy is required in patients who are $HBeAg^-$ or $HBeAg^+$ and who do not maintain off-treatment virological suppression and in those with advanced liver disease. Certain situations may need to be discussed and the recommendation to treat or not to treat may need to be amended, for example, acute hepatitis, prevention of mother-to-child transmission, preemptive therapy in immunocompromised patients, a family history of HCC in inactive carriers or immune tolerant patients.

Indications in chronic hepatitis B

The indications for treatment are generally the same for both $HBeAg^+$ and $HBeAg^-$ CHB. These are mainly based on three criteria: serum HBV DNA levels (patients should be considered for treatment when HBV DNA levels are above 2000 IU/ml); serum alanine transaminase (ALT) levels (above the upper limit of normal); and the severity of liver disease, assessed by liver biopsy (or noninvasive markers once they have been validated in patients with HBV infections) showing moderate to severe active necroinflammation or moderate fibrosis based on a standardized scoring system (A > 1 or F > 1 according to the METAVIR score) [EASL, 2012]. Treatment may be begun even if ALT levels are normal in patients with certain virological and histological criteria. Indications for treatment may also take into account age, health status, family history of HCC or cirrhosis and extrahepatic manifestations. Due to the dynamic process of HBV infection, 30% of patients who are initially ineligible for therapy according to international guidelines become eligible after 3 years of follow up [Nguyen *et al*. 2013].

Acute hepatitis

After acute HBV infection, most adults recover spontaneously and seroconvert to anti-HBs. However, over 1–5% of patients have fulminant or severe hepatitis and must be evaluated for liver transplantation. It has been suggested that Nucs treatment with entecavir or tenofovir is beneficial and should be used in these cases. Guidelines recommend continuing antiviral therapy for at least 3 months after anti-HBs seroconversion or at least 12 months after anti-HBe seroconversion without HBsAg loss [Xie *et al*. 2013]. Because it is sometimes difficult for clinicians to distinguish severe acute hepatitis B from reactivation of CHB, liver biopsy may be considered to differentiate acute from acute on chronic hepatitis, and Nucs therapy is the first-line treatment in both cases [Xie *et al*. 2013; Garg *et al*. 2011].

Immune-tolerant patients

EASL guidelines recommend considering treatment in patients over 30 years of age or with a family history of HCC or cirrhosis. However, some argue that treatment with very potent Nucs with a high barrier to resistance (i.e. tenofovir or entecavir) should be considered in all immune-tolerant patients to decrease the risk of HCC [Zoulim and Mason, 2012]. In a study by Chan and colleagues in 126 Asian patients, mean age 33 years old and treated with tenofovir plus placebo or tenofovir plus emtricitabine for 192 weeks, a virological response i.e. undetectable HBV DNA (< 69 IU/ml), was found in 55% and 76% of patients respectively ($p = 0.016$) with a low rate of HBeAg loss (6% *versus* 2%, nonsignificant) and anti-HBe seroconversion (5% *versus* 0%, nonsignificant). There was no HBsAg loss or anti-HBs seroconversion and no viral resistance in any of the patients in this study [Chan *et al.* 2013]. Since it is nearly impossible to demonstrate a clinical benefit in studies that are nonrandomized controlled studies *versus* placebo, treatment in immune-tolerant patients is still a subject of debate. However, we hope that a study funded by the National Institutes of Health on treatment in the immune-tolerant phase will help clarify these questions.

Inactive carriers

There is strong evidence that inactive carriers do not require antiviral therapy. The definition of inactive carrier status has become less restrictive since EASL guidelines were published so that patients with persistently normal ALT (every 3 months), HBV DNA levels between 2000 and 20,000 IU/ml (every 6–12 months), without any evidence of liver disease for at least 3 years should be considered and followed as inactive carriers. However, Tseng and colleagues recently found a positive correlation between HBsAg levels and the development of HCC in patients who are $HBe^-$with HBV DNA at least 2000 and less than 19,999 IU/ml ($p = 0.002$), suggesting that HBsAg levels could play a role in stratifying the risk of HCC in patients with intermediate viral load and deciding on the treatment strategy in these patients [Tseng *et al.* 2013a].

It can be difficult to distinguish true inactive carriers from patients with CHB who are $HBeAg^-$ and have fluctuating ALT and viral load. Careful and long-term follow up of patients as well as the HBsAg titres, makes it possible to differentiate between the two phases of the disease: an HBsAg titre below 1000 IU/ml seems to provide an accurate diagnosis of inactive carriers [Brunetto *et al.* 2010]. In addition, Tseng and colleagues showed that in a group of patients who were $HBeAg^-$ in Taiwan with HBV DNA less than 2000 IU/ml the risk of developing HCC was 13.7 times higher in patients with HBsAg titres of 1000 IU/ml or more than in those with a HBsAg titres below 1000 IU/ml over a mean 14.7 years [Tseng *et al.* 2012b]. This suggests that HBsAg titres may be predictive of HCC and should be used to differentiate patients with $HBeAg^-$ CHB from true inactive carriers, then consider earlier treatment in the latter. Another study by Tseng and colleagues evaluated 1068 patients who were $HBeAg^-$ and had a low viral load (<2000 IU/ml) for a mean of 13.0 years [Tseng *et al.* 2012a; 2013a]. Two hundred and eighty of these patients developed $HBeAg^-$ hepatitis with an annual incidence of 2.0%. The only risk factor for $HBeAg^-$ hepatitis was HBsAg level of at least 1000 IU/ml, while the combination of low levels of HBV DNA, ALT and HBsAg (<1000 IU/ml) was found to define HBV carriers (so-called inactive carriers) with a low risk of developing $HBeAg^-$ hepatitis (with an annual incidence of less than 1.1%). These studies show that in Asian patients with HBe^- CHB, DNA less than 2000 IU/ml and normal ALT, the HBsAg cutoff of 1000 IU/ml effectively distinguishes patients at risk of both liver disease and HCC who need to be treated and inactive carriers with a low risk who do not need to be treated.

Prevention of mother-to-child transmission

Mother-to-child (or vertical) transmission is a common mode of HBV transmission, which may occur either *in utero* or perinatally. Serovaccination is a very potent but not totally effective method for preventing vertical HBV transmission [Lee *et al.* 2006; Tran, 2009]. High maternal HBV DNA levels are associated with a risk of HBV vertical transmission despite complete serovaccination, which probably reflects *in utero* transmission (unsuccessful serovaccination occurred at levels as low as 10^5 copies/ml but the risk is only significant above 10^7–10^8 copies/ml) [Wen *et al.* 2013].

Administration of Nucs in late pregnancy associated with serovaccination reduces the risk of vertical HBV transmission. A recent meta-analysis showed that the combination of lamivudine after 28 weeks of gestation and serovaccination was beneficial against *in utero* HBV transmission at

birth and perinatal transmission at 6–12 months of life, evaluated by HBsAg or HBV DNA positivity [Han *et al*. 2011b]. The benefit of late administration of lamivudine in pregnancy was only effective if the maternal viral load was reduced to below 10^6 copies/ml at delivery. Similar results have been recently reported with telbivudine and there is no benefit to introducing preemptive treatment in the second instead of the third trimester of pregnancy [Han *et al.* 2011a; Deng *et al*. 2012]. Finally, when treatment is not indicated for maternal liver disease, Nucs can be stopped between 1 and 3 months after delivery without a significant increase in the risk of ALT flares.

Safety data in pregnancy are only available for lamivudine, telbivudine and tenofovir [Brown *et al*. 2012]. The safety of telbivudine and tenofovir in pregnancy are listed as B by the US Food and Drug Administration (animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well controlled studies in pregnant women), although lamivudine is classified as C (animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks). Tenofovir, contrary to lamivudine or telbivudine, is safe during breastfeeding because there are low concentrations in breast milk as it is a prodrug [Benaboud *et al.* 2011]. Even if the safety profile of these drugs is encouraging, more data are needed on long-term safety in children exposed to these analogues *in utero*.

Preemptive treatment

All patients who are $HBsAg^+$ receiving chemotherapy or immunosuppressive therapy should be treated during therapy and for 12 months after therapy has stopped, regardless of HBV DNA levels [EASL, 2012]. Patients with low (<2000 IU/ml) HBV DNA levels and a finite and short duration of immune suppression should be protected with lamivudine. However, high potency antiviral Nucs, that is entecavir or tenofovir with a high barrier to resistance, should be used in patients with high HBV DNA levels or in those who receive long-term or indefinite immune suppression. In patients who are $AgHBs^+$ with a high viral load and hepatic indications for anti-HBV treatment, Nucs should be continued indefinitely, as in nonimmunocompromised patients.

Patients who are $HBsAg^-$ with positive anti-HBc antibodies and detectable HBV DNA in serum (so-called occult B hepatitis) should be treated in the same way as patients who are $HBsAg^+$ while patients who are $HBsAg^-$ with positive anti-HBc antibodies and undetectable HBV DNA in serum should be followed carefully whatever the anti-HBs status: ALT and HBV DNA should be tested every1–3 months depending on the immunosuppressant therapy and comorbidities and patients should be treated with Nucs if HBV reactivation is confirmed and before ALT elevation. HBV reactivation may occur as long as 2 years after stopping the immunosuppresive regimen, which suggests that follow up should be extended [Zachou *et al*. 2013]. However, some experts recommend preemptive lamivudine treatment in all patients who are $HBsAg^-$ or $anti\text{-}HBc^+$ who receive monoclonal antibodies (antiCD20, antiCD52), combined regimens for haematological malignancies (fludarabine, allogenic or autologous bone marrow transplantations, hematopoietic stem cell transplantations, induction of acute leukaemias) in patients with $anti\text{-}HBs^-$ if close monitoring is not possible [Mandala *et al*. 2013] or in Asian patients. Patients should receive Nucs for at least 12 months after stopping the immunosuppresive therapy, however the optimal duration of therapy has not been determined [Mandala *et al.* 2013].

Finally, patients who are $HBsAg^-$ and receive liver grafts from $anti\text{-}HBc^+$ donors should be preemptively treated with lamivudine indefinitely [EASL, 2012].

Human immunodeficiency virus and HBV coinfection

Experts now recommend early dual antiviral therapy in patients who are coinfected with human immunodeficiency virus and HBV. Thus, treatment is simplified since coinfected patients should receive a tenofovir and emtricitabine containing regimen whatever the immunological, virological or histological considerations for HBV [Piroth *et al*. 2011].

When should HBV treatment be stopped?

It is clear that pegylated interferon should be stopped either early within the first 12 weeks in the absence of a 'significant' HBV DNA or HBsAg decline, or after 48 weeks of treatment. The

stopping date is less clear for Nucs. Anti-HBe seroconversion, HBsAg loss or anti-HBs seroconversion with undetectable HBV DNA are clear indications to discontinue treatment, but stopping treatment in patients with anti-HBe and sustained undetectable HBV DNA may be discussed if there is no significant fibrosis [Lok and McMahon, 2007, 2009; Liaw *et al*. 2012; EASL, 2012; Tujios and Lee, 2013]. Whenever treatment is stopped, regular biochemical and ultrasound follow up should be continued because of the risk of reactivation and direct hepatocarcinogenesis in patients with sustained undetectable HBV DNA.

Stopping interferon

The efficacy of interferon therapy depends upon baseline factors. In selected patients who are AgHBe$^+$ (ALT more than two to five times the upper normal value, HBV DNA < 2×10^8 IU/ml and genotype A) pegylated interferon can be administered for a finite duration (12 months) and anti-HBe seroconversion will occur in 30% [EASL, 2012]. The *IL28B* polymorphism could be a baseline predictive factor of response in patients with CHB since it strongly predicts interferon end-of treatment response with greater decreases in HBV DNA, higher rates of anti-HBe seroconversion or HBAg loss in genotype *CC* versus *CT* and *TT* [Sonneveld *et al.* 2012; Wu *et al*. 2012]. The higher rates of interferon response have also been found in patients who are HBeAg$^-$ with a greater proportion of patients with HBV DNA less than 2000 IU/ml at the end of treatment and higher rates of HBsAg seroconversion after a median follow up of 11 years in patients with *CC* compared with those who are non-*CC* [Lampertico *et al*. 2012].

The efficacy of interferon therapy also depends on monitoring the treatment response. There is now strong evidence that both an HBV DNA and HBsAg decline at week 12 are the best early predictors of a sustained viral response. In patients who are HBeAg$^+$, HBV DNA decrease to less than 20,000 IU/ml and a decline in HBsAg levels to below 1500 at week 12 IU/ml are strongly associated with anti-HBe seroconversion. However, HBsAg levels greater than 20,000 IU/ml or no decline in HBsAg levels at week 12 are associated with a very low probability of anti-HBe seroconversion so that early withdrawal from futile therapy should be considered [Liaw *et al*. 2011; Lampertico and Law, 2012].

In patients who are HBeAg$^-$, an HBV DNA decrease to less than 20,000 IU/ml at 12 weeks and a decline in HBsAg of more than10% at weeks 12 and 24 are associated with a sustained off-treatment response [EASL, 2012]. Inversely, no HBsAg decline and a decline in HBV DNA of less than 2 $\log_{10}$ IU/mL at week 12 is predictive of no response [Rijckborst *et al*. 2012]. Thus, a week 12 stopping rule based on HBsAg and HBV DNA decline must be used in patients who are HBe$^+$ and HBe$^-$.

Stopping Nucs

Current guidelines recommend discontinuing Nucs 6–12 months after anti-HBe seroconversion in patients who are HBeAg$^+$ and after HBsAg loss in those who are HBeAg$^-$ with undetectable HBV DNA. The rate of anti-HBe seroconversion is low (20% after 1 year of therapy) and increases with continued therapy, except if resistance occurs, which is rare with entecavir and tenofovir. The rates of anti-HBe seroconversion with entecavir at 4 years and with tenofovir at 5 years are 38% and 40%, respectively [Marcellin *et al.* 2013; Ono *et al*. 2012]. A sustained off-treatment response (persistence of anti-HBe seroconversion) can be expected in 40–80% of these patients [Reijnders *et al*. 2010; Lee *et al*. 2010]. Anti-HBe seroconversion is less durable after therapy is stopped compared with spontaneous anti-HBe seroconversion [Chaung *et al*. 2012] and compared with pegylated interferon therapy [Wong *et al*. 2010]. In a recent study, patients who achieved HBeAg seroconversion with Nucs had a yearly risk of HBV reactivation of 13.2% compared with 6.2% in patients with spontaneous anti-HBe seroconversion, with higher rates in patients under the age of 30 (12% at 2 years *versus* 2.9% respectively, $p = 0.004$) [Tseng *et al.* 2012; Tseng *et al*. 2013b]. The rate of HBsAg loss after 12 months of treatment is low with Nucs (<1%) and increases with the duration of therapy (HBsAg loss occurs at 5 years in 10% of patients with HBeAg$^+$ who receive tenofovir treatment) [Chan *et al*. 2013]. Finally, anti-HBs seroconversion occurs in 8% of patients who are HBeAg$^+$ after 5 years of tenofovir treatment [Marcellin *et al*. 2013]. In summary, after 4 years of entecavir or 5 years of tenofovir, the endpoint of therapy (i.e. anti-HBe seroconversion in patients who are HBeAg$^+$, only 30% of treated patients in Europe, and HBsAg loss in patients who are HBeAg$^-$with undetectable HBV DNA) allowing treatment withdrawal is achieved in around 40% and 1–10%

of patients respectively. Thus, 60% of patients who are HBeAg$^+$ and 90–100% of those who are HBeAg$^-$must continue Nuc therapy.

The results of attempts to discontinue Nucs have been interesting. In a randomized, controlled study of vaccine therapy in patients with CHB and undetectable HBV DNA after at least 1 year of Nucs, in 97% of cases discontinuation was associated with HBV reactivation and Nucs had to be resumed in patients with HBV DNA above 120 IU/ml [Fontaine *et al.* 2014]. In a Greek cohort of 33 patients who were HBe$^-$ and discontinued Nucs after at least 5 years of viral suppression with adefovir, 100% had detectable HBV DNA at 1 month but at 1 year 67% had biochemical remission and 21% had HBV DNA less than 10,000 copies/ml; this reached 40% after 2 years. Finally, HBsAg loss was achieved in 13 of the 33 patients 6 years after discontinuation [Hadziyannis *et al.* 2012]. Similar results were reported in 32 German patients who were HBe$^-$ and discontinued Nucs after a median 46 months of viral suppression: Nucs discontinuation resulted in relapse in71.8% but 22% had HBV DNA less than 300 copies/ml after 2 years [Petersen *et al.* 2011]. These results suggest that Nucs discontinuation in patients who are HBe$^-$ with sustained viral suppression during treatment may be associated with sustained off-treatment viral suppression in around one-fifth of patients. Future studies are needed to better define the characteristics of patients who can discontinue Nucs therapy without reactivation, in whom the sustained viral suppression may have resulted in an enhanced specific immune restoration [Boni *et al.* 2001].

Although indefinite Nucs therapy should be considered in patients with cirrhosis, EASL guidelines suggest considering discontinuation after at least 12 months of consolidation therapy in the following cases: in patients who are HBeAg$^+$ if they achieve anti-HBe seroconversion or ideally HBsAg loss and anti-HBs seroconversion; and in patients who are HBeAg$^-$if they achieve HBsAg loss and anti-HBs seroconversion. Treatment discontinuation, especially in patients with cirrhosis, should be considered in these situations only if regular biochemical and virological follow up can be continued because of the risk of life-threatening HBV reactivation. However, treatment cessation is not yet recommended in individuals who do not achieve treatment endpoints and should only be considered in patients who are low risk with limited fibrosis as defined by biopsy or by other modalities (Fibroscan, Echosens, Paris, France), as opposed to individuals with advanced fibrosis or cirrhosis.

In conclusion, recent international guidelines, especially the updated EASL clinical guidelines for HBV, have clarified how to treat HBV, who should be treated and when antiviral therapies should be stopped. Nevertheless, certain situations still require discussion or amendments of the recommendations to treat or not to treat: fulminant or severe acute hepatitis, the prevention of mother-to-child transmission in the third trimester of pregnancy, preemptive therapy in patients who are immunocompromised and not only patients who are immune tolerant for more than 30 years with a family history of HCC or cirrhosis but all patients who are immune tolerant and selected HBV inactive carriers at risk of HCC (especially Asian patients, those with a family history of HCC or with HBsAg levels above 1000IU/ml).

In relation to stopping treatment, pegylated interferon may be discontinued earlier depending on the decline in HBV DNA and HBsAg. Nucs cannot be stopped in most patients since only 40% of patients who are HBeAg$^+$ achieve anti-HBe seroconversion after 4 or 5 years of entecavir or tenofovir and no patients who are HBeAg$^-$achieve HBsAg loss. In the future, with prolonged therapy, the rates of anti-HBe seroconversion, HBsAg loss or anti-HBs seroconversion could be higher and the benefit/risk ratio associated with Nucs discontinuation must be evaluated in patients achieving long-term undetectable HBV DNA.

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