Hepatitis B Virus Treatment: Which Patients Should Be Treated with Nucleos(t)ide Analogue?

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Chronic hepatitis B virus (HBV) infection affects about 400 million people worldwide and is among the world's leading causes of death.[1] Antiviral therapy of chronic hepatitis B (CHB) is aimed to improve survival by preventing progression of liver damage to cirrhosis, end-stage liver disease, or hepatocellular carcinoma (HCC), thus preventing anticipated liver-related death. This goal can be achieved by suppressing HBV replication either by short-term treatment with pegylated interferon (PegIFN) or long-term suppressive therapy with oral nucleos(t)ide analogue (NUC).[2–4] Both strategies have advantages and disadvantages, but oral administration of potent anti-HBV analogues has become the most popular treatment strategy worldwide given the excellent efficacy and safety of third-generation NUC such as entecavir and tenofovir, not only in registration trials but also in clinical practice. In this article, we review the indications and management of these oral analogues.

Which Should Be the First-Line Drug?

The first-line drugs recommended for CHB treatment in naïve patients include PegIFN and third-generation NUCs such as entecavir (ETV) and tenofovir (TDF). Lamivudine (LMV), adefovir (ADV), and telbivudine (LdT) are no longer recommended due to their limited efficacy and moderate to high resistance rates.[2–4] Indications to start antiviral therapy according to different international guidelines are summarized in Table 1.

Although PegIFN treatment is indicated for young patients with mild to moderate liver disease and favorable baseline predictors of response, NUC treatment could be potentially given to every patient, independently of age, disease severity, baseline viremia, or concomitant diseases. It is indeed the only therapeutic strategy for patients with decompensated cirrhosis, and the recommended approach for patients with compensated cirrhosis and for all those patients in whom PegIFN is contraindicated or ineffective. Indeed, >90% of patients with CHB are currently treated with oral NUCs, worldwide.

Although more expensive than first- or second-generation drugs, monotherapies with ETV or TDF are indeed cost-effective in the long-term treatment of both hepatitis B e antigen (HBeAg)-positive and HBeAg-negative HBV-infected patients.

ETV or TDF administration suppresses viral replication in 95% of patients over 5 years of continuous treatment, coupled with increasing rates of HBeAg seroconversion (50%), hepatitis B surface antigen (HBsAg) loss (10% in HBeAg-positive patients), alanine aminotransferase (ALT) normalization (85%), and low drug resistance (0%-1.2%).[5–8] Histological progression from chronic hepatitis to cirrhosis is prevented and regression of fibrosis among cirrhosis has been demonstrated to occur in 75% of the cases over 5 years of therapy.[8] Clinical decompensation is prevented over 5 years of antiviral therapy with ETV or TDF, because they are characterized by high potency and low resistance rates, with no patient developing ascites, hepatic encephalopathy, jaundice, or gastrointestinal bleeding. On the other hand, effective antiviral treatment does not eliminate, though it may reduce, the risk of HCC development in HBV patients with cirrhosis or advanced fibrosis. Indeed, liver cancer develops at 1.4% to 2.8% yearly rates in effectively treated

Abbreviations: ADV, adefovir; ALT, aminotransferase; CHB, chronic hepatitis B; DEXA, dual energy X-ray absorptiometry; eGFR, estimated glomerular filtration rate; ETV, entecavir; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LdT, telbivudine; LMV, lamivudine; NUC, nucleos(t)ide analogue; PegIFN, pegylated interferon; TDF, tenofovir.

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Potential conflict of interest: Nothing to report.

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doi: 10.1002/cld.161

TABLE 1: Indications for CHB Treatment According to International Guidelines

Guidelines	HBeAg	HBV DNA	ALT	Liver Histology	Treatment Strategy
APASL	+	>20,000 IU/mL	>2 ULN		Treatment should be considered
	−	>2,000 IU/mL	>2 ULN		Treatment should be considered
AASLD	+	>20,000 IU/mL	>2 ULN	Moderate or severe hepatitis	Treatment should be considered*
	−	>20,000 IU/mL	>2 ULN	Moderate or severe hepatitis	Treatment should be considered†
	+/−	>2,000 IU/mL		Compensated cirrhosis	Treatment should be considered
	+/−	<2,000 IU/mL	Elevated	Compensated cirrhosis	Treatment should be considered
EASL	+/−	>2,000 IU/mL	>ULN	Moderate to severe necroinflammation and/or fibrosis	Treatment should be considered‡
	+/−	Detectable	<ULN	Compensated or decompensated cirrhosis	Urgent antiviral therapy

Abbreviations: APASL, Asian-Pacific Association for the Study of the Liver; AASLD, American Association for the Study of Liver Diseases; EASL, European Association for the Study of the Liver (EASL); ULN, upper limit of normal.

*Treatment should be delayed for 3 to 6 months in patients with compensated liver disease to determine whether spontaneous HBeAg seroconversion occurs, whereas patients with icteric ALT flares should be treated promptly. Treatment should be considered for patients with normal or minimally elevated ALT levels if there is moderate or severe necroinflammation or significant fibrosis on liver biopsy.

†Treatment should also be considered for these patients if the HBV DNA levels are between 2,000-20,000 IU/mL and/or ALT are borderline normal or minimally elevated in the presence of moderate-to-severe necroinflammation or significant fibrosis on liver histology.

‡In patients who fulfill the above criteria for HBV DNA and histological severity of liver disease, treatment may be initiated even if ALT levels are normal.

TABLE 2: Definitions for NUC Treatment Failure

Primary nonresponse	<1 $\log_{10}$ IU/mL decrease in HBV DNA level at 12 weeks of therapy compared with baseline
Partial virological response	Detectable levels of HBV DNA after 24 weeks (LMV, LdT, ADV) or 48 weeks (ETV, TDF) of therapy in a compliant patient
Virological breakthrough	Confirmed increase in HBV DNA level of >1 $\log_{10}$ IU/mL compared with the lowest HBV DNA level on therapy (nadir)

compensated cirrhotics.[9–11] This shift from decompensation to HCC as the sole complication among treated patients with cirrhosis is indeed reflected by the changing patterns in liver transplantation, where HCC is now the main indication for treated patients with cirrhosis. Among patients with decompensated liver disease, survival is significantly improved by antiviral therapy though early mortality, and HCC do still represent a major clinical challenge.[12,13] Safety in clinical trials has been excellent for both drugs independently of disease severity. The excellent efficacy and safety profile of ETV and TDF in naïve patients has also been confirmed in clinical practice worldwide, though experience is still limited to 5 years for ETV and 3 years for TDF.[9,14] According to manufacturer indications, TDF should be avoided in patients with concurrent or recent use of nephrotoxic drugs.

Given these features, ETV and TDF can be used as a first-line treatment in any patient with CHB, independently of age, serology, levels of viremia, levels of ALT, disease severity, and concomitant diseases, the only disadvantage of this therapeutic strategy being the need for decades of antiviral therapy in many of these patients. In countries where ETV and TDF are not available or affordable, viral suppression can be achieved and maintained in the long term by either *de novo* LMV/LdT+ADV combination therapy or LMV/LdT monotherapy with add-on ADV rescue in patients with partial response at week 24 or with virological breakthrough. In the latter case, early rescue, i.e. defined as a rescue started when the first increase of viremia during an intensive program of HBV DNA monitoring occurs, is crucial to maximize the efficacy of ADV.

How Should Patients be Monitored During Therapy?

Independent of the NUC, the only efficacy endpoint for patients under NUC therapy is long-term viral suppression as assessed by undetectable HBV DNA (<10-15 IU/mL). Once therapy is started, viremia should be tested every 3 months until undetectability is confirmed on two separate occasions, then HBV DNA can be monitored every 6 months for the following years. These serum HBV DNA assessments are important to differentiate between primary nonresponse occurring in 2% to 3% of the patients only, partial virological response that ranges from 5% to 50% according to baseline levels of viremia, and virological breakthrough, a rare event during long-term ETV or TDF therapy (Table 2). In patients with partial virological response on LMV, ADV, or LdT, a switch at week 24 to a more potent drug (e.g., ETV or TDF) is recommended. If TDF is not available, add-on ADV is indicated for partial responders to nucleosides. The optimal management of patients having partial virological response after 48 weeks of ETV or TDF is currently debatable. In such patients, the HBV DNA levels at week 48 and their kinetics must be taken into account. Patients with residual viremia ≤1,000 IU/mL or with continuous decline of serum HBV DNA levels may continue the same treatment given that virological response rates increase over time and the risk of resistance remains low. Conversely, patients who have a flat pattern of HBV DNA, a residual viremia >1,000 IU/mL at week 48, should be declared a partial responder and considered for a rescue therapy, (i.e., they should be switched to a non–cross-resistant analogue that is tenofovir [TDF] for entecavir [ETV] and vice versa).

When the initial HBeAg is positive, HBeAg/anti-Hbe should be assessed every 6 months, whereas HBsAg should be tested every 6 to 12 months in patients who are HBeAg-negative with persistently undetectable serum HBV DNAe. In addition, all patients should have serum creatinine at baseline and during treatment for to estimate creatinine clearance (estimated

glomerular filtration rate [eGFR]) by MDRD formula to adjust the NUC dose if the eGFR falls below 50 mL/minute. In patients receiving TDF or ADV, serum phosphate should also be monitored every 3 months to allow for dose adjustment or drug discontinuation if tubular damage occurs.[4] Closer renal monitoring is required in patients who have mild renal impairment or are at risk for renal impairment.[4] Assessment of bone mineral density by dual energy X-ray absorptiometry (DEXA) should be considered for patients who have a history of pathologic bone fractures or other risk factors for osteoporosis or bone loss (e.g., cirrhosis) independently of NUC therapy. At present, there is no clinical evidence to recommend patients receiving TDF-based antiviral regimens to be specifically monitored with DEXA scan.

When Can Treatment Be Stopped?

The best stopping rule for NUC-treated patients is HBsAg loss and anti-HBs seroconversion. However, this endpoint is rarely achieved in HBeAg-negative patients (1% at 5 years, 5% at 10 years) and HBeAg-positive patients infected at birth (1% at 5 years). Conversely, in NUC-treated HBeAg-positive patients with good predictors of response (e.g., short duration of infection, genotype A, elevated ALT levels, and moderate levels of HBV DNA), this stopping rule can be achieved in 10% to 20% of patients at 5 years. HBsAg seroconversion is also the sole safe stopping rule for patients with cirrhosis.

In HBeAg-positive patients without cirrhosis, an alternative stopping rule has been suggested. NUC treatment could be stopped in patients who have achieved a confirmed and sustained ($\geq$12 months) anti-HBe seroconversion plus undetectable HBV DNA ($<$10-15 IU/mL), an event that is observed in approximately 40% to 50% of the HBeAg-positive treated patients after 5 years of therapy. However, viremia and hepatitis will relapse in up to 50% of these patients after NUC discontinuation, thus suggesting a very strict monitoring strategy (i.e., every month) in posttreatment follow-up for early detection of an increase in viremia and to restart antiviral therapy.

To avoid lifelong NUC treatment, new strategies are being assessed in clinical trials, including switching to or adding on PegIFN, combination with oral immunomodulatory agents, and discontinuation in selected HBeAg-negative patients according to HBsAg levels. However, these strategies should not be implemented in clinical practice until more definitive results are available.

Conclusion

The most popular and effective anti-HBV therapeutic strategy is long-term administration of third-generation NUCs such as ETV and TDF. Advantages of this strategy include the excellent tolerability, effective inhibition of HBV replication, high rates of biochemical remission, histological improvement, and prevention of clinical decompensation but not of HCC development, at least in patients with cirrhosis. Monitoring of serum HBV DNA levels together with proactive management of partial virological response or virological breakthrough by early switching to a non–cross-resistant drug ensures long-lasting virological suppression in the vast majority of cases independently of baseline features. However, NUC treatment cannot eradicate HBV, making long-term therapy necessary in most patients, with increasing cost, compliance issues, unproven safety profiles, and a significant residual risk of HCC in patients with cirrhosis. ■

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