Current treatment indications and strategies in chronic hepatitis B virus infection

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Abstract
The optimal approach to the management of several marginal cases with chronic hepatitis B virus (HBV) infection is controversial. Serum HBV DNA and aminotransferase levels, and the degree of necroinflammation and fibrosis determine the therapeutic decisions. All patients with elevated aminotransferase (> twice the upper limit of normal) and serum HBV DNA above 20000 IU/mL should be treated. Liver biopsy is important for therapeutic decisions in cases with mild aminotransferase elevations and serum HBV DNA below 20000 IU/mL. Chronic HBV patients who do not receive treatment should be followed for life. There are seven agents licensed for chronic hepatitis B: standard and pegylated interferon-alpha, lamivudine, adefovir, entecavir, telbivudine and tenofovir. One-year courses with pegylated interferon-alpha induce sustained off-therapy remission in 30%-32% of patients with HBeAg-positive chronic hepatitis B and in a smaller proportion of patients with HBeAg-negative chronic hepatitis B. Oral antivirals achieve initial on-therapy responses in the majority of patients, but are intended as long-term therapies. Viral suppression has favourable effects on patients’ outcome and modifies the natural course of the disease. Viral resistance, however, is the major drawback of long-term oral antiviral therapy. Lamivudine monotherapy is associated with the highest and entecavir monotherapy with the lowest resistance rate so far. There has been no resistance to tenofovir, but after only 18 mo of treatment to date. The optimal first-line anti-HBV therapy with the best long-term cost/benefit ratio remains unclear. If oral antiviral agents are used, compliance should always be ascertained and HBV DNA levels should be regularly tested.

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Key words: Hepatitis B; Hepatitis B virus DNA; Interferon; Antivirals; Resistance

INTRODUCTION
Despite the universal vaccination of neonates and infants during the last years and the subsequent reduction in the incidence of new infections with hepatitis B virus (HBV), chronic HBV infection remains a significant public health problem worldwide[1,2]. It is estimated that there are approximately 400 000 000 people with chronic HBV infection and that more than 500 000 people die every year due to complications of HBV related chronic liver disease[3]. Although considerable improvements in the evaluation and treatment of patients with chronic HBV infection have occurred during the last decade, several issues regarding the optimal management of such patients still remain controversial. This short review focuses on two such controversies: the most appropriate treatment indications and the optimal therapeutic strategy for patients with chronic hepatitis B (CHB).

TREATMENT INDICATIONS
Every patient with chronic HBV infection is potentially infectious and at risk for liver complications and is ide-
ally a candidate for therapy, if the virus can be eradicated\[3,4\]. However, current medications rarely achieve viral eradication in patients with chronic HBV infection and therefore only patients who are at risk for progression to advanced liver disease should be considered for treatment\[5,5,6\]. Thus, the knowledge of the natural history and the significance of the elements used in the evaluation of disease are necessary for decisions on treatment indications. Moreover, the efficacy and safety of current therapies may also affect the treatment indications, as there is no reason to recommend an ineffective therapy to any patient, even if they have progressive liver disease.

In general, the natural history of chronic HBV infection includes four phases of variable duration distinguished by the presence of hepatitis B e antigen (HBeAg) or its antibody (anti-HBe) in the serum and the serum HBV DNA and aminotransferases levels\[7-9\]. It starts with an HBeAg-positive, immune-tolerant phase, characterized by high viremia, normal serum aminotransferases and minimal histological changes. The phase of HBeAg-positive CHB follows at a variable rate. It may also be called the HBeAg seroconversion phase and is characterized by positive HBeAg, high serum HBV DNA levels, elevated aminotransferases and active necroinflammation and/or fibrosis. The annual probability of HBeAg seroconversion (disappearance of HBeAg and development of anti-HBe) depends on several factors, such as the age of acute infection and HBV genotype, and is lower in Asian patients infected at birth (lower in those with genotype C than B) and higher in Caucasian patients infected during childhood, adolescence or adulthood\[10,11\]. If HBeAg seroconversion occurs, patients progress to the HBeAg-negative phases, which can be separated into the inactive carrier state and the HBeAg-negative CHB phase. The inactive chronic HBV carrier state is characterized by low levels of viral replication, normal aminotransferases and minimal histological lesions, while HBeAg-negative CHB is characterized by higher viral replication, elevated aminotransferases and active liver necroinflammation and fibrosis\[12,13\]. HBeAg-negative CHB may develop immediately after the HBeAg seroconversion phase or after several years of an inactive chronic carrier state\[9\], but many inactive chronic HBV carriers never progress to the HBeAg-negative CHB phase.

**General indications for treatment in chronic hepatitis B**

Significant histological lesions and progression of liver disease are observed almost exclusively in patients with HBeAg-positive and HBeAg-negative CHB, therefore these patients are considered as cases with widely accepted treatment indications. In clinical practice, HBeAg-positive or HBeAg-negative CHB can be diagnosed in patients with compensated chronic HBV infection (positive or negative HBeAg respectively) by evidence of viral replication (high serum HBV DNA levels) and biochemical and histological evidence of hepatocellular injury [increased alanine aminotransferase (ALT) activity and liver histological lesions at liver biopsy]. On the other hand, treatment indications are based on specific criteria and require certain cut-off points, which may sometimes be arbitrary due to the lack of strong data to support them. Treatment indications currently focus on serum HBV DNA levels, ALT activity and severity of liver histological lesions.

According to the most recent guidelines, treatment is recommended to all patients with either HBeAg-positive or HBeAg-negative CHB who have serum HBV DNA > 20000 IU/mL and ALT higher than two times the upper limit of normal (> 2 xULN) for at least 3 mo\[14,15\]. In such cases, liver biopsy is considered to be optional, as it may offer prognostic information but it is not expected to affect the decision to treat. On the other hand, treatment is also recommended in HBeAg-positive CHB patients with ALT between 1-2 x ULN or HBeAg-negative CHB patients with ALT between 1-2 xULN and serum HBV DNA between 2000-20000 IU/mL who have at least moderate necroinflammatory activity and/or significant fibrosis\[16\]. So, liver biopsy is mandatory in the latter cases with mild ALT elevations or relatively low viremia levels.

**Controversial issues-The role of serum HBV DNA**

All patients with chronic HBV infection are at increased risk for hepatocellular carcinoma (HCC) compared with the general population; while the risk increases substantially in patients with prolonged high viremia and cirrhosis\[15,16\]. Recent data suggest that patients with chronic HBV infection and HBV DNA above 10\(^7\) copies/mL (approximately 2000 IU/mL) are at increased risk for cirrhosis and HCC regardless of ALT activity and are therefore possible candidates for treatment\[15,17\]. Such data have created some debate on whether patients in the HBeAg-positive immune tolerant phase, who have very high serum HBV DNA levels, should be left untreated. However, because they have minimal to mild histological liver lesions and the currently available agents may reduce viremia but offer minimal chances to induce HBeAg seroconversion\[15,16,18\], there is currently no widely accepted indication for treatment in such cases.

Despite the recent advances in the treatment indications, several issues remain unanswered, most probably because of the fluctuating activity of chronic HBV infection and the existence of patients who do not fulfil all criteria. HBeAg-negative CHB is defined as increased ALT/AST, serum HBV-DNA > 2000 IU/mL and moderate/severe necroinflammation, while inactive HBV carrier state is defined as persistently normal ALT/AST on ≥ 3-4 3-monthly determinations (then every 6-12 mo) and HBV-DNA < 2000 IU/mL\[19\]. However, it is well known that viremia levels fluctuate substantially in patients with prolonged high viremia and cirrhosis\[15,16\]. So, liver biopsy is mandatory in the latter cases with mild ALT elevations or relatively low viremia levels.

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serum samples had HBV DNA levels < 2000 IU/mL, while HBV DNA was persistently ≥ 2000 IU/mL in 82% or occasionally < 2000 IU/mL in 18% of our HBeAg-negative CHB patients[19]. Although some patients may eventually develop HBV DNA levels > 2000 IU/mL after repeated testing, it is not clear how often and how many times HBV DNA determinations should be repeated. Since the current treatment indications include increased ALT and HBV DNA > 2000 IU/mL[3], HBeAg-negative patients with increased ALT/AST and HBV DNA < 2000 IU/mL are not considered for liver biopsy and are excluded from treatment. However, they may represent a sizeable proportion of HBeAg-negative CHB patients in clinical practice. In a retrospective, multicenter Greek study including 399 HBeAg-negative chronic HBV patients with increased ALT, at least moderate necroinflammation and/or moderate fibrosis were detected in the majority (62%) of such cases, who had HBV DNA < 2000 IU/mL and represented 14% of the total study population[38]. Therefore, liver biopsy is an useful tool in the evaluation of patients with persistent or transient mild transaminase elevations, regardless of the levels of serum HBV DNA.

On the other hand, if viremia is considered as the main criterion for performing a liver biopsy in order to decide the treatment indications, then the 2000 IU/mL cut-off serum HBV DNA level may cause a substantial proportion of inactive carriers to undergo unnecessary liver biopsies. In our prospective cohort of 150 HBeAg-negative chronic HBV patients with close biochemical and virological follow-up, a substantial proportion (22% of cases or 28% of 228 serum samples tested) of 85 patients with persistently normal ALT have HBV-DNA > 2000 IU/mL (2000-5000 IU/mL: 15%, 5000-20000 IU/mL: 7%)[39]. According to our data, in 35 such HBeAg-negative cases with persistently normal ALT and HBV DNA > 2000 IU/mL, liver biopsies showed minimal necroinflammation in all but one (mild in one case) and minimal to mild fibrosis in 29 (83%) of them [fibrosis score of 2 in Ishak's scoring system was detected in the remaining 6 (17%) cases][39]. Thus, such cases seem to represent true inactive chronic HBV carriers, who require only close follow-up but no therapeutic intervention. It should be noted, however, that all HBeAg-negative cases with persistently normal ALT had HBV DNA < 20000 IU/mL and that HBeAg-negative cases with persistently normal ALT and HBV DNA ≥ 20000 IU/mL are extremely rare in Greece. Close follow-up still remains the cornerstone of diagnosis. HBeAg-negative cases with relatively high normal ALT values (> 30 IU/L for men and > 20 IU/L for women) and/or serum HBV DNA ≥ 2000 IU/mL warrant closer follow-up, because they are at increased risk of developing HBeAg-negative CHB in the future[39].

**Indications for treatment in specific settings**

Current guidelines support the view that all patients with decompensated liver disease and detectable serum HBV DNA should receive antiviral treatment regardless of aminotransferases and viremia levels[3]. The main goal of treatment in this group of severely ill patients is to completely inhibit viral replication in order to improve liver function and survival and, in case of liver transplantation, to prevent graft re-infection[21-23].

Another very important indication of anti-HBV therapy is the prevention of HBV reactivation in chronic HBV patients who are treated with corticosteroids or any other immunosuppressive therapy or cancer chemotherapy. It is well known that reactivation occurs in 29%-56% of chronic HBV carriers treated with chemotherapy and even in a small proportion of HBsAg negative and anti-HBe positive subjects regardless of anti-HBs status[24,25]. HBV reactivation after immunosuppressive therapy may have deleterious effects, often resulting in acute liver failure and death, therefore all patients who are going to be treated with any type of immunosuppression should be tested for HBsAg and receive pre-emptive anti-HBV therapy in case they are positive for HBsAg[5,29].

**THERAPEUTIC STRATEGIES**

In CHB, the more realistic therapeutic targets are suppression of HBV replication, induction of biochemical remission and ultimately prevention of cirrhosis and HCC[5,6,36]. Studies in non-Asian patients have shown that long-term benefits on survival are strongly linked to the induction of sustained HBeAg seroconversion in HBeAg-positive CHB[27-30] and with sustained biochemical and virological remission in HBeAg-negative CHB[9,32]. HBeAg seroconversion, however, may not be a sufficient therapeutic end-point in all patients with HBeAg-positive CHB, since some of them may subsequently develop HBeAg-negative CHB. This might depend on the patients’ origin and perhaps the HBV genotype. Asian studies suggested that interferon-alpha (IFNα) induced HBeAg seroconversion improves the long-term outcome[33,34] but others reported no long-term benefit from IFNα therapy[38]. Thus, the induction of persistent biochemical and virological remission appears to be the most important therapeutic target in CHB, as the risk of major complications is strongly related to the viremia levels being independent of the HBeAg status[36,37,38]. Effective long-term antiviral therapy has been shown to prevent or diminish the development of decompensation and major complications in patients with advanced fibrosis or cirrhosis and to improve patients’ outcome and survival[32,37,38].

Currently, there are seven drugs licensed for treatment of CHB: standard IFNa, pegylated IFNα-2a (Peg-IFNa-2a) (Peg-IFNα-2b is also licensed in some countries), lamivudine (LAM), adefovir dipivoxil (ADV), entecavir (ETV), telbivudine (TBV) and tenofovir disoproxil fumarate (TDF). These drugs may be broadly classified into (1) IFNAlphas (standard or pegylated), which have both antiviral and immunomodulatory activities and are administered subcutaneously, and (2) the pure antiviral agents (LAM, ADV, ETV, TBV, TDF), which are analogs of natural nucleosides (LAM, ETV, TBV) or nucleotides (ADV, TDF) and are administered orally once daily.
Anti-HBV agents can be given as therapies of finite duration or as long-term therapies.\(^{[1]}\)

**Therapies of finite duration**

Therapies of finite duration are usually given for 12 mo and aim to induce sustained off-treatment response.\(^{[2,3]}\) In current clinical practice, only IFNα/PEG-IFNα are used as therapy of finite duration in chronic hepatitis B, because sustained off-therapy responses after one-year courses with oral antivirals are rather limited.

In HBeAg-positive CHB, HBeAg seroconversion rates were reported to be 25%-33% with IFNα (5 MU daily or 10 MU thrice weekly for 4-6 mo) or Peg-IFNα (Peg-IFNα-2a: 180 μg/wk, Peg-IFNα-2b: 100 μg/wk for 12 mo)\(^{[4,5]}\), 18%-22% after 12-mo courses with LAM (100 mg daily)\(^{[6,7]}\), ETV (0.5 mg daily)\(^{[8]}\), TBV (600 mg daily)\(^{[9]}\) or TDF (300 mg daily) and only 12% with ADV (10 mg daily)\(^{[10]}\). The antiviral expressed by the reduction in serum HBV DNA levels differs among the anti-HBV agents (highest with TDF, ETV and TBV, intermediate with LAM and lowest with IFNα/Peg-IFNα and ADV), but these differences do not translate into different HBeAg seroconversion rates, at least within the first year of therapy. Patients with genotypes A and B respond better to IFNα/PEG-IFNα than those with genotypes D and C\(^{[11,12]}\), while response rates to oral antivirals are not affected by the HBV genotype\(^{[13]}\).

In HBeAg-negative CHB, cohort studies using insensitive virological assays showed that 12- or 24-mo courses of standard IFNα (3 or 5 MU thrice weekly) may achieve sustained long-term off-therapy biochemical and virological responses in 22%-30% of patients\(^{[14,15]}\), who often (> 40%) clear HBSAg after some years\(^{[16,17]}\). More recently, Peg-IFNα-2a (180 μg/wk for 12 mo) was reported to induce biochemical and virological response rates of 35% at 24 wk post-treatment\(^{[18]}\), which decreased with further follow-up to 25%-30% at 1-3 post-treatment years\(^{[19,20]}\). Again, 35% of sustained responders lost HBSAg over the 3-year post-treatment follow-up\(^{[21]}\). On the other hand, 12-mo courses with oral antivirals achieve high on-therapy response rates (> 75%), but sustained off-therapy responses are rare (< 8%-11%)\(^{[22-24]}\) and therefore these agents are only given as long-term therapies.

Anti-HBV treatment is also given for finite duration in chronic inactive HBV carriers who receive immunosuppressive therapy\(^{[25-27]}\). In such cases, most of the data comes from pre-emptive LAM therapy, which has been shown to prevent or ameliorate the course of HBV reactivation\(^{[28,29]}\). However, it is anticipated that all oral anti-HBV agents will also be effective in the prevention of HBV reactivation, while the newer, more potent agents are expected to be more effective in patients who develop clinically apparent HBV reactivation after immunosuppressive therapy. Pre-emptive oral anti-HBV therapy should ideally start at least 2 wk before the onset of immunosuppressive therapy and should continue for at least 6-12 mo after the completion of immunosuppressive courses\(^{[28]}\).

**Long-term therapies**

Long-term or “maintenance” therapy is the most commonly used treatment strategy in CHB, because IFNα/Peg-IFNα as a therapy of finite duration can achieve sustained off-therapy responses only in a minority of cases\(^{[3,4,5,30]}\), while a proportion of patients do not wish to be treated with IFNα/Peg-IFNα because of the frequently anticipated side effects or cannot tolerate or have contraindications to IFNα/Peg-IFNα therapy\(^{[40,41,49]}\). Only oral antiviral agents are used as long-term therapies because of their good tolerability, safety profile and on-therapy efficacy\(^{[3,40,41]}\). In particular, for patients with HBV decompensated cirrhosis, life-long treatment with a potent oral anti-HBV agent is the only possible therapeutic option\(^{[3,4]}\).

In HBeAg-positive CHB, prolongation of therapy with oral antiviral agents has been shown to increase the probability of HBeAg seroconversion, although the interpretation of most of such long-term data needs close scrutiny as protocols for treatment after one year have differed markedly. The duration of therapy after HBeAg seroconversion induced by oral antivirals seems to be rather important for the maintenance of response\(^{[5,31]}\). There are no good studies to define the optimal duration of antiviral therapy, but most experts and recommendations now agree that any oral antiviral agent should continue for at least 6 mo after HBeAg seroconversion in order to maximize the possibility of sustained off-therapy responses\(^{[41]}\). Thus, treatment may stop after a certain consolidation period in HBeAg-positive CHB patients who achieve HBeAg seroconversion.

In HBeAg-negative CHB, however, it is still unclear whether long-term courses with oral antivirals can induce sizeable sustained off-therapy response rates. In particular, there are some conflicting reports for long-term LAM courses\(^{[32-34]}\) and one encouraging report for ADV\(^{[35]}\). In the latter study, 67% of 33 patients maintained sustained off-therapy biochemical and virological (HBV DNA < 50 000 cp/mL) remission for a median of 17 mo after discontinuation of a 4-5-year effective ADV course\(^{[36]}\). Thus, sustained off-therapy responses may be achieved in a proportion for HBeAg-negative CHB patients treated successfully for some years with oral antivirals, but more studies are needed before firm conclusions can be drawn.

**Viral resistance**

The main limitation of long-term therapies with antiviral agents is the progressively increasing rates of viral resistance due to selection of treatment resistant HBV mutant strains\(^{[37,38]}\). The emergence of genotypic viral resistance is clinically expressed by the subsequent development of virological breakthrough or secondary antiviral treatment failure, which is usually defined as reappearance or ≥ 1 log₁₀ IU/mL increase after initial lack of detection or initial ≥ 1 log₁₀ IU/mL reduction of serum HBV DNA\(^{[39,40]}\). Genotypic resistance may be also detected in patients without virological response or with primary antiviral treatment failure (no or < 1
log_{10} IU/mL decrease of HBV DNA), while virological breakthroughs may also develop from non-compliance to therapy\textsuperscript{(61,85,94)}. Virological breakthroughs are usually followed by biochemical breakthroughs\textsuperscript{(87,88)}, which eventually worsen liver histology\textsuperscript{(87,99)} and may even result in decompensation and death, particularly in patients with pre-existing cirrhosis\textsuperscript{(21,22,32,96)}.

Viral resistance may develop under any anti-HBV oral agent, but the rate of resistance differs markedly among the different agents. Long-term LAM monotherapy results in rather high rates of resistance due to emergence of HBV strains with mutation within the YMDD motif (rtM204V/I with or without rtL180M)\textsuperscript{(90,91,94,95,97)}. LAM resistance rates usually exceed 15%-20% at year-1 and 60%-65% at year-4\textsuperscript{(90,91,92,93,97)}. Due to the high probability of resistance, LAM monotherapy is not currently considered as an optimal first-line long-term therapy for CHB\textsuperscript{(94,95)}. However, LAM is still used in many countries because of its low cost. Resistance also increases progressively with prolongation of ADV monotherapy but at much slower rates compared to LAM\textsuperscript{(98)}. There are no good long-term ADV data in naïve patients with HBeAg-positive CHB. In HBeAg-negative CHB, ADV resistant strains (rtN236T and/or rtA181V/T mutations)\textsuperscript{(63,71,79)}, first emerge during the second year of therapy reaching cumulative rates of 3% at week-96 and 29% at week-240\textsuperscript{(96)}. Resistance to ETV in nucleoside naïve CHB patients seems to be rather rare, since it has been detected in < 1.5% of naïve patients treated with ETV monotherapy for up to five years\textsuperscript{(96)}. ETV resistance requires selection of two LAM resistant mutations (rtM204V/I and rtL180M) and at least one additional substitution (rtI169, rtT184, rtS202, or rtM250)\textsuperscript{(93)}. TBV also selects for mutations in the YMDD motif with only rtM204I resistant strains being detected to date\textsuperscript{(98)}. TBV resistance has been observed in 4.4% and 21.6% of HBeAg-positive and 2.7% and 8.6% of HBeAg-negative CHB patients treated with TBV for 1 and 2 years, respectively\textsuperscript{(98,99)}. No resistance to TDF has been reported to date after 18 mo of therapy in monoinfected CBH patients.

Resistance is the major limitation of long-term oral antiviral therapy, therefore its management is of great importance. First, there are several strategies to prevent the development of resistance. Such strategies include: (1) the use as first-line therapy of agents with high genetic barrier or low resistance profile, such as TDF and ETV; (2) the non-use of agents with high probability of resistance, such as LAM; and (3) the careful on-treatment monitoring and the prompt modification of therapy that does not result in complete suppression of HBV replication. Since residual viremia at 6 mo of TBV or LAM and at 12 mo of ADV monotherapy represents the strongest risk factor for subsequent resistance\textsuperscript{(7,88)}, some treatment algorithms suggest that antiviral therapy should be modified in CHB patients who remain viremic after the first 6 or 12 mo therapy with these agents.

Whatever strategy is adopted, resistance may eventually develop and therefore management of HBV strains with resistance against some agents is often required. The wide use of LAM monotherapy in CHB during the last 7-8 years, an anti-HBV therapeutic strategy with a poor resistance profile\textsuperscript{(83,86)}, has progressively increased the numbers of patients with LAM resistant HBV mutant strains\textsuperscript{(97,98)}. ADV, ETV (1.0 mg daily) and TDF have been shown to be effective in patients with LAM resistance\textsuperscript{(80,82-85)}. Pre-existing LAM resistant mutations favour the emergence of resistance to ETV\textsuperscript{(77,91)}, therefore the cumulative ETV resistance rates are substantially higher in LAM resistant than in naïve patients (6% at year-1 and 51% at year-5)\textsuperscript{(76)}. These data make ETV a less attractive therapeutic option for the long-term treatment of patients with LAM resistance. The prompt addition of ADV to on-going LAM therapy was for years the treatment of choice for CHB patients with LAM resistance\textsuperscript{(91,94,97,99,90)}. However, after the recent license of TDF, which is a more potent agent for both naïve and LAM resistant patients compared to ADV, TDF will probably be used for the treatment of patients with LAM resistance.

In vitro data and clinical studies reported that ADV resistant mutants are susceptible to LAM, ETV and TBV\textsuperscript{(90,93,81,84,90)}. Some recent in vitro data, however, suggested that LAM, ETV and TBV are effective against the N236T HBV mutant strain, which represents the most frequent ADV resistant mutant, while all three agents may have relatively reduced efficacy against the A181V HBV mutant strain, which seem to be more sensitive to TDF\textsuperscript{(91)}. It should be noted that LAM should be avoided in patients with prior LAM resistance who develop ADV resistance under ADV monotherapy, as re-introduction of LAM was reported to be associated with rapid re-emergence of LAM resistant strains\textsuperscript{(99)}. There are very few data regarding management of patients with ETV or TDV resistance. Since resistance against these two agents requires the presence of M204V/I (± L180M) mutations, LAM will be ineffective. However, according to in vitro resistance data and the type of resistant mutations, ADV or now, TDF, seem to be the most reasonable currently available therapeutic options for patients with ETV or TDV resistance due to lack of cross-resistance\textsuperscript{(14)}.

CONCLUSION

The decision to treat any patient with chronic HBV infection should be based on reasonable clinical judgment. Treatment should be given to all chronic HBV patients with HBV DNA > 20000 IU/mL, elevated ALT > 2 xULN, regardless of HBeAg status. Liver biopsy does not affect the therapeutic decisions in this group of patients and therefore has only prognostic significance. In contrast to above, treatment indications remain debatable in the group of patients in the HBeAg-positive immunotolerant phase (high HBV DNA and normal ALT) as well as in marginal HBeAg-negative chronic HBV patients. Liver biopsy is extremely important for therapeutic decisions in patients with marginal ALT elevations (1-2 xULN) and/or relatively low HBV DNA levels (< 20000 IU/mL). All existing data suggest that
there is no clear cut-off HBV DNA level to differentiate inactive chronic HBV carriers from HBeAg-negative CHB patients. Any such a cut-off level would not correctly diagnose a substantial proportion of inactive carriers perhaps leading to unnecessary liver biopsies as well as a proportion of HBeAg-negative CHB patients who may not receive appropriate treatment. In clinical practice, all HBeAg-negative patients with any persistent or transient mild ALT elevation may benefit from a liver biopsy regardless of viremia levels, while HBeAg-negative patients with persistently normal ALT and HBV DNA < 20000 IU/mL should be followed for life.

Therapeutic strategies for CHB can be summarized as therapies of finite duration aiming to offer sustained off-therapy response and long-term therapies aiming to maintain remission under oral antiviral agents. Peg-IFNa, or even standard IFNa, therapy represents the only practical treatment given for finite duration, which offers a chance of sustained off-therapy response with a considerable probability of HBsAg loss. However, IFNα/Peg-IFNα therapy has relatively poor safety and tolerance profile, is contraindicated in specific patient populations and eventually achieves sustained off-therapy responses in the minority of CHB patients. Long-term treatment with oral anti-HBV agents represents the therapeutic option for the majority of chronic HBV patients who require treatment. They achieve high initial on-therapy biochemical and virological response rates, but viral resistance may develop with prolongation of therapy. Therefore, judicious use of oral anti-HBV agents is recommended, particularly in patients with mild liver disease. The optimal strategy for oral anti-HBV therapy with the best long-term cost/benefit ratio has not been completely clarified. LAM monotherapy is associated with the highest resistance rates and therefore is considered as a suboptimal first-line long-term monotherapy in CHB. However, despite the current availability of more potent agents with better resistance profile, such as ETV and TDF, which have become the treatment of choice in Western countries, LAM is still widely used in many parts of the world because of its low cost. Regardless of the anti-HBV agent used, compliance should always be ascertained and most current guidelines recommend HBV DNA testing at least every 6 mo for the prompt diagnosis of lack of response or virological breakthroughs and timely treatment modification. Whether the 6-monthly HBV DNA determinations are necessary during the long-term treatment with any anti-HBV agent, even those with very low resistance rates after 4-5 years of therapy, is currently unclear.

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