Chronic HBV infection with persistently normal ALT b. not to treat

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Introduction

Chronic hepatitis B (CHB) is a lifelong, progressive and potentially fatal disease if not properly treated. Fortunately, successful therapy with antiviral agents resulted in sustained improvements in virologic, biochemical, histologic features of disease and clinical outcome. Although the recent development of a new and potent anti-hepatitis B virus (HBV) agents may offer many therapeutic options against HBV, there are still unsolved issues and areas for the optimal antiviral therapy. The various clinical courses and different status of the diseases, the variable response to antiviral agents, and the lack of long-term outcome of antiviral treatment contribute to the difficulties in establishment of ideal guidelines, particularly in some special patient groups [1]. It is very important to establish optimal guidelines for whom to treat and when to start, as well as how to treat in Asian patients with CHB.

An individual patient's alanine aminotransferase (ALT) level is an important factor in the decision to initiate the treatment of CHB because the elevated ALT levels indicate immune-mediated inflammation to eliminate HBV-infected hepatocytes and a higher rate of hepatitis B virus e antigen (HBeAg) seroconversion [1–3]. However, up to 40–50% of all HBeAg-positive patients may have normal ALT levels for prolonged periods [4]. The primary goal of treatment for CHB is to induce sustained suppression of HBV replication and to prevent progression of disease. APASL guidelines recommended that HBeAg-positive patients

with HBV DNA levels of $\geq 20,000$ IU/ml ($\geq 10^5$ copies/ml) and elevated ALT levels should be considered for treatment. However, the following issues remain unsettled: Should patients with an ALT level of less than two times upper limit of normal (ULN) be treated, and if so when and how? At that time, APASL guidelines recommended that patients with persistently normal or minimally elevated ALT should not be treated except in cirrhotic patients, but need adequate follow-up [1]. The newer therapeutic options have been shown to offer clinical benefits over lamivudine and may represent better therapeutic choices. Emerging evidence suggests that the more appropriate HBV DNA threshold for the treatment of HBeAg-negative patients is $\geq 2,000$ IU/ml ($\geq 10^4$ copies/ml) [2, 3]. This review discusses the key issues and current challenges in the management of chronic HBV infection with persistently normal ALT (PNALT), which is usually defined as ALT remaining normal for at least 2 years in periodic biochemical examinations, to treat or not to treat [5].

Key issues and challenges

It is important to recognize that most arguments for expansion of candidates for antiviral treatment up to patients with PNALT are also based upon the natural course of CHB and cost-effectiveness of such therapy. The understanding of natural course of CHB might help to decide whether we should treat or not such patients.

The natural history of chronic HBV infection can be conventionally divided into four phases in relation to HBV DNA level, HBeAg status, and serum ALT levels [6]. After the immune tolerant phase characterized by high serum HBV DNA levels, normal ALT, and positive HBeAg, most HBV carriers enter into the immune clearance phase,

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during which the serum ALT levels increase and HBeAg converts to anti-HBe. Such HBeAg seroconversion usually represents a transition from CHB to an inactive HBsAg carrier state in which there are lower levels of serum HBV DNA and little evidence of clinical hepatitis. However, a proportion of patients experience HBV replication and sustained or intermittent ALT increases in spite of HBeAg seroconversion owing to the emergence of so-called pre-core and double basic core promoter mutation [7, 8]. Hence, the clinical course and prognosis vary significantly from patient to patient, especially in patients who are infected with HBV in early period of life.

Most Asian patients acquire HBV infection through vertical or early horizontal transmission and are often diagnosed during the immune-tolerant phase of infection, when serum HBV DNA levels are high but ALT values are persistently normal [9]. These patients, who are HBeAg-positive with PNALT and high HBV DNA levels, are usually young and have minimal liver disease. In addition, patients with PNALT tend to have a poor response to antiviral therapy [10–15] and often are not considered for treatment. Therefore, current guidelines do not recommend treatment for such group of patients.

Recently, this principle has been challenged with proposals to expand the candidates for anti-viral therapy, including the patients with viremia and PNALT. In a longitudinal cohort study of 3,653 CHB patients, it was demonstrated that the incidence of HCC increased with serum HBV DNA level at study entry in a dose–response relationship ranging from 108 per 100,000 person-years for HBV DNA level of less than 300 copies/ml to 1,152 per 100,000 person-years for HBV DNA level of 1 million copies/ml [16]. Recent other studies also supported that high levels of HBV DNA could be a more important factor than ALT level for the subsequent development of cirrhosis and HCC [16–18]. Now, there is no argument to recommend antiviral therapy for patients with compensated cirrhosis who have HBV DNA levels of $\geq 2,000$ IU/ml, regardless of ALT level [19]. As significant histologic diseases were found in asymptomatic HBsAg carriers >40 years with PNALT, liver biopsy may be considered in older patients. Therefore, older age (>40 years) as well as high level of HBV DNA could be risk factors associated with the progression of HBV-related liver disease [20–22]. Furthermore, Kim et al. [23] reported that current upper normal levels of serum ALT might not be truly normal.

Should we recommend treatment for patients with high level of HBV DNA as early as possible, regardless of ALT level?

The above-mentioned prospective study of large cohorts from Asia was not enough to support the recommendation of antiviral therapy for those patients [16]. HBV DNA level was measured only one time at the entry in that study.

Taking into account the sustained effect of viral replication on HCC development, it may be argued that such single measurement of HBV DNA could truly represent the dynamic nature of HBV replication. In addition, their mean age in these studies at enrollment was around 40 years, and 85% of the cohorts were HBeAg-negative. These data indicate that high levels of HBV replication persisting for more than four decades are associated with an increased risk of HCC [3]. Notwithstanding, the authors suggested that elevated serum HBV DNA level ($\geq 10,000$ copies/ml) is a strong risk predictor of HCC independent of HBeAg, ALT, genotype, and presence of cirrhosis. Besides serum HBV DNA levels, the level of ALT was predictive for HCC occurrence. While the incidence of HCC was 337 per 100,000 person-years among 3,435 (94%) patients with ALT <45 IU/l, it was 1,342 per 100,000 person-years among 218 (6%) patients with ALT ≥ 45 IU/l at study entry.

In a study of a long-term outcome of 188 patients with CHB based on histological grade and stage [24], the serum ALT level at the time of biopsy was well correlated with the histological grade of lobular and porto-periportal activity. Interestingly, the probability of developing cirrhosis, decompensation, and HCC was significantly higher in patients whose ALT levels were persistently elevated than in patients whose ALT levels were normally sustained. Serum ALT level significantly represented the histological inflammatory activity and long-term prognosis of patients with normal ALT was favorable than those with elevated ALT. In a cohort study of 57 Chinese CHB patients with immune-tolerant phase, nine patients (15.8%) had developed elevated serum ALT during follow-up [25]. Disease progression, which was defined as at least a 1-point increase in fibrosis score in liver biopsies performed at entry and at the end of study, was greater in patients who developed elevated serum ALT compared with those who remained in the immune-tolerant phase (5 of 9 vs. 3 of 48, respectively, $P = 0.001$). From this prospective longitudinal study, they concluded that HBV-infected patients in the immune-tolerant phase do not require antiviral therapy, but should be monitored for transition to the immune clearance phase due to slow disease progression. Accordingly, the data from this cohort study contradicts the expansion of candidates for antiviral therapy to CHB patients with viremia and PNALT.

Treatment approaches

Although the extent of hepatocyte necrosis and the degree of ALT elevation do not always correlate, patients with PNALT tend to have a poor response (HBeAg loss or seroconversion) to antiviral therapy and often are not considered for treatment. The response to IFN- α in CHB

patients with PNALT was very poor [10]. In a study of 271 patients treated with pegylated IFN- α , the pretreatment ALT level was also a predictor for HBeAg seroconversion [15]. Regarding lamivudine therapy, in patients with pre-treatment ALT levels < two times ULN, the HBeAg seroconversion rate was 10% after 1 year compared to 16–18% of patients with elevated ALT [11–13]. Based on the previous several multi-national clinical trials, there is a general agreement that CHB patients with PNALT should be excluded from antiviral treatment irrespective of age and ethnicity, and such an approach has been a standard therapeutic principle for CHB patients [14]. Entecavir appears to be effective in a wide range of pre-treatment HBV DNA and ALT levels. However, HBeAg seroconversion rates were lower in patients with lower ALT level, being 12, 23, and 39% among those with pre-treatment ALT <2, 2–5, and >5 times ULN, respectively [26–28]. Although both telbivudine and clevudine are known to be more potent than lamivudine in suppressing HBV replication, there are not enough data on treatment response according to pre-treatment ALT level [29–32].

Despite the absence of data on the efficacy of entecavir, telbivudine, and clevudine in patients with normal ALT, three regional associations (AASLD, EASL, and APASL) recommend that antiviral therapy for patients with chronic HBV infection should be initiated for those with HBV DNA >10⁵ copies (or 20,000 IU/ml) and ALT level >2 times ULN [1, 3]. These guidelines also suggest commencement of antiviral therapy for patients with compensated liver cirrhosis if HBV DNA is detectable in serum. This therapeutic strategy is based on the rationale that treatment is indicated if the risk of liver-related morbidity and mortality is present in the foreseeable future (10–20 years).

At this point, it should be stressed that such a therapeutic strategy as early administration of nucleos(t)ide analog in patients with PNALT might evoke the development of drug-resistance HBV mutants. A clinical trial showed that 4 years of continuous lamivudine therapy resulted in up to 67% of resistance to the drug [33]. Furthermore, resistance to adefovir and entecavir may appear more frequently in patients with pre-existing lamivudine resistance than treatment-naïve patients [34–36].

The most cost-effective strategy in the management of CHB remains unclear. In addition, the costs of therapy of CHB are considerable. Since nucleos(t)ide analog therapy may be continued indefinitely unlike interferon therapy, cumulative costs correlate directly with the duration of treatment. Considering that health insurance system in sizable proportion of countries has a strong regulation in reimbursing the cost of antiviral therapy in patients with CHB, pharmaco-economic data will be urgently needed to solve cost burden in Asian patients [37, 38].

Conclusion and recommendations

In conclusion, in the face of incomplete efficacy of approved antiviral agents, the application of therapy to CHB patients with PNALT may not be justified. Moreover, in the absence of randomized-controlled trial to evaluate the effectiveness of such therapy, there is a possibility that early administration of antiviral agents will only give an economic burden and problem of emergence of complex HBV variants. Obviously, further studies should be conducted to identify the appropriate CHB patients with PNALT in whom disease progression is more likely and for whom antiviral treatment will be more efficacious.

Recommendations for treatment of patients with PNALT

In deciding therapy for their patients with CHB, clinicians should consider not only efficacy, safety, and resistance data but also economic factors such as drug availability, reimbursement, and cost. ALT values should be considered in conjunction with the level of serum HBV DNA and patient's age and onset of HBV infection. Younger patients with an early age of infection who are HBeAg-positive with high HBV DNA levels are often immune tolerant and can be followed. However, if any clinical, biochemical, or radiologic evidence of liver disease is present, the patient can be considered for histologic assessment and possible antiviral therapy.

1. HBeAg-positive patients with HBV DNA >20,000 IU/ml and persistently normal or minimally elevated ALT. These patients should not be recommended to receive antiviral therapy and should be monitored every 3 months; Liver biopsy can be considered in older adults (>40 years) with some evidence of progressive liver disease by imaging study or Fibroscan (transient elastography). If moderate or greater inflammation (or moderate or greater fibrosis) is detected on biopsy, the patient can be considered for treatment.
2. HBeAg-positive patients with HBV DNA levels of <20,000 IU/ml (<10⁵ copies/ml) and normal ALT do not require treatment. These patients should be monitored every 3–6 months.
3. HBeAg-negative patients with HBV DNA levels of <2,000 IU/ml (<10⁴ copies/ml) and normal ALT do not recommend treatment. These patients are most often inactive HBsAg carriers and should be monitored every 6–12 months. Liver biopsy may be considered, particularly if ALT and HBV DNA levels fluctuate above the levels.

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