Review

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Follow-up and indications for liver biopsy in HBeAg-negative chronic hepatitis B virus infection with persistently normal ALT: A systematic review

George V. Papatheodoridis[1,*], Spilios Manolakopoulos[1], Yun-Fan Liaw[2], Anna Lok[3]

[1]*2nd Department of Internal Medicine, Athens University Medical School, "Hippokration" General Hospital of Athens, Greece;* [2]*Liver Research Unit, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taipei, Taiwan;* [3]*Division of Gastroenterology and Hepatology, University of Michigan Health System, Ann Arbor, MI, USA*

Background & Aims: The adequacy of monitoring HBeAg-negative patients based on ALT activity is controversial and current guidelines favor liver biopsy in HBeAg-negative cases with normal ALT and HBV DNA >2000 IU/ml. We systematically reviewed all the available histological data on HBeAg-negative patients with persistently normal ALT (PNALT) to determine the prevalence of significant liver disease and its associating factors.

Methods: Literature search to identify studies with adult HBeAg-negative patients who had PNALT as defined by the authors, a minimum follow-up of 1 year and histological data. Traditional cut-off values of normal ALT were used in all studies. The definitions of PNALT were considered as acceptable or good if there were $\geqslant$3 ALT determinations at unspecified intervals during 6–12 months or predefined intervals during $\geqslant$12-month periods, respectively.

Results: Six studies including 335 patients met our inclusion criteria. Of these, four studies with 246 patients had good or acceptable definitions of PNALT. In the latter four studies, more than minimal (usually mild) necro-inflammatory activity was observed in 10% and more than mild fibrosis in 8% of all patients (moderate fibrosis: 7%, severe fibrosis: 1%, cirrhosis: 0%), and in 3% and 5% of patients with HBV DNA $\leqslant$20,000 IU/ml, respectively.

Conclusions: Histologically significant liver disease is rare in HBeAg-negative patients with PNALT based on stringent criteria and serum HBV DNA $\leqslant$20,000 IU/ml. Such cases can be considered as true inactive HBV carriers, who require neither liver biopsy nor immediate therapy but continued follow-up.

Keywords: Hepatitis B; Inactive carrier; ALT; HBV DNA; Liver biopsy.

Received 22 July 2011; received in revised form 24 November 2011; accepted 30 November 2011

*Corresponding author. Address: 2nd Department of Internal Medicine, Athens University Medical School, "Hippokration" General Hospital of Athens, 114 Vas. Sophias Ave., 115 27 Athens, Greece. Tel.: +30 210 7774742; fax: +30 210 7706871.

E-mail address: gepapath@med.uoa.gr (G.V. Papatheodoridis).

Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HBeAg, hepatitis B e antigen; ALT, alanine aminotransferase; PNALT, persistently normal ALT; PCR, polymerase chain reaction.

Introduction

Worldwide, approximately 400 million people have chronic infection with hepatitis B virus (HBV), which usually runs a variable course lasting for decades and often the entire life, with outcomes ranging from asymptomatic carrier state to cirrhosis, liver failure, and hepatocellular carcinoma (HCC) [1–4]. The natural history of chronic HBV infection has been divided into different phases, based on hepatitis B e antigen (HBeAg) status, serum HBV DNA levels, and alanine aminotransferase (ALT) activity [1,2].

In the HBeAg-negative phases, the majority of patients remain in an inactive, low-replicative state (inactive HBV carrier state). Inactive carriers are negative for HBeAg; and have persistently normal ALT (PNALT), low or undetectable serum HBV DNA levels, minimal or no necroinflammation and generally minimal to mild fibrosis on liver biopsy. A proportion of HBeAg-negative patients, however, may progress to an immune active phase (HBeAg-negative chronic hepatitis B) with persistently or transiently elevated ALT and high serum HBV DNA levels [1–3].

Theoretically, serum levels of ALT, an enzyme that is released from hepatocytes during liver injury, should reflect the degree of liver damage [5]. However, several reports have suggested that patients with chronic HBV infection who are HBeAg negative and have normal ALT may have high serum HBV DNA levels and significant histological liver damage [6,7]. Such cases have created debates and clinical dilemmas regarding the adequacy of monitoring HBeAg-negative patients based on ALT activity only, the need for liver biopsy, and the indication for treatment [3]. We systematically reviewed all the available histological data on HBeAg-negative patients with PNALT focusing on those with serum HBV DNA below 20,000 IU/ml to determine the prevalence of significant liver disease in this setting and its associating factors.

Search strategy and selection criteria

Medline/Pubmed from January 2000 to December 2010 was searched to identify all medical literature included under the search text terms "normal ALT" or "HBV DNA", and "carriers". In addition, a manual search of all relevant review articles and the references of the retrieved original studies was performed.

All studies published in English as full papers were included, if they fulfilled all of the following criteria: (1) adult patients with HBeAg-negative chronic HBV infection and PNALT as defined by the authors, (2) minimum mean or median follow-up of 1 year, (3) data on liver histology in relation to ALT and serum HBV DNA levels in a minimum of 20 HBeAg-negative patients with PNALT. Patients with co-infections with other hepatitis viruses and/or human immunodeficiency virus, other causes of liver disease, or antiviral or immunosuppressive therapy in the past were excluded.

Literature search was performed by two independent reviewers (GVP, SM), who determined which studies might meet the inclusion and exclusion criteria. Two lists of selected papers were compared for concordance. The same two independent reviewers extracted data from the selected papers using a standardized form. Two data summary tables were prepared and compared for concordance. Discrepancies were resolved during a joint review of the papers by the two reviewers.

Studies and patients characteristics

There were 1015 manuscripts initially identified from the literature search. Of these, only five studies were included and 1010 were excluded (978 after reviewing the abstract and 32 after reading the full manuscript). A manual search of the references of the 37 manuscripts reviewed found 12 additional potentially eligible studies; one of them was found to fulfill the inclusion criteria. Thus, six studies were finally included [7–12].

In total, there were 451 HBeAg-negative patients with PNALT (from 25 to 116 patients in each study, but only 335 of them had undergone liver biopsies (from 25 to 95 patients in each study). Their mean or median age ranged from 34 to 43 years, and the majority of patients were males. The racial origin of patients varied among the studies, with two studies including patients of several races [8,10], two studies included exclusively Caucasian patients [11,12], one study had exclusively Japanese patients [9] and another study had exclusively patients from India [7]. Alcohol abuse was reported by almost no patient in five studies [7,8,10–12] and by 16% of patients in one study [9] (Table 1). The definitions of alcohol abuse varied widely among studies ranging from >20 g/day [11], >30/20 g/day in males/females during the previous year [12], >50 g/day for $\geqslant$5 years [10], >500 kg in total [9] to unspecified [7,8].

Definition of PNALT

The definition of PNALT varied widely among the six studies. The traditional upper limit of normal was used (40 IU/L in four and 50 IU/L in one study and unspecified in the remaining study), and the minimum number of ALT determinations prior to liver biopsy varied from 2 to 5. The frequency of initial ALT determinations was specifically defined in only one study [12] and the minimum duration of monitoring prior to biopsy varied from 0 to 12 months. Liver biopsies were reported to be performed at presentation in one study [11] and after a minimum follow-up of 2, 6 and 12 months in one [9], two [8,10] and two studies [7,12], respectively. There was less variation in the frequency of ALT determinations after the first year of follow-up (every 6 months in three studies [8,11,12], every 1–3 months in one study [9] and not reported in two studies [7,10]), but the duration of follow-up differed substantially among studies ranging from 2 to >48 months (Table 2). In this review, definitions of PNALT were considered to be poor if they were based on a minimum of two ALT determinations, acceptable if they were based on a minimum of three ALT determinations at unspecified intervals during a period of 6–12 months and good if they were based on a minimum of three ALT determinations at predefined intervals (at least 2 months apart) over a minimum observation period of 12 months.

Table 1. Main characteristics of studies with histological data in patients with HBeAg-negative chronic hepatitis B virus (HBV) infection and persistently normal ALT (PNALT).

Author, year [Ref.]	Study design	Primary study question	Patients, n	Age*, yr	Gender, M/F	Race, C/A/B	Alcohol abuse, n
Martinot-Peignoux *et al.*, 2002 [8]	RE-PR cohort	Correlation of HBV DNA levels and their changes with liver histology	85 (58#)	34 ± 11	46/39	45/12/28	0
Ikeda *et al.*, 2006 [9]	RE cohort	Incidence of advanced liver disease in HBeAg-negative patients with normal ALT	95	39 (18-67)	75/20	Japanese: 95	15
Lai *et al.*, 2007 [10]	RE cohort	Incidence of significant histology in patients with PNALT and HBV DNA >10,000 copies/ml	25	43	10/15	2/18/4	1
Kumar *et al.*, 2008 [7]	PR cohort	Histological lesions in patients with PNALT and HBV DNA cut-off levels as predictors of histology	116 (58#)	35 ± 15	79/37	India: 116	0
Zacharakis *et al.*, 2008 [11]	PR cohort	The role of HBV DNA levels in the long-term outcome of chronic HBV infection	95	36 (20-45)	n.a.	95/0/0	0
Papatheodoridis *et al.*, 2008 [12]	RE cohort	Severity of histological lesions in relation to ALT and HBV DNA levels	35	43 ± 13	22/13	35/0/0	0

RE, retrospective; PR, prospective; M/F, males/females; C, Caucasians, A; Asians; B, Blacks; n.a., not available.
*Age as mean ± standard deviation or median (range).
#Only 58 patients underwent liver biopsy.

Serum HBV DNA levels

Serum HBV DNA levels were determined once for each patient, usually at baseline, in three studies [7,10–12] and more than once for each patient in the remaining three studies [8,9,11]. Only the serum HBV DNA determinations closest to the liver biopsy were taken into account in our review. Serum HBV DNA levels were determined by Amplicor HBV Monitor polymerase chain reaction (PCR) assay with lower limit of detection of approximately 40–80 IU/ml in four studies [8,9,11,12] and by multiple assays with varying sensitivity in two studies [7,10]. Patients with serum HBV DNA above 2000 IU/ml were included in one study [10], between 2000 and 20,000 IU/ml in another study [12] and varying serum HBV DNA levels in the remaining four studies [7–9,11]. The median serum HBV DNA level ranged from 260 to 5084 IU/ml in five studies [7–9,11,12]; only the mean serum HBV DNA level (39,905 IU/ml) was reported in one study [10]. The maximum serum HBV DNA level ranged from 3800 to more than 300,000,000 IU/ml. Serum HBV DNA levels above 20,000 IU/ml were detected in none (0/95 and 0/35) of the patients in two studies [11,12], in only 2% (2/85) of patients in one study [8] and in 29–50% of patients (28/95 and 29/58) in two additional studies which provided such data [7,9] (Table 2).

Liver histology

Liver biopsies were evaluated by a single pathologist in three studies [8,11,12] and by two pathologists in two studies [7,9]. This information was not provided in one study [10]. The pathologists were reported to be blinded to clinical and laboratory data in all three studies providing such information [7,11,12]. The interval between the initial presentation and the liver biopsy ranged from 0 to >12 months. Different histological classification systems were used for grading of inflammation and staging of fibrosis (Table 3).

The mean or median inflammation grade and fibrosis stage were within the range of minimal to mild severity in all five studies, which reported such data [7,8,10–12]. However, there was wide variation in the proportion of patients with active histological lesions among the five studies providing such information [7–9,11,12]. In three studies from Europe [8,11,12], 99.5% (187/188) of patients were found to have minimal (grade 0–4 of 18 in the Ishak or grade 0 of 4 in the Scheuer classification system) and only one (0.5%) patient had mild necroinflammatory activity (grade 5 of 18 in the Ishak classification system), while no or mild fibrosis (stage 0–1/2 of 6 in the Ishak or stage 0–1 of 4 in the Scheuer classification system) was present in 96% (177/188) and at least moderate fibrosis (stage $\geqslant$2/3 of 6 in the Ishak classification system) in only 4% (11/188) of patients. The diagnosis of at least moderate fibrosis was based on Ishak stage $\geqslant$2 in one [12] and Ishak $\geqslant$3 in another study [8]. Fibrosis staging $\geqslant$3 was present in only 5 (3%) of these 188 patients (4 with staging score of 3, 1 with staging score of 4, none with cirrhosis (staging score of 5–6)) and it was always accompanied by minimal necroinflammatory activity (grade 1–4 of 18 in the Ishak classification system) [8,11,12]. These three studies had good (n = 2) [11,12] or acceptable (n = 1) [8] definitions of PNALT activity, ALT determinations every 6 months after the first year of follow-up, and included mainly but not exclusively Caucasian patients. Serum HBV DNA levels were below 20,000 IU/ml in 99% (186/188) of the patients in these three studies.

In contrast to the above studies, in two studies from Asia (one from Japan [9] and one from India [7]), at least mild necroinflammatory activity (HAI score $\geqslant$4 of 18 in the Knodell or Desmet classification system) was reported to be present in 81% (77/95) and 40% of cases (23/58) and at least moderate fibrosis (stage $\geqslant$2 of 4 in the Knodell or Desmet classification system) in 35% (33/95) and 14% (8/58) of patients, respectively. In the study from the USA with 72% Asian patients [10], the reported ranges of grading and staging scores revealed that cases of more than mild necroinflammatory activity and of advanced fibrosis and even cirrhosis were detected although the exact proportions of patients with advanced histological lesions could not be determined.

Besides the patients' origin, there were additional important differences between the three European and the other three studies. The Japanese study [9], which reported the highest proportion of patients with active histological lesions, had poor definition of PNALT activity prior to biopsy (ALT <50 IU/L in $\geqslant$2 determinations $\geqslant$2 months apart). Careful ALT follow-up after the biopsy showed that 55% (52/95) of the patients had abnormal ALT. In fact, 52% (49/95) of the patients in that study were reported to have a history of ALT elevation (n = 41) or evidence of advanced liver disease on ultrasonography or blood tests (n = 8) and would not meet the standard definition of inactive HBV carriers. In that same study [9], the highest prevalence of alcohol abuse was reported (16%) and 29% of patients had baseline serum HBV DNA >20,000 IU/ml but histological data according to viremia levels were not provided. In the study from India [7], there was an acceptable definition of PNALT (ALT <40 IU/L in $\geqslant$3 determinations within 12 months, but at unspecified intervals) and no defined post-biopsy ALT follow-up. In addition, this study included the highest proportion of patients with baseline serum HBV DNA >20,000 IU/ml (29/58 or 50%) and very few patients with serum HBV DNA <2000 IU/ml (9/58 or 16%). Viremia levels were found to be significantly related to the presence of active histological lesions, with at least mild necroinflammatory activity detected in 59% (17/29) of patients with serum HBV DNA >20,000 IU/ml and in 15% (3/20) of those with serum HBV DNA between 2000 and 20,000 IU/ml ($p = 0.003$) [7]. In the US study, there were both poor PNALT definition and undefined post-biopsy ALT follow-up. In addition, patients with clinical evidence of cirrhosis were included [10]. Of greater importance is that only patients with baseline serum HBV DNA >2000 IU/ml were included [10].

When the analysis was limited to the 215 patients with serum HBV DNA $\leqslant$20,000 IU/ml from the four studies with good or acceptable definitions of PNALT [7,8,11,12], more than minimal (always mild) necroinflammatory activity was reported to be present in only 7 (3%) and more than mild fibrosis in only 10 (5%) patients (moderate fibrosis: 9, severe fibrosis: 1, cirrhosis: 0). The patients with more than mild fibrosis all had minimal necroinflammatory activity. More than minimal necroinflammatory activity was present in 5 (7%) and more than mild fibrosis in 7 (10%) out of 73 patients with serum HBV DNA between 2000 and 20,000 IU/ml and in 2 (1.4%) and 1 (0.7%) of 142 patients with serum HBV DNA <2000 IU/ml.

Table 2. ALT and HBV DNA characteristics of patients with HBeAg-negative chronic hepatitis B virus infection and persistently normal ALT (PNALT).

Author, year [Ref.]	F-UP, mo	Definition of PNALT	ALT determinations			Serum HBV DNA at baseline		
			Within 1st yr of F-UP		After 1st yr	Median*	Patients with HBV DNA	Method
			n	Frequency	Frequency	IU/ml	<2000/ 2000-20,000/ >20,000	
Martinot-Peignoux *et al.*, 2002 [8]	38 ± 31 (6-132)	≤40 IU/L in 3 determinations within 6 mo	4	3 determinations within 6 mo then every 6 mo	Every 6 mo	260 (<40-35,800)	69/14/2	Amplicor HBV monitor
Ikeda *et al.*, 2006 [9]	≥2	≤50 IU/L in ≥2 determinations ≥2 mo apart	n.a.	After biopsy: every 1-3 mo	Every 1-3 mo	5023 (<80-7962,143)	33/34/28	Amplicor HBV monitor
Lai *et al.*, 2007 [10]	≥6	≤40 IU/L in ≥2 determinations ≥6 mo apart	n.a.	n.a.	n.a.	mean: 39,905	Unknown	Non-PCR/ PCR assays
Kumar *et al.*, 2008 [7]	≥12	≤40 IU/L in ≥3 determinations within 12 mo	3	n.a.	n.a.	3990 (<130-316,978,638)	9/20/29#	Digene/PCR assay
Zacharakis *et al.*, 2008 [11]	≥48	≤40 IU/L in ≥3 determinations every 6 mo within first ≥12 mo	3	Every 6 mo	Every 6 mo	520 (84-3800)	91/4/0	Amplicor HBV monitor
Papatheodoridis *et al.*, 2008 [12]	≥12	40 IU/L in ≥5 determinations every 3 mo within first 12 mo	5	Every 3 mo	Every 6 mo	5084 (2000-18,700)	0/35/0	Amplicor HBV monitor

F-UP, follow-up; mo, months; n.a., not available; PCR, polymerase chain reaction.
*Median (range) values are expressed in IU/ml (values given as copies/ml were converted to IU/ml by dividing by a factor of 5).
#Of the 58 patients who underwent liver biopsy.

Table 3. Histological characteristics of patients with HBeAg-negative chronic hepatitis B virus infection and persistently normal ALT.

Author, year [Ref.]	Single pathologist	Blind evaluation	Biopsy timing#, mo	Scoring system	Grading	Staging	Activity, min/mild/≥mod.	Fibrosis, no-mild/≥mod.
Martinot-Peignoux *et al.*, 2002 [8]	Yes	Unknown	Unknown	Ishak	2 ± 1 (0-4)	1.4 ± 0.9 (0-4)	58/0/0	53!/5
Ikeda *et al.*, 2006 [9]	No (2)	Unknown	≥2	Desmet	-	-	18/72/5	62/33
Lai *et al.*, 2007 [10]	Unknown	Unknown*	≥6	Metavir	1.4 (0-3)	0.8 (0-4)	Unknown	Unknown
Kumar *et al.*, 2008 [7]	No (2)	Yes	≥12	Knodell	3 (1-10)	1 (0-3)	35/23¶	50/8
Zacharakis *et al.*, 2008 [11]	Yes	Yes	0	Scheuer	0	0 (0-1)	95/0/0	95/0
Papatheodoridis *et al.*, 2008 [12]	Yes	Yes	≥12	Ishak	2.9 ± 0.9 (0-5)	1.0 ± 0.6 (0-2)	34/1/0	29/6

min, minimal; mod, moderate.
*Inclusion of cases with clinical cirrhosis as well.
#Mean interval from baseline to liver biopsy.
¶Twenty-three patients had at least mild necroinflammatory activity (HAI >3).
!Fifty-three patients had fibrosis score ⩽2.

Discussion

This systematic review was conducted to ascertain the prevalence of histologically significant liver disease in HBeAg-negative patients with PNALT. Our findings showed a wide range in prevalence of significant liver disease among studies that was predominantly related to the quality of the definition of PNALT and the serum HBV DNA levels. Thus, only 10% of patients had at least mild inflammatory activity and 8% had at least moderate fibrosis in the four studies with good or acceptable definitions of PNALT [7,8,11,12] compared to 81% and 35% of patients, respectively, in one study with poor criteria for PNALT [9].

Although the optimal definition of PNALT has not been established, the fluctuating nature of chronic HBV infection reasonably

justifies serial ALT determinations with a minimum of 4–5 readings 3–4 months apart within the first year of presentation, before determining whether an HBeAg-negative patient truly has PNALT. An initial follow-up of at least 1 year is supported by the finding of mild histological lesions in HBeAg-negative patients with truly PNALT during the first year [12,13]. Since the risk of developing abnormal ALT in HBeAg-negative patients with normal baseline ALT has been reported to be higher during the first year (15–20%) [12,14] and declines after 3 years of follow-up [9,14,15], frequent monitoring during the first 1–3 years is critical in determining whether a patient has PNALT.

Besides the frequency of determinations and duration of follow-up, definition of PNALT should include standardized criteria for the upper limit of normal (ULN) of ALT. Some investigators have suggested that lower cut-offs than the traditional values defined by most diagnostic laboratories (around 40 IU/L) should be used. These suggestions were derived from studies based on single ALT values in Italian blood donors [16], the associations between normal ALT and increased rates of liver related deaths in Koreans applying for life insurance [17], and high serum HBV DNA levels or increased risks of complications of liver disease in patients with chronic HBV infection [6,18]. However, several studies of chronic HBV patients with PNALT based on multiple ALT readings found that HBeAg-negative carriers with low normal or high normal ALT values according to the traditional cut-offs had similar severity of liver histological lesions and similarly excellent long-term clinical outcomes [7,12,15,19,20]. Thus, available data do not support the need for lowering the traditional cut-offs for the ULN of ALT values in patients with HBeAg-negative chronic HBV infection.

Severe liver histological lesions were rare among HBeAg-negative patients with truly PNALT. In the four studies with good or acceptable definitions of PNALT [7,8,11,12], more than a minimal (always mild) inflammatory activity was detected in only 3% and more than mild fibrosis always with minimal inflammatory activity in only 5% (moderate fibrosis: 4.5%, severe fibrosis: 0.5%, cirrhosis: 0%) of 215 patients with serum HBV DNA ⩽20,000 IU/ml. The prevalence of mild inflammatory activity and moderate fibrosis was 7% and 10% among patients with HBV DNA levels between 2000 and 20,000 IU/ml and 1.4% and 1% among those with HBV DNA levels <2000 IU/ml. Similar mild histological findings in HBeAg-negative patients with HBV DNA ⩽20,000 IU/ml

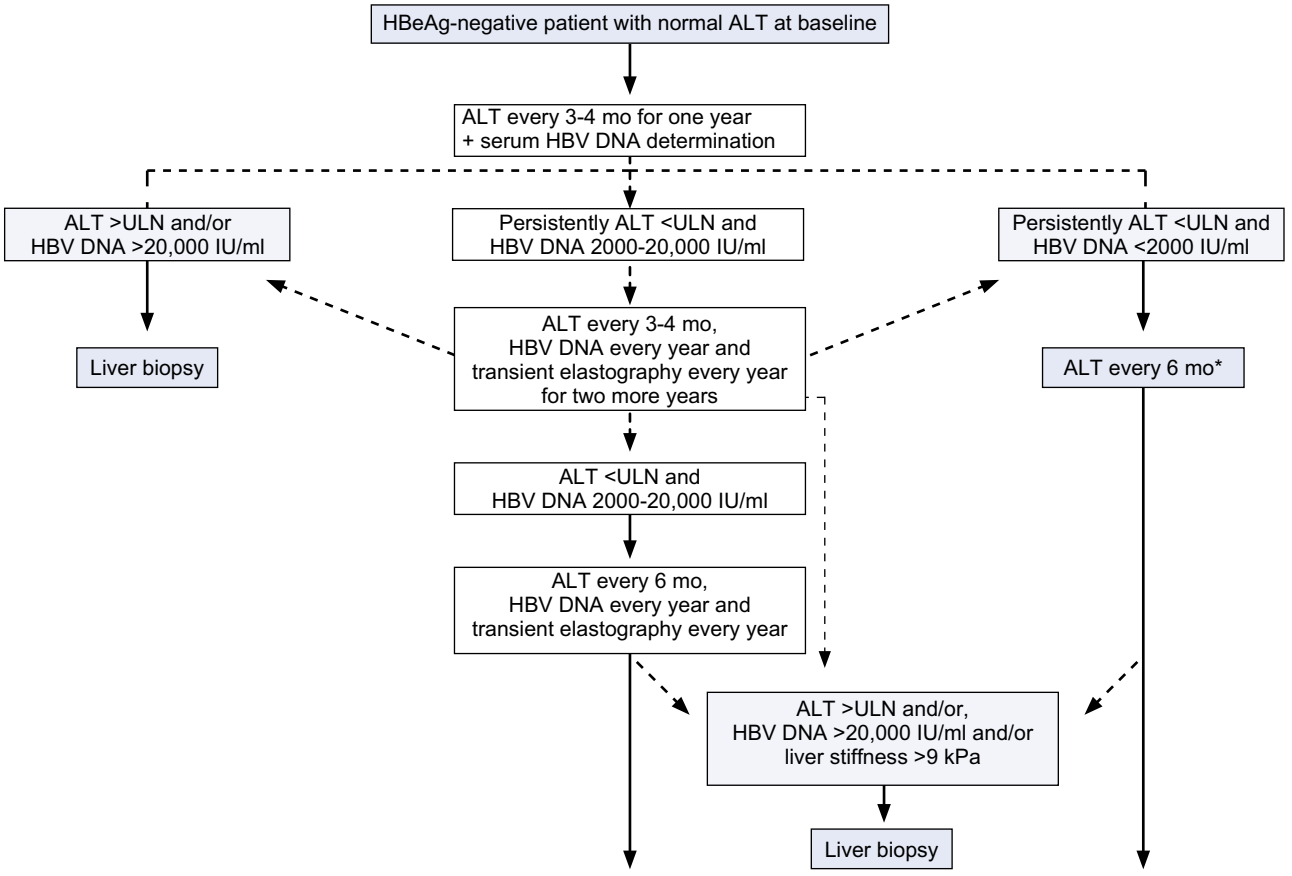

Fig. 1. Clinical algorithm for the optimal follow-up and management of patients with HBeAg-negative chronic HBV infection and normal alanine aminotransferase (ALT) activity at baseline. All patients should have ALT and HBV DNA monitoring every 3–4 months during the first year. Patients with ALT persistently below ULN and HBV DNA <2000 IU/ml during the first year may be monitored with ALT every 6 months. *Periodical HBV DNA measurements may be also helpful, although the optimal frequency of HBV DNA monitoring is unclear. Patients with ALT persistently below the upper limit of normal (<ULN) and HBV DNA 2000–20,000 IU/ml during the first year should undergo transient elastography and continue every 3–4 months ALT and annual HBV DNA and transient elastography monitoring during the second and third year because of a higher risk of exacerbations during the first 3 years, and then ALT every 6 months together with HBV DNA and transient elastography every year. Patients with abnormal ALT, HBV DNA >20,000 IU/ml and/or liver stiffness >9 kPa should be considered for liver biopsy and treatment. The optimal liver stiffness cut-off for liver biopsy needs further evaluation. All patients, including those with persistently normal ALT and HBV DNA <2000 IU/ml, should be monitored for life.

have also been reported in three additional studies with good definitions of PNALT, one from Italy [13], one from Taiwan [19] and one from the USA [21]. These studies were not included in this review because of the small number of patients who underwent liver biopsy. In particular, minimal activity and no or mild fibrosis (grade 3–4 of 18 and stage 0–1 of 6 in the Ishak classification system) were found in all 10 HBeAg-negative Italian patients with PNALT and HBV DNA levels persistently <20,000 IU/ml and at least one HBV DNA level >2000 IU/ml based on monthly ALT and HBV DNA determinations for 1 year [13], while minimal activity was found in all 9 and mild fibrosis (grade 0–3 of 18 and stage 0–2 of 6 in the Ishak classification system) in 5 of 9 HBeAg-negative Taiwanese patients with PNALT and HBV DNA persistently <20,000 IU/ml based on 6-monthly ALT and 2-yearly HBV DNA determinations for $\geqslant$10 years [19]. These data suggest that histologically significant liver disease is rare in HBeAg-negative carriers with PNALT based on stringent criteria and serum HBV DNA $\leqslant$20,000 IU/ml. Thus, such patients can be considered as true inactive HBV carriers, who require neither liver biopsy nor immediate therapy but continued follow-up (Fig. 1).

We acknowledge that a 10% prevalence of moderate fibrosis in HBeAg-negative patients with truly PNALT and HBV DNA 2000–20,000 IU/ml is not negligible. However, this was always accompanied by minimal necroinflammatory activity and the benefits of treatment in these patients is unclear. Instead of recommending liver biopsy for all of these patients, further studies to identify predictors of significant liver histology (e.g. age, serial HBV DNA, precore/core promoter HBV variant) to allow more targeted recommendation for liver biopsy in this group of patients are warranted. Alternatively, these patients may be evaluated for liver fibrosis with non-invasive methods such as panels of serum markers or liver stiffness measurement. Transient elastography has been shown to correlate with fibrosis in patients with chronic hepatitis C [22], and also in patients with chronic hepatitis B [23–25]. In chronic hepatitis B, cut-off liver stiffness values of 9–10 kPa were reported to offer satisfactory predictive values for the diagnosis of severe fibrosis [23,24], even in patients with transiently normal ALT [23]. The predictive value of elastography may be lower in HBeAg-negative patients with truly PNALT and low prevalence of severe fibrosis or cirrhosis, but this is offset by the lack of confounding by inflammation associated with high ALT or ALT flares [26], making liver stiffness measurements an ideal tool to monitor disease progression in these patients.

Apart from the possibility of severe liver histological lesions, arguments supporting treatment initiation in HBeAg-negative patients with HBV DNA >2000 IU/ml regardless of ALT have been based on concerns for increased risks of adverse long-term outcomes. These concerns were mainly generated from the finding of the population-based REVEAL study suggesting that HBeAg-negative carriers with HBV DNA >2000 IU/ml have increased risk of cirrhosis, HCC and liver-related mortality regardless of ALT [27]. However, most of the analyses were based on baseline HBV DNA and ALT levels or paired values (baseline and after ~10 years follow-up). Thus, these data cannot be generalized to HBeAg-negative patients with truly PNALT. Indeed, a long-term study from Taiwan showed no evidence of disease progression over 10 years in HBeAg-negative patients with truly PNALT and HBV DNA levels up to 20,000 IU/ml [19].

Another argument for initiating therapy immediately in patients with PNALT and HBV DNA levels >2000 IU/ml is that patients may not attend regular follow-up and would miss the opportunity to initiate treatment at the right moment. However, these same persons may not be adherent to long-term or lifelong antiviral therapy. Adherence to nucleos(t)ide analogs for CHB in clinical practice has been shown to be suboptimal and these patients may not derive the desired benefit of preventing disease progression and may instead run the risk of antiviral drug resistance [28].

Summary and recommendations

In summary, we found very few studies with liver histology in an adequate number of HBeAg-negative carriers with PNALT. Available data showed that in those studies with stringent definition of PNALT, histologically significant liver disease was rare, particularly in patients with serum HBV DNA <2000 IU/ml. Even among HBeAg-negative carriers with serum HBV DNA between 2000 and 20,000 IU/ml, histologically significant liver disease is uncommon if they meet stringent criteria for PNALT. These data do not support routine liver biopsy or treatment for HBeAg-negative carriers with PNALT and serum HBV DNA 2000–20,000 IU/ml. Instead, we recommend lifelong monitoring with more frequent testing during the first 3 years. Patients with high baseline viremia levels have higher risk of subsequent exacerbation [14,29]. These patients may benefit from non-invasive assessment of liver fibrosis. Liver biopsy should be recommended if ALT becomes abnormal, HBV DNA increases above 20,000 IU/ml or liver stiffness exceeds 9 kPa on reliable measurements, although the most appropriate liver stiffness cut-off needs further evaluation (Fig. 1).

Key Points

- Current guidelines favour liver biopsy in HBeAg negative chronic HBV patients with normal ALT and HBV DNA levels >2000 IU/ml
- However, the existing data show that histologically significant liver disease is rare in HBeAg-negative patients with persistently normal ALT based on stringent criteria (ALT determinations at least every 3-4 months during the first year of follow-up) and serum HBV DNA ≤20,000 IU/ml
- Therefore, HBeAg-negative chronic HBV patients with persistently normal ALT can be considered as true inactive HBV carriers, even if they have serum HBV DNA levels between 2000-20,000 IU/ml. These patients require neither liver biopsy nor immediate therapy but continued follow-up

Conflict of interest

George Papatheodoridis has received research grants from Bristol-Myers Squibb, Gilead and Roche and has acted as an advisor and/or lecturer for Bristol-Myers Squibb, Gilead, Novartis, Roche, Schering-Plough/Merck.

Spilios Manolakopoulos has received research grants from Bristol-Myers Squibb and has been acted as an advisor and/or lecturer for Bristol-Myers Squibb, Gilead, Novartis, Roche, Schering-Plough/Merck.

Yun-Fan Liaw has been involved with clinical trials and served as a global advisory board member for Bristol-Myers Squibb, Gilead, Novartis, Roche.

Anna Lok has received research grants from Bristol-Myers Squibb, Gilead, Glaxo-Smith-Kline, Roche/Genentech, Schering/Merck and has attended advisory meetings for Bristol-Myers Squibb, Gilead, Roche.

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