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Monitoring and comorbidities in patients with chronic hepatitis B currently treated with nucleos(t)ide analogs

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Abstract

Background Long-term monotherapy with nucleos(t)ide analogs (NAs) represents the treatment option for the majority of patients with chronic hepatitis B (CHB), an aging population with a greater likelihood of comorbidities. We assessed the prevalence of concurrent non-hepatic diseases and the safety monitoring in a large cohort of CHB patients receiving NAs and their potential impact on disease outcomes.

Methods We included 500 consecutive CHB patients from 5 major tertiary Greek centers, under long-term therapy with an NA. Epidemiological/clinical characteristics and data on concomitant disease, drug use and investigations ordered were collected.

Results The mean age was 58 years and 66% were male. Most patients were receiving tenofovir disoproxil fumarate (TDF, 60%) or entecavir (ETV, 37%) monotherapy. Decompensated cirrhosis at baseline was present in 10%, while hepatocellular carcinoma (HCC) under therapy developed in 21 patients. The median duration of total NA therapy was 56 and of latest therapy 42 months. The most common (prevalence >10%) comorbidities were hypertension (28%), non-HCC cancer(s) (12%), and diabetes (11%). Patients with a longer duration of latest therapy (≥4 vs. <4 years) were older (mean age: 58 vs. 56 years, P=0.004), had more frequent history of prior use of NA(s) (53% vs. 35%, P<0.001), and less frequent liver decompensation (5% vs. 13%, P=0.008) and non-HCC cancers (8% vs. 15%, P=0.020). HCC developed more frequently in patients with than in those without diabetes (11% vs. 3%, P=0.022).

Conclusion Greek CHB patients currently treated with NAs, almost exclusively ETV or TDF, are often older than 60 years, have several comorbidities, and thus require careful management.

Keywords Chronic hepatitis B, nucleos(t)ide analog, comorbidities, monitoring

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Introduction

Chronic infection with hepatitis B virus (HBV) constitutes an important global public health problem [1]. While its prevalence has been decreasing as a result of comprehensive vaccination programs and improvement in socioeconomic status, the number of cases with chronic HBV infection is not decreasing dramatically because of the increasing global population [1,2]. In addition, given the increasing age of patients with HBeAg-positive or HBeAg-negative chronic hepatitis B (CHB), the active phases of chronic HBV infection, increases in morbidity and mortality are expected in the near future [1]. A significant development contributing to the better management of this disease has been the introduction of nucleos(t)ide analogs (NAs). The potent long-term inhibition of HBV replication by NAs has repeatedly been shown to improve all clinical outcomes in CHB patients. Moreover, NAs have been shown to have an advantageous tolerance and safety profile, very favorable compared to pegylated interferon alpha, the other therapeutic option for CHB patients [3,4]. Furthermore, they comprise the only choice for a variety of patient

subgroups, such as those with advanced cirrhosis, indications for immunosuppression, or extrahepatic manifestations [3,5,6]. Therefore, the vast majority of CHB patients are currently treated with NAs. There are quite a few NAs approved for use in CHB, but the use of those with a low genetic barrier to virologic resistance, such as lamivudine, adefovir dipivoxil and telbivudine, is not recommended. Thus, the currently recommended NAs for naïve CHB patients are entecavir (ETV), tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF), while TDF and TAF are the only options for patients who have previous exposure and are particularly resistant to lamivudine or any other nucleoside analog (telbivudine, ETV) [1].

Therapeutic administration of ETV, TDF or TAF provides an excellent option for the long-term management of CHB, with the caveat that it rarely leads to HBV surface antigen (HBsAg) clearance or "functional cure". Therefore, treatment is usually continued indefinitely, making careful long-term monitoring necessary [1,7,8]. Given that the CHB patient population is gradually aging, additional health issues may either coexist from the onset of therapy or accumulate on the way. Thus, current CHB patients treated with NAs have a greater likelihood of coexisting comorbidities and more contemporaneous use of other pharmaceutical products.

Regarding the safety monitoring of CHB patients treated with NAs, baseline and periodical on-therapy laboratory tests are recommended, with special focus on renal function [1]. Although long-term NA administration is generally considered to have minimal effects on kidney function and bone mineral density, based mostly on long-term ETV and TDF data, there have been reports of progressive worsening of renal function and bone mineral density as well as of renal tubulopathy and even Fanconi syndrome in patients on TDF [10-12]. On the other hand, recent phase III trials have shown that, in terms of renal and bone laboratory parameters, TAF has a more favorable safety profile than TDF [13,14]. Currently, selection of ETV or TAF instead of TDF, as well as switching from TDF to ETV or TAF, is recommended for CHB patients with or at high risk for renal or bone disorders, with TAF being the only recommended option for lamivudine-experienced patients [1].

In view of the aforementioned issues, we decided to conduct a study in CHB patients receiving NAs with the following objectives: a) to assess the prevalence of underlying concurrent non-hepatic medical issues and their potential impact on the liver disease course and outcomes; and b) to observe the safety monitoring in real-life situations at tertiary hepatology centers in our country.

Patients and methods

Patient population

A retrospective analysis was conducted in a cohort of 500 consecutive CHB patients receiving NAs and visited the outpatient liver clinics of 5 tertiary Hepatology Centers in our country between January and April 2017; 100 patients from each center were included. All patients fulfilled the national indications for treatment with NAs. In particular, all patients had chronic HBV infection, defined by HBsAg seropositivity for at least 6 months before the onset of NA therapy, and a) HBV DNA >20,000 IU/mL and alanine aminotransferase (ALT) activity higher than twice the upper limit of normal; or b) HBV DNA >2000 IU/mL and/or elevated ALT and at least moderate necroinflammatory activity and/or fibrosis stage; or c) cirrhosis and detectable HBV DNA, regardless of ALT levels. The only exclusion criterion was the presence of coinfection with hepatitis D virus, hepatitis C virus or human immunodeficiency virus. All patients were treated with NA(s) at the recommended daily dosage, according to the summary product characteristics of each medication, while the recommended dosage adjustments were applied in patients with glomerular filtration rate (eGFR) <50 mL/min, as estimated by serum creatinine levels, and patient characteristics using the Cockcroft-Gault equation.

All relevant demographic, clinical and pharmacologic information, in addition to data regarding concomitant diseases and investigations ordered, were retrospectively collected from the patient records and entered into a specifically designed database. In particular, the parameters recorded were: age, nationality, height, weight, body mass index (BMI), alcohol and smoking habits, diagnosis date, previous (including prior lamivudine use) and latest treatments (with initiation and end dates if applicable), history of liver biopsy, liver stiffness measurements, presence of decompensated cirrhosis at onset of NA treatment, hepatocellular carcinoma (HCC) development during NA treatment, concomitant (non-hepatic) diseases, other medications taken, tests performed, and frequency of relevant investigations while on NA therapy. At least moderate fibrosis or compensated cirrhosis was diagnosed by either liver biopsy, or liver stiffness >9 or >14 kPa by reliable liver elastography, respectively. Decompensated cirrhosis was diagnosed in patients with development of ascites, history of hepatic encephalopathy or variceal bleeding and/or jaundice (total bilirubin >3 mg/dL) of non-obstructive cause. All patients were informed regarding the anonymous use of their personal data and consented to their inclusion in the study.

Statistical analysis

The SPSS and GraphPad statistical software programs were used for the analysis. Quantitative variables were expressed as mean±standard deviation (SD) or as median (range) values, depending on whether they had normal or abnormal distribution, respectively. Categorical variables were compared using the chi-squared test, whereas the *t*-test and ANOVA testing (where more than 2 groups were compared) were used for comparisons between quantitative variables. Spearman's *r*-test was used to assess correlations between quantitative variables. In all cases, an alpha level of <0.05 was considered to be statistically significant.

Results

Patient characteristics

The main patient- and disease-related characteristics are shown in Table 1. Of the 500 patients, 46% were older than

60 years. The majority of patients (n=407, 81%) were Greek and a considerable minority were immigrants living in Greece and born in Albania (n=59, 12%). Interestingly, the Greek patients in our cohort were significantly older than those born in Albania or other countries (60.5±14.2 vs. 45.5±11.0 years, P<0.001). Greek patients also tended to have higher weight and BMI, but this difference may be attributed to their being older, as it did not remain significant after adjustment for age. There were no significant differences in the basic demographic characteristics among the patients of the different tertiary centers participating in the study (data not shown).

As TAF was not available in Greece at the time of patients' enrolment in this study, most patients were receiving either TDF (60%) or ETV (37%) monotherapy, while only a small minority were receiving combination treatment with both TDF and ETV. The median duration of antiviral therapy with the last NA was 42 months (range 1-186), while the median duration of the total antiviral therapy was 56 months (range 1-212). A substantial portion of the patients of this cohort were lamivudine-experienced (31%), while two thirds of this subgroup had documented lamivudine resistance. In the lamivudine-experienced group, 85% of the patients were receiving TDF, while this percentage rose to about 90% in the subgroup of patients with documented lamivudine resistance.

Before treatment initiation, liver biopsy had been performed in 124 (25%) patients, while liver stiffness measurement by FibroScan or Shear-Wave elastography was available in another 210 (42%) cases. At least moderate fibrosis was detected in 67% and compensated cirrhosis in 21% of 334 patients with pretreatment assessment of fibrosis. Of our study population, 48 (10%) patients had decompensated cirrhosis at the onset of the last antiviral therapy, while no new case of liver decompensation was observed after the onset of the last NA. HCC was diagnosed in 21 (4%) patients during on-treatment follow up. No patient died or underwent liver transplantation. Virological remission defined by undetectable serum HBV DNA was observed in 96% and biochemical remission defined by normal ALT in 92% of 422 patients who had completed at least 12 months of last NA therapy.

We also examined our patient characteristics in relation to the duration of treatment with their latest NA, which also defines the

Table 1 Clinical and demographic characteristics of 500 consecutive patients with chronic hepatitis B receiving nucleos(t)ide analogs

Characteristics	Value
Age, years	57.7±14.9 (20-88)
Male sex	329 (66%)
Body mass index, kg/m^2	26.4±4.3 (15.6-43.0)
Place of birth	
Greece	407 (81%)
Albania	59 (12%)
Other country	34 (7%)
Alcohol consumption	
None	375 (75%)
Social use (<40/20 g/day for males/females)	105 (21%)
Abuse (≥40/20 g/day for males/females)	20 (4%)
Smoking	
Never smoked	353 (71%)
Former smoker	52 (10%)
Current smoker	95 (19%)
Latest antiviral treatment	
Tenofovir disoproxil fumarate (TDF)	301 (60%)
Entecavir (ETV)	185 (37%)
TDF+ETV	14 (3%)
Duration of last antiviral treatment, months	42 (1-168)
Previous antiviral treatment, Yes	213 (43%)
Total duration of antiviral treatment, months	56 (1-212)
Patients with lamivudine experience	156 (31%)
Patients with lamivudine resistance	104 (21%)
At least moderate fibrosis before the onset of last therapy	224/334* (67%)
Compensated cirrhosis before the onset of last therapy	70/334* (21%)
Decompensated cirrhosis at the onset of last therapy	48 (10%)
Hepatocellular carcinoma diagnosed during therapy	21 (4%)

Quantitative variables are expressed as mean±SD or median (range) values

*334 patients had available liver biopsy or reliable liver elastography before the onset of their latest antiviral therapy

time when treatment with that NA began. Using 4 years (close to the mean value of 45 months for latest treatment duration) as cutoff, our patients were classified into those with old (>4 years) and recent (≤4 years) treatment onset. The main differences in the patient characteristics in relation to their duration of treatment are summarized in Fig. 1. In particular, patients with old NA therapy onset were older (mean age: 58 vs. 56 years, P=0.004), more likely to have received another NA in the past (53% vs. 35%, P<0.001), more likely to have undergone liver biopsy at baseline (39% vs. 14%, P<0.001), less likely to have decompensated disease at baseline (5% vs. 13%, P=0.008), and less likely to have concurrent non-hepatic neoplasia (8% vs. 15%, P=0.020).

Comorbidities

The most common (prevalence >2%) concurrent conditions observed in our patient cohort can be seen in Table 2 and Fig. 2. The most commonly encountered comorbidities in our study were arterial hypertension (n=139, 28%), non-hepatic malignancy (n=61, 12%), diabetes mellitus (n=56, 11%), rheumatologic diseases (n=51, 10%), and thyroid disorders (n=47, 9%). Metabolic bone disorder and severe renal impairment, which constitute a concern in patients receiving NAs, were present in 8% and 3% of patients, respectively. Of particular interest is the fact that 11 (85%) of the 13 patients with renal failure (estimated creatinine clearance <30 mL/min) were receiving ETV, while 2 were on TDF, albeit under very close renal monitoring. Moreover, of the 40 patients with metabolic bone disorder (including both osteopenia and osteoporosis), 75% were on TDF and only 25% on ETV. Another interesting observation was the greater prevalence (n=24, 39%) of hematologic malignancies among the 61 patients with non-hepatic malignancies.

Monitoring of patients

In our cohort, patients were generally seen approximately every 6 months (6.0±2.7), as recommended by our National Guidelines for the management of CHB, similar to those developed by the European Association for the Study of the Liver (EASL) [1]. The most common tests used for efficacy and safety monitoring of our patients, the proportion of patients undergoing each test and the frequency of each test can be seen in Table 3.

Across all 5 centers, a standard laboratory panel, including at least complete blood count, liver function tests and serum creatinine, was performed in more than 90% of patients almost every 6 months, while serum phosphate levels were also measured with similar frequency in 35% of all patients, or 56% of patients treated with TDF. Abdominal ultrasonography, often combined with alfa fetoprotein measurements, was performed

Table 2 Most common comorbidities in chronic hepatitis B patients under treatment with entecavir and/or tenofovir disoproxil fumarate

Comorbidity	Patients, n (%)
Hypertension	139 (27.8)
Non-hepatocellular malignancy	61 (12.2)
Diabetes mellitus	56 (11.2)
Rheumatologic disease	51 (10.2)
Thyroid disease	48 (9.4)
Obesity	46 (9.2)
Metabolic bone disease	40 (8.0)
Hyperlipidemia	31 (6.2)
Organ transplantation	16 (3.2)
Severe renal impairment*	13 (2.6)

*Estimated glomerular filtration rate <30 mL/min estimated by the Cockcroft-Gault equation

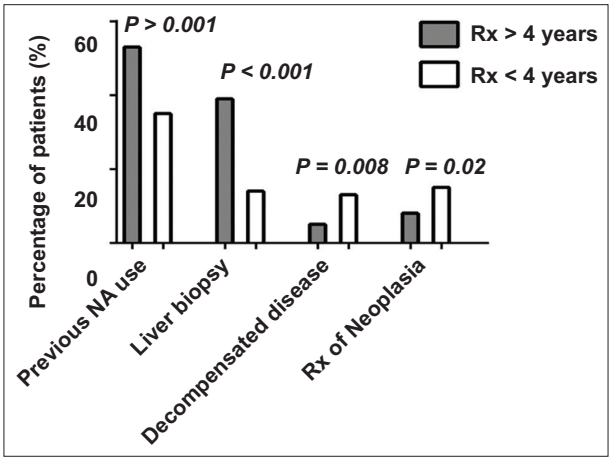

Figure 1 Main differences in characteristics of treated patients with chronic hepatitis B in relation to their duration of treatment (>4 vs. ≤4 years)
NA, nucleos(t)ide analog

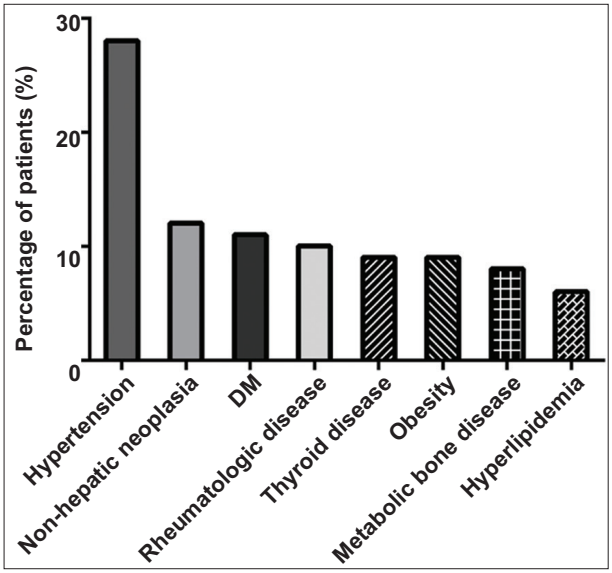

Figure 2 Prevalence of common comorbidities in patients with chronic hepatitis B under treatment with entecavir and/or tenofovir disoproxil fumarate
DM, diabetes mellitus

approximately every 10 months in up to 89% of patients. The proportion of patients who underwent HCC surveillance at least with ultrasonography did not differ significantly between cases with or without pretreatment for compensated or decompensated cirrhosis (110/118 or 93% vs. 243/264 or 92%), or between cases at low (PAGE-B <10) and medium-high HCC risk (PAGE-B ≥10) (92/102 or 90% vs. 329/367 or 89%). However, HCC surveillance was performed more frequently in patients at medium-high risk than in those with low HCC risk (mean frequency: 9.1±4.8 vs. 9.5±3.7 months, P=0.002), but it did not differ significantly between patients with or without pretreatment cirrhosis (mean frequency: 9.7±4.4 vs. 11.4±4.5 months, P=0.506). It is worth mentioning that the tests performed less frequently than once annually were serum HBV DNA determination (91% of patients), as well as liver stiffness in 46% and bone mineral density measurement in only 6% of patients.

Disease outcome associated with presence of specific comorbidities

There was a trend for decompensated cirrhosis to be more commonly present in obese than in non-obese CHB patients (17% vs. 9%, P=0.068). More importantly, HCC was found to have developed more often in diabetic CHB patients than in those without diabetes mellitus (11% vs. 3%, P=0.022) (Fig. 3), more common in patients with pretreatment cirrhosis (20% vs. 8%, P<0.001). In addition, patients with HCC development were significantly older than those without (mean age: 69±11 vs. 57±15 years, P=0.004) and were more likely to have had pretreatment for compensated (5/70 or 7.1% vs. 1/264 or 0.4%, P<0.001) or decompensated cirrhosis (11/21 or 52.4% vs. 37/479 or 7.7%, P<0.001). HCC patients also had a higher mean PAGE-B score (19±4 vs. 14±6, P<0.001), while the 2 groups did not differ significantly in relation to patients' place of birth, sex, BMI, alcohol or smoking habits. None of the patients who developed HCC had low risk (<10) according to PAGE-B score.

Table 3 Most common tests used for the monitoring of chronic hepatitis B patients under treatment with entecavir and/or tenofovir disoproxil fumarate

Test	Proportion of patients	Frequency of test in months (mean±SD, range)
Liver function tests	100%	6.1±3.1 (2-12)
Complete blood count	95%	6.2±2.9 (2-12)
Serum HBV DNA	92%	15.8±9.2 (3-48)
Serum creatinine	94%	6.2±2.8 (1-12)
Serum phosphate	35%*	6.3±2.9 (3-12)
Alfa fetoprotein	69%	10.0±4.2 (3-24)
Liver ultrasound	89%	10.2±4.5 (3-24)
Liver elastography	46%	16.5±6.8 (3-60)
Bone mineral density scan	6%	14.5±4.9 (12-24)

*56% of patients treated with tenofovir disoproxil fumarate

HBV, hepatitis B virus; SD, standard deviation

Discussion

In the current study, we provide evidence from real-life data that CHB patients currently treated with NAs are an aging population, as almost 50% are close to or older than 60 years. Thus, they may exhibit a variety of coexisting non-hepatic diseases. These concurrent medical issues may potentially impact the liver disease course and pose significant challenges regarding their management.

According to our results, CHB patients seen and treated in Greece nowadays comprise 2 distinct subgroups. The largest subgroup includes the indigenous Greek patients, who tend to be older as chronic HBV infection has almost disappeared in young Greeks as a result of the universal adoption of neonate HBV vaccination during the last 20 years. On the other hand, there is a smaller but growing subgroup that includes mostly younger CHB patients who immigrated to Greece from countries with a higher HBsAg prevalence, such as Albania. This finding is in accordance with the changing HBV epidemiology in Greece that has already been reported in previous studies [15,16]. Thus, while HBV prevalence is decreasing in Greece, chronic HBV infection is not a medical disease that will disappear soon, and the pool of CHB patients receiving NAs is only expected to increase.

The NAs used in Greece over the last years were almost exclusively ETV and TDF, as TAF has only recently become available. Given that almost one third of our patients were lamivudine-experienced and one fifth had documented resistance to lamivudine, it seems that there is a substantial subgroup of CHB cases that should optimally be treated with TDF. However, the presence of comorbidities may raise valid concerns regarding the use of TDF. While severe renal impairment was not commonly encountered in our cohort, bone mineral density disorders including osteopenia represented the sixth most commonly observed concomitant medical condition. In addition, 46% of the patients in our study were over 60 years old, the age cutoff recommended by the latest EASL guidelines to be used for selection of patients who may benefit by avoiding TDF. Considering all the above, TAF, the newer HBV therapeutic option, seems to be quite

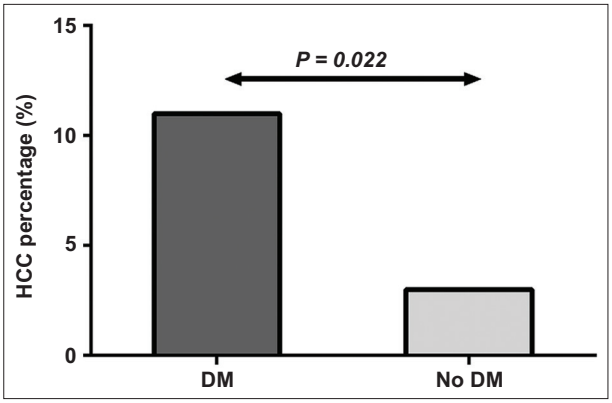

Figure 3 Proportion of treated chronic hepatitis B patients who developed hepatocellular carcinoma (HCC) in relation to the presence of diabetes mellitus (DM)

helpful in the management of aging CHB patients, who often have a history of lamivudine exposure, and may be at risk of developing NA-related or unrelated bone or kidney disorders.

The prevalence of comorbidities encountered in our cohort does not seem to differ from that expected in the general Greek population of similar age groups [17-20]. As expected, hypertension and diabetes mellitus were the most common comorbidities observed in our CHB patients, who had a mean age close to 60 years. The high proportion of hematologic malignancies in the non-hepatic neoplasia group may be attributed to the great number of referrals from a busy hematology department of the hospital of one of the tertiary centers, as well as to the known frequent HBV reactivation in patients with hematologic malignancies [21]. On the other hand, it should be noted that HBV infection has been associated with increased risk for several types of cancers, including hematologic malignancies [22].

Regarding the differences observed between patients with old and recent treatment onset, the different age was self-explanatory, whereas the higher likelihood of a history of prior exposure to another NA and of having undergone liver biopsy in the older treatment onset subgroup reflects the changes in clinical practice over time. It is clear that more patients receiving ETV and mostly TDF had been treated with another NA in the past, mostly with lamivudine, as the *ab initio* use with ETV or TDF became standard practice in the last decade. Similarly, liver biopsy was a standard procedure for the majority of CHB patients before the onset of therapy in the past, while noninvasive methods, mainly liver elastography, have been widely used for the assessment of the severity of liver fibrosis over the last 5-10 years in Greece. Interestingly, the higher duration of suppression of HBV replication was associated with a lower prevalence of non-hepatic neoplasia, implying that HBV might also be somehow implicated in extrahepatic carcinogenesis, perhaps via dysregulation of the host's immune responses. However, such a finding needs confirmation as it might also represent a type I error. The higher proportion of patients with decompensated cirrhosis before treatment among those who started NA therapy more recently was also interesting and may reflect changes in the stages of chronic HBV patients at initial diagnosis in our country. Non-cirrhotic patients with earlier stages of fibrosis can be diagnosed only though asymptomatic screening, which is probably decreasing, while symptomatic patients who develop decompensated cirrhosis seek medical advice, which leads to diagnosis and immediate treatment.

Monitoring of treated CHB patients in tertiary centers in our country was found to be generally in line with the recommendations put forth by our National Association and EASL [1]. The main clear discrepancy was related to the frequency of serum HBV DNA determinations, repeated at a mean interval of 16 months, whereas the recommended interval is every 6-12 months. This is probably related to our national state insurance policy, as HBV DNA was not reimbursed until October 2017 and was available for free in very few public hospitals with very long waiting times. Given that the cost of HBV DNA testing in private laboratories was high, repeat testing was not often performed, mainly because of financial constraints. Bone mineral density measurements and liver elastography were also repeated less than once annually, but there have been no clear recommendations regarding the need and the frequency of these tests for CHB patients under long-term NA therapy. Moreover, gastroenterologists, who often follow CHB patients in Greece, may not be as familiar or comfortable managing osteopenia and osteoporosis, and even tend to underestimate and therefore not to monitor these conditions. The latter suggestion may also be related to the finding that 75% of our CHB patients with bone mineral disorders were receiving TDF, whose avoidance is currently recommended in such patients [1]. Therefore, appropriate close follow up is imperative to ensure the optimal management of these cases. Finally, facilities for liver stiffness measurements are not readily available throughout Greece and the examination remains currently out of the national health reimbursement list. Given these obstacles, the frequency of liver elastography monitoring observed in our study could even be considered as satisfactory.

The most significant impact on the liver disease outcomes from the presence of comorbidities in our study was the

Summary Box

What is already known:

- Long-term monotherapy with a nucleos(t)ide analog (NA) of high genetic barrier represents the treatment option for the vast majority of chronic hepatitis B (CHB) patients
- Treatment with a NA is usually given long-term, perhaps indefinitely, making careful long-term monitoring necessary
- Current CHB patients treated with NAs have an increased likelihood of coexisting comorbidities and increased use of comedications

What the new findings are:

- CHB patients currently treated with NAs in Greece are an aging population, as almost 50% are close to or older than 60 years, and often have several comorbidities, thus requiring careful management
- Higher duration of inhibition of hepatitis B virus (HBV) replication is associated with a lower prevalence of non-hepatic neoplasia
- Monitoring of treated CHB patients in tertiary centers in Greece is in line with the EASL recommendations, except for the low frequency of serum HBV DNA determinations
- The concomitant presence of diabetes mellitus in CHB patients is associated with an increased risk for hepatocellular carcinoma (HCC) development; therefore, a high degree of alertness is essential in this subgroup for prompt diagnosis of HCC development at an early stage

association of diabetes mellitus with the development of HCC. Diabetes has been already recognized as an independent risk factor for HCC in previous studies [23,24], and it has reasonably been suggested that the presence of diabetes and obesity exerts additional nefarious effects on the liver, acting in a synergistic manner with the underlying chronic HBV infection. Moreover, recent studies further highlight this association, raising a high degree of alertness in CHB patients with diabetes mellitus, essential in order not to miss the early signs of HCC development [25,26].

In conclusion, CHB patients currently treated with NAs in Greece receive exclusively TDF and/or ETV as long-term maintenance therapy; this may raise safety and compliance issues [27]. They are often older than 60 years and have several comorbidities; they thus require careful management. The coexisting non-hepatic conditions may affect the optimal choice of their anti-HBV agent and their disease course. Therefore, close follow up for an extended period, as well as careful management of the existing comorbidities in collaboration with relevant specialties (such as rheumatology and diabetes specialists), are warranted in this setting, in order to ensure better long-term clinical outcomes.

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