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Original article

Chronic hepatitis B treatment initiation and modification patterns in five European countries: a 2-year longitudinal, non-interventional study

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Abstract

Background: Chronic hepatitis B (CHB) is an important health concern, but there are few studies describing its management in different countries. This prospective, longitudinal, non-interventional study aimed to assess differences in CHB management in five European countries (Germany, France, Poland, Romania, and Turkey).

Methods: Data were collected from CHB patients' records between 2008 and 2010. Patients were stratified by treatment status at baseline (Treated or Untreated). The primary objective was to estimate the probability of a CHB management modification (treatment initiation or change) among patients from each country during a 2 year follow-up.

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Results: 1,267 patients were included (567 Treated, 700 Untreated). Baseline characteristics between countries and treatment status groups were broadly comparable. Most patients had an alanine aminotransferase (ALT) measurement in the 12 months prior to baseline; proportions of patients with an HBV DNA assessment varied by country and treatment status. The Kaplan-Meier-estimated probability of any treatment modification ranged from 9.4% (Turkey), to 30.1% (Poland) at 12 months, and 10.0% (Turkey) to 40.0% (Poland) at 24 months. Modifications were more common in Treated than Untreated patients. The most frequently reported reasons for modifying treatment were HBV DNA-related. The majority of Treated patients were treated with monotherapy; however, choice of therapy differed between countries.

Conclusions: This is the first longitudinal study describing CHB management in European countries. Differences were observed in treatment and monitoring between countries, but ALT and HBV DNA levels consistently emerged as key tests in the management of CHB in all five countries.

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Running head: Chronic hepatitis B treatment initiation and modification patterns in Europe

Introduction

Chronic hepatitis B (CHB) remains an important health concern across Europe, despite the widespread implementation of surveillance and immunization programs. It has been estimated that around 14 million people are chronically infected with hepatitis B virus (HBV) within the World Health Organization Europe region alone (which includes Turkey) [1]. Despite advances in our knowledge of the natural history of HBV infection, and expanding treatment options, there is a lack of awareness and understanding of HBV across Europe. This is reflected in healthcare policy decisions, under-diagnosis, and under-treatment [1] [2].

Between 15% and 40% of untreated CHB cases will progress to cirrhosis, hepatic decompensation, or hepatocellular carcinoma (HCC) during the patients' lifetime [3,4]. The ultimate goal of CHB therapy is to induce immune control of HBV, prevent disease progression and improve quality of life and survival [5,6] [5,6]. Morbidity and mortality in CHB are linked to persistent viral replication [7], and sustained viral suppression has been shown to reduce the risk of disease progression and to have positive clinical benefits in terms of improved liver histology [8–12]. Clinical practice guidelines for the management of CHB patients have been produced by the European Association for the Study of the Liver (EASL), the American Association for the Study of Liver Diseases, and the Asian Pacific Association for the Study of the Liver [5,6,13]. In addition, the majority of countries produce individual national guidelines. These guidelines make recommendations on initiating therapy based primarily on serum HBV DNA and alanine aminotransferase (ALT) levels, with liver biopsy recommended for determining the degree of necroinflammation and fibrosis in patients with elevated ALT and HBV DNA.

Guideline recommendations and policy decisions are generally based on evidence from clinical trials. Patients from real-world populations differ from homogeneous clinical trial populations;

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they may be of a broader age range, suffer from co-morbidities and have poorer treatment adherence. In addition access to healthcare and specific therapies differ between countries. There is a paucity of information from well-designed studies on how disease characteristics and patient management strategies for real-world CHB patient populations compare across Europe. In particular, there is a lack of longitudinal observational studies, which have the benefit of allowing predictors of outcomes to be identified. This is the first European non-interventional study prospectively following country-specific populations of CHB with the aim of assessing the frequency and characteristics of changes in CHB management during follow-up of up to 2 years. This paper describes the study population, CHB management prior to study entry and the frequency of changes in CHB management during follow-up.

Patients and Methods

Study design and patient population

This was a prospective, longitudinal, non-interventional study of CHB populations from five countries followed for up to 2 years between March 2008 and December 2010. Participating countries were Germany (8 centers), France (8 centers), Poland (5 centers), Romania (8 centers), and Turkey (5 centers). Participating centers were chosen by the sponsor on the basis of an information survey sent to all CHB treatment centers in the five countries. The survey determined willingness to participate and collected information regarding number of patients with CHB, treatment setting (community vs. hospital), type of institution (academic vs. non-academic), and physician specialty. The distribution of centers by geographic location, institution type, facility type and specialty was computed and a stratified random sample method using PROC SURVEYSELECT from SAS 9.1 was used to select 15 sites from those willing to participate, in addition to the site of the principal investigator. Participating centers were then chosen among this list of 16 centers per country.

Consecutive CHB patients aged greater than 18 years attending the selected study centers were eligible for recruitment. Patients were required to have two positive hepatitis B surface antigen (HBsAg) tests, at least 6 months apart, or, in the absence of a second HBsAg test, chart documentation of a confirmed diagnosis and evidence for at least 6 months of continuous follow-up for CHB. Patients were excluded if they were HIV or hepatitis C virus (HCV) co-infected, currently enrolled in a randomized controlled trial, or had evidence of decompensated cirrhosis (Child-Pugh score $\geq$7), hepatocellular carcinoma (HCC), or liver failure at time of enrollment. Patients with HBV-hepatitis D virus (HDV) co-infection were not excluded. Physicians used a case report form to retrospectively extract information from patient charts, comprising: sociodemographic data (age, gender); disease characteristics (history of CHB diagnosis, hepatitis B e antigen [HBeAg]/hepatitis B e antibody [HBeAb] status, CHB status, genotype); co-morbidities (diabetes, hypertension, psychiatric disorders, renal impairment, tuberculosis); assessments of viral load, liver biopsy and ALT level in previous 12 months; treatment history in previous 12 months and current CHB treatment. Following recruitment further data were prospectively collected over a follow-up period of up to 2 years. These data comprised: changes in disease characteristics and CHB management; resource utilization (hospitalization, emergency department visits, tests, concomitant medication, clinic visits, other care); and any reasons for termination of follow-up. There was no imposed visit schedule or number of visits

during follow-up. HBV DNA assay methodology varied between centers and undetectable HBV DNA was defined as under the threshold indicated for each assay method used. Written informed consent was obtained from all participants with the exception of France, where local requirements mean this is not mandatory. Data collection complied with all privacy and confidentiality requirements applicable in the selected countries.

The primary objective of the study was to determine the proportion of patients from each country who underwent a modification of CHB management during the follow-up period; for the overall population and for subgroups based on treatment status at baseline. Patients who were not receiving treatment at baseline were categorized as “Untreated”, regardless of any treatment prior to baseline; those who were on treatment at baseline, including those who were previously untreated but had treatment initiated at the baseline visit, were categorized as “Treated”. Key secondary objectives for which the results are presented in this paper were to describe demographics and disease characteristics at baseline, and treatment patterns for each country-specific patient population in the 12 months prior to baseline and during follow-up.

Analyses and statistics

Sample size was calculated based on the assumption that 20% of patients would have a treatment modification during follow-up. In this case a study population of 200 patients per country would be sufficient to allow a 95%confidence interval (CI) of +/- 5.54%. Assuming a 20% drop out the target sample size was 240 patients per country with a minimum of 120 patients per country. The primary analysis was carried out using the Kaplan-Meier method to estimate, for each country, the probability of treatment initiation or modification in the overall population, the probability of treatment initiation in Untreated patients and the probability of treatment modification in Treated patients. Estimates of probabilities, with corresponding 95% confidence intervals, were provided for Months 6, 12, 18 and 24 of follow-up. Patients without treatment initiation or modification during the follow-up period were censored at their last visit date.

The full analysis population comprised patients meeting the eligibility criteria with a date for CHB diagnosis (or at least one positive HBsAg test), and baseline and at least one follow-up visit. Missing data were not replaced; all patients contributed to the analysis with available data. Partial dates with missing days were assumed to be the 1st of the month, and missing months as July (mid-year). Completely missing dates were not imputed. The start of study was considered as the date of baseline visit or of informed consent signature if the baseline visit date was unavailable. The results presented here are descriptive; no statistical analyses were calculated for observed values.

Two *post-hoc* analyses were performed. Because no specific definitions of treatment initiation, switch, add-on or stop were presented in the protocol there was some variation between investigators in classifying treatment modifications among patients defined as Untreated or Treated at baseline. Therefore, in the first post-hoc analysis, actual types of treatment modification were identified from the start and stop dates of medications and were categorized using the following rules: treatment initiation was applicable only to Untreated patients with no history of treatment during the 12

months prior to baseline ('treatment-naïve' patients); other treatment modifications were applicable to Treated patients and Untreated patients with a history of treatment during the 12 months prior to baseline (collectively, 'treatment-experienced') and included treatment switch (replacement of one treatment by another, a dose change, a new treatment course after latency of ≥1 visit, or initiation of therapy in Untreated classified as 'treatment-experienced'), treatment add-on (addition of a drug to the current treatment regimen), and treatment stop (complete discontinuation of the current regimen). A second post-hoc analysis was carried out to determine the probability of treatment switch during follow-up stratified by antiviral agent prescribed at baseline. In this analysis, because patient numbers in each group became too small to allow for any meaningful interpretation of results after one year of follow up, results are presented for the first year only.

Results

Study population and baseline characteristics

In total, 1,458 patients were enrolled of whom 1,267 were included in the full analysis population. Among the 191 patients not included in the full analysis population 55 did not meet eligibility criteria, 135 did not attend at least one follow up visit and one patient had an informed consent signature dated one year after the baseline visit. Baseline characteristics were generally comparable across countries and are shown in Table 1. Overall, there were more Untreated patients (n=700, 55.2%) than Treated patients (n=567, 44.8%). This difference was seen in all countries except Germany. Differences in age and gender distribution between Treated and Untreated patients were observed in all countries studied. Overall, the proportion of male patients was 62.8% (796/1,267), with a higher proportion seen in Treated than Untreated patients (411/567; 72.5% versus 385/700; 55.0%, respectively). The mean age was 41.7 ± 12.97 years, ranging between 18 and 99 years. Treated patients where generally older than Untreated patients (44.0 ± 13.33 years [95% CI: 42.9; 45.1] versus 39.9 ± 12.37 years [95% CI: 39.0; 40.8], respectively). Mean duration of follow-up ranged between 12.9 ± 1.99 months (Romania) and 15.0 ± 5.68 months (Germany). Genotyping was rarely performed in any country (5.4–11.6% of patients), and not available at all in Poland. The most frequently recorded co-morbidities were hypertension (Treated patients: Germany 5.9%, France 7.7%, Poland 12.8%, Romania 10.9%, Turkey 4.7%; Untreated patients: Germany 5.9%, France 10.8%, Poland 10.1%, Romania 9.2%, Turkey 4.4%) and diabetes (Treated patients: Germany 4.1%, France 6.3%, Poland 4.3%, Romania 1.8%, Turkey 2.8%; Untreated patients: Germany 2.4%, France 1.9%, Poland 1.9%, Romania 2.5%, Turkey 4.4%).

Mean HBV DNA level at the last measurement prior to baseline was lower in Treated than in Untreated patients in Germany and France, but lower in Untreated than Treated patients in the remaining countries (Table 1). Median ALT level at last measurement prior to baseline was generally lower in Untreated than Treated patients. HBeAg seroconversion in patients with available samples from the 12 months prior to baseline was seen in 11/170 (6.5%) and 3/84 (3.6%) of treated and untreated patients from Germany; 7/139 (5.0%) and 3/157 (1.9%) from France; 6/94 (6.4%) and 3/157

(1.9%) from Poland; 1/55 (1.8%) and 3/161 (1.9%) from Romania; and 15/106 (14.2%) and 15/135 (11.1%) from Turkey.

CHB management at baseline and during the 12 months prior to baseline

The majority of patients had at least one ALT level measurement in the 12 months prior to baseline. ALT assessments tended to be more frequent in Treated patients than in Untreated patients (Table 2). The proportion of patients with at least one HBV DNA level assessment in the 12 months prior to baseline varied depending on country, and was lowest among Untreated patients in Romania and Poland. HBV DNA level was more frequently measured in Treated patients than Untreated patients (Table 2). The proportion of patients with a recorded treatment history (excluding current therapy at baseline) was: 25.5% (65/255) in Germany; 15.7% (47/300) in France, 18.2% (46/253) in Poland; 13.8% (30/218) in Romania; and 8.7% (21/241) in Turkey.

Among Treated patients, the majority were receiving monotherapy at baseline. The proportion ranged from 54.9% (78/142) in France, to between 87.6% and 98.9% in the other countries. A summary of baseline monotherapies is shown in Table 3. Entecavir (ETV) or tenofovir disoproxil fumarate (TDF) were the most commonly prescribed monotherapies at baseline in Germany (97/148), France (50/78), and Turkey (64/103). Lamivudine (LVD) was the most commonly prescribed monotherapy at baseline in Poland (48/93) and Romania (22/53). The use of combination therapies was most prevalent in France, the most frequent of which were LVD + adefovir dipivoxil (ADV) (31/64, 48.4%) and LVD + TDF (18/64, 28.1%).

Changes in CHB management during follow-up

The results of the primary analysis – Kaplan Meier estimates of the probability of any first treatment modification during follow up – are shown in Fig. 1A. The probability of any treatment modification ranged from 9.4% (Turkey), to 30.1% (Poland) at 12 months, and 10.0% (Turkey) to 40.0% (Poland) at 24 months. To allow for investigator differences in classifying treatment modifications during follow-up the probabilities of treatment initiation versus treatment modification were estimated using the post-hoc analysis where treatment initiation was considered only for ‘treatment-naïve’ patients. Among the 700 Untreated patients 666 were ‘treatment-naïve’. The probability of treatment modification in ‘treatment-experienced’ patients was greater than the probability of treatment initiation in ‘treatment-naïve’ patients (Table 4). Further analysis of different types of modification revealed that the majority of treatment modifications in Germany and France were treatment switches while treatment stop was more common in Poland, Romania and Turkey (Table 4). The most frequent investigator-reported specific reasons for modifying therapy (irrespective of type of change) were ‘HBV DNA level’ and ‘Undetectable HBV DNA’; in Romania ‘ALT level’ was also commonly cited as a reason for treatment modification (Table 4).

A further ‘*post-hoc’* analysis investigated the cumulative probability of treatment switch during follow up according to drugs prescribed at baseline. The numbers of patients and events in each group in this analysis are low so the results should be interpreted with caution. However, the data

suggest that patients treated with either ETV or TDF had a lower probability of treatment switch at 12 months compared with patients receiving other agents (Fig. 1B).

The proportion of patients treated with monotherapy at the end of follow-up was 68.6% (107/156) in France, and ranged from 91.0% (152/167) in Germany, to 99.3% (140/141) in Poland among the other countries (Table 3). ETV or TDF were the most commonly prescribed drugs in Germany (110/152), France (85/107), Romania (33/84), and Turkey (72/114). LVD was the most commonly prescribed drug in Poland (69/140). PegIFN-α 2a was prescribed in 23.6% and 29.8% of patients in Poland and Romania, respectively, compared with 1.3–1.9% of patients from other countries. pegIFN-α 2b was only prescribed in Turkey (5.8% of patients). The most frequently prescribed combination regimens in France were LVD+ADV (15/49; 30.6%), LVD+TDF (18/49; 36.7%), or ETV+TDF (9/49; 18.4%).

Discussion

The results from this observational study of CHB management in Europe suggest that there are marked differences in the way patients are managed across the five countries included in this analysis. Differences were seen both between countries, and between patients who were treated or untreated at the baseline visit. Observed differences were unlikely due to differences in patient characteristics since demographics and baseline characteristics were generally comparable across the countries. There were more male than female patients, and Treated patients tended to be older and more likely to be male than Untreated patients across all countries. Male gender and older age are known to be predictors of HBeAg-negative CHB infection and of developing advanced liver disease, as seen in this population [7,14]. The most common HBe status at baseline was HBeAg-negative in all countries, with a higher proportion among Untreated patients.

The majority of patients in this study were treated with monotherapy, and the chosen agents differed little between those administered prior to baseline and those administered during follow-up. In France, Germany, and Turkey, the majority of patients receiving monotherapy received a guideline-recommended potent antiviral with low rates of resistance. In Poland and Romania, higher proportions of patients received LVD, which was also used as a switch or add-on therapy. The use of pegIFN-α 2a tended to be higher in Poland and Romania, throughout the study, which may reflect the availability of treatments across the countries, or may be explained in Romania by a proportion of patients with HDV coinfection, not part of the exclusion criteria for this study. HBV-HDV coinfection may also explain the high proportion of severe hepatic disease seen in the Romanian cohort. Turkey was notable in its use of pegIFN-α 2b, a drug not prescribed in any other country. The use of ADV and LVD is not in line with current EASL treatment guidelines (which recommend pegIFN-α 2a, ETV, and TDF as first-line, with ADV as a second-line therapy only) [6]. These recommendations were first issued in the 2009 EASL guidelines [15] and recruitment for this study was completed in October 2009, therefore treatment history in this study refers to a period before the guidelines were available. The availability and reimbursement status of medications may have influenced the way patients were

treated, for example, in Romania entecavir only became available in 2009. Further analyses are indicated to explore this.

Overall, the majority of both Treated and Untreated patients remained free from treatment modification during the 2 years of follow-up. The probability of any treatment modification during follow-up in the overall cohort was highest in Poland and lowest in Turkey. In all countries during follow-up, the proportion of patients with a treatment modification during follow up was higher in Treated than Untreated; however, variation was seen in the type of modifications across the countries. Treatment initiation was the main change reported in Romania, whereas treatment switch was the most common in Germany and France. This might be explained in France by the high number of patients treated with combination therapy at baseline, in accordance with local treatment guidelines, who were subsequently switched to monotherapy following the 2009 update of EASL treatment guidelines. HBV DNA-related reasons were the most commonly given for modifying treatment across the countries studied, despite the differences seen in measuring viral load across the countries in the 12 months prior to baseline and during follow-up. In general, patients classified as 'treatment-naïve' appeared to be more likely to be free of treatment modification during follow-up than 'treatment-experienced' patients. Patients who were treated with the currently recommended first-line agents ETV or TDF (i.e. potent antivirals with a low risk of resistance development) were less likely to have a treatment switch during 12 months of follow up than those treated with ADV, LVD or telbivudine, or interferons. Patients who were on combination therapy were most likely to experience a treatment switch during 12 months of follow up. This may reflect the changes in EASL treatment recommendations made during this study, or have been influenced by drug availability and reimbursement changes.

This was a multicenter, observational study with the associated study-design limitations. Observational studies typically have less strict selection criteria than randomized controlled trials, and confounding factors can easily interfere with interpretation of results. The use of stratified analysis can be used to overcome this. One potentially confounding factor that was not controlled for in this study was the inclusion of patients with HDV con-infection, since information on co-infection was not recorded. There are several further limitations to the data presented here, related to the way data were extracted from patient records. Current treatment status at baseline did not take into account treatment history or changes in treatment at baseline visit. Untreated at baseline should not, therefore, be considered treatment-naïve. The opposite is also true for patients treated at baseline. To address this, a *post-hoc* analysis was performed to determine the probability of treatment change in 'treatment-naïve' and 'treatment-experienced' patients. The protocol required only treatment administered in the 12 months previous to baseline to be recorded; however, some patients' treatment history will have included medications stopped more than 12 months prior to baseline. Additionally, only therapies from the prior 12 months that differed from current therapy at baseline were collected. Among reasons for treatment decisions, HBV DNA level and ALT level were options on the case report form but had no direction. Tolerability could refer to a patient experience, investigator expectation, or both. Undetectable HBV DNA could also indicate investigators expectation of the new treatment. Data were taken from patient medical charts, which can result in

large proportions with missing data. It must also be considered that this analysis describes patient management between 2008 and 2010, during which time there were changes in the available treatment options, reimbursement strategies of individual countries and treatment guidelines, therefore, the results may not reflect the management of CHB in 2012. Despite these limitations, common to the majority of observational studies, the results can provide valuable information about similarities and differences in the clinical management of CHB in the five participating European countries.

The results of this longitudinal study are the first to provide an insight into the management practice of CHB patients across Europe. Differences were seen in patient characteristics between those treated and untreated at baseline, and differences in the way patients are managed between countries.

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Figure/table legends

Fig. 1. Kaplan-Meier plot and probability of (A) any first treatment modification (treatment initiation in Untreated patients or switch, add-on, or stop in Treated patients) during follow up according to country (primary analysis) and (B) treatment switch during the first 12 months of follow up among Treated patients according to specific antiviral treatment (post-hoc analysis). The numbers of patients and events in each group in this analysis are low so the results should be interpreted with caution

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Table 1. Baseline characteristics.

	Germany, N=255		**France, N=300**		**Poland, N=253**		**Romania, N=218**		**Turkey, N=241**	
BL treatment status	Treated n=170	Untreated n=85	Treated n=142	Untreated n=158	Treated n=94	Untreated n=159	Treated n=55	Untreated n=163	Treated n=106	Untreated n=135
Mean age, years (95% CI)	44.2 (42.2, 46.3)	41.9 (39.0, 44.9)	45.4 (43.4, 47.5)	38.7 (36.8, 40.5)	42.6 (39.4, 45.8)	37.5 (35.6, 39.4)	42.1 (38.5, 45.6)	41.1 (39.1, 43.0)	44.0 (41.7, 46.4)	41.5 (39.4, 43.5)
Male, n (%)	109 (64.1)	44 (51.8)	117 (82.4)	93 (58.9)	65 (69.1)	90 (56.6)	46 (83.6)	94 (57.7)	74 (69.8)	64 (47.4)
CHB diagnosis per guideline definition, n (%)	113 (66.5)	46 (54.1)	71 (50.0)	78 (49.4)	72 (76.6)	137 (86.2)	38 (69.1)	142 (87.1)	73 (68.9)	104 (77.0)
Mean time since CHB diagnosis, years, (95% CI)	5.8 (4.9, 6.8)	4.7 (3.1, 6.3)	10.4 (9.0, 11.6)	6.1 (5.1, 7.1)	3.9 (3.0, 4.8)	2.9 (2.3, 3.6)	3.2 (2.3, 4.1)	4.4 (3.5, 5.3)	6.1 (5.0, 7.1)	5.7 (4.8, 6.5)
Compensated cirrhosis, n (%)	3 (1.8)	1 (1.2)	20 (14.2)	2 (1.3)	0 (0.0)	1 (0.6)	8 (14.5)	6 (3.7)	3 (1.9)	0 (0.0)
HBeAg-negative, n/N (%)	108/166 (65.1)	70/79 (88.6)	99/140 (70.7)	137/157 (87.3)	54/94 (57.4)	150/158 (94.9)	42/54 (77.8)	143/159 (89.9)	78/105 (74.3)	122/134 (91.0)
HBeAb-positive, n/N (%)	111/158 (70.3)	67/75 (67)	100/137 (73.0)	123/149 (82.6)	56/94 (59.6)	148/156 (94.9)	42/54 (77.8)	144/159 (90.6)	78/105 (74.3)	123/134 (91.8)
Co-morbidities, n (%)	37 (21.8)	12 (14.1)	47 (14.2)	44 (27.8)	25 (26.6)	26 (16.4)	15 (27.3)	33 (20.2)	14 (13.2)	21 (15.6)
ALT <ULN at BL, n/N (%)	113/168 (67.3)	53/80 (66.3)	97/142 (68.3)	109/153 (71.2)	54/93 (58.1)	107/140 (76.4)	20/54 (37.0)	73/136 (53.7)	73/105 (69.5)	108/135 (80.0)
Median last ALT level prior to BL, U/L (min, max)[a]	36.0 (10–1115)	32.0 (6–58700)	34.0 (11–182)	34.0 (7–432)	38.0 (10–236)	25.0 (9–207)	60.0 (14.4–747)	47.5 (15–579)	30.0 (3.2–555)	21.0 (10–134)
Mean last HBV DNA level prior to BL, log IU/mL (95% CI)	2.5 (2.2–2.9)	2.7 (2.4–3.1)	1.8 (1.6–2.1)	3.5 (3.2–3.8)	4.3 (3.8–4.8)	3.4 (3.0–3.7)	4.2 (3.3–5.2)	4.0 (3.6–4.4)	3.7 (3.2–4.2)	3.3 (3.0–3.7)

[a]Data presented as median (min,max) due to outlier in cohort not treated at baseline from Germany. Whole numbers are reported without a decimal place.

ALT, alanine transaminase; BL, baseline; CHB, chronic hepatitis B; CI, confidence interval; HBeAb, hepatitis B e antibody; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; ULN, upper limit of normal. All percentages were calculated based on patients with available data.

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Table 2. HBV DNA and ALT monitoring in the 12 months prior to baseline

	Germany, N=255		**France, N=300**		**Poland, N=253**		**Romania, N=218**		**Turkey, N=241**	
BL treatment status	Treated n=170	Untreated n=85	Treated n=142	Untreated n=158	Treated n=94	Untreated n=159	Treated n=55	Untreated n=163	Treated n=106	Untreated n=135
Assessment in prior 12 months										
Any ALT assessment, n (%)	168 (98.8)	80 (94.1)	142 (100)	153 (96.8)	93 (98.9)	140 (88.1)	54 (98.2)	136 (83.4)	105 (99.1)	135 (100)
Mean number of ALT assessments (95% CI)	3.2 (3.0;3.4)	2.3 (2.0;2.5)	3.6 (3.4;3.9)	2.4 (2.2;2.6)	3.7 (3.4;4.0)	2.3 (2.0;2.6)	3.3 (2.4;4.1)	1.9 (1.7;2.2)	3.8 (3.4;4.2)	2.2 (1.9;2.4)
Any HBV DNA level assessment, n (%)	166 (97.6)	80 (94.1)	142 (100)	150 (94.9)	86 (91.5)	88 (55.3)	39 (70.9)	79 (48.5)	104 (98.1)	128 (94.8)
Mean number of HBV DNA level assessments (95% CI)	2.9 (2.7;3.1)	1.9 (1.7;2.2)	3.3 (3.1;3.5)	1.9 (1.8;2.1)	1.4 (1.2;1.5)	1.3 (1.2;1.4)	1.2 (1.1;1.4)	1.1 (1.0;1.2)	2.1 (1.9;2.3)	1.5 (1.4;1.7)

ALT, alanine transaminase; BL, baseline; CI, confidence interval; HBV, hepatitis B virus. All percentages were calculated based on patients with available data.

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Table 3. Monotherapies at baseline and end of follow-up.

	Germany		France		Poland		Romania		Turkey	
Number of patients receiving monotherapy	**BL n=148**	**EOF n=152**	**BL n=78**	**EOF n=107**	**BL n=93**	**EOF n=140**	**BL n=53**	**EOF n=84**	**BL n=103**	**EOF n=114**
Monotherapy, %										
Entecavir	34.5	36.2	28.2	29.9	23.7	25.0	17.0	39.3	28.2	26.3
Tenofovir	31.1	36.2	35.9	49.5		-	-	-	34.0	36.8
Lamivudine	18.9	15.1	10.3	5.6	51.6	49.3	41.5	23.8	16.5	19.3
Adefovir	5.4	3.9	19.2	7.5	1.1	2.1	-	-	12.6	10.5
Telbivudine	10.1	7.2	-	-	-	-	-	-	-	-
PegylatedIFN-α 2a	-	1.3	2.6	3.7	23.7	23.6	24.5	29.8	2.9	1.8
PegylatedIFN-α 2b	-	-	-	-	-	-	-	-	5.8	5..3
IFN-α 2a	-	-	2.6	-	-	-	9.4	3.6	-	-
Other	-	-	1.3	1.9	-	-	7.5	3.8	-	-

BL, baseline; EOF, end of follow-up

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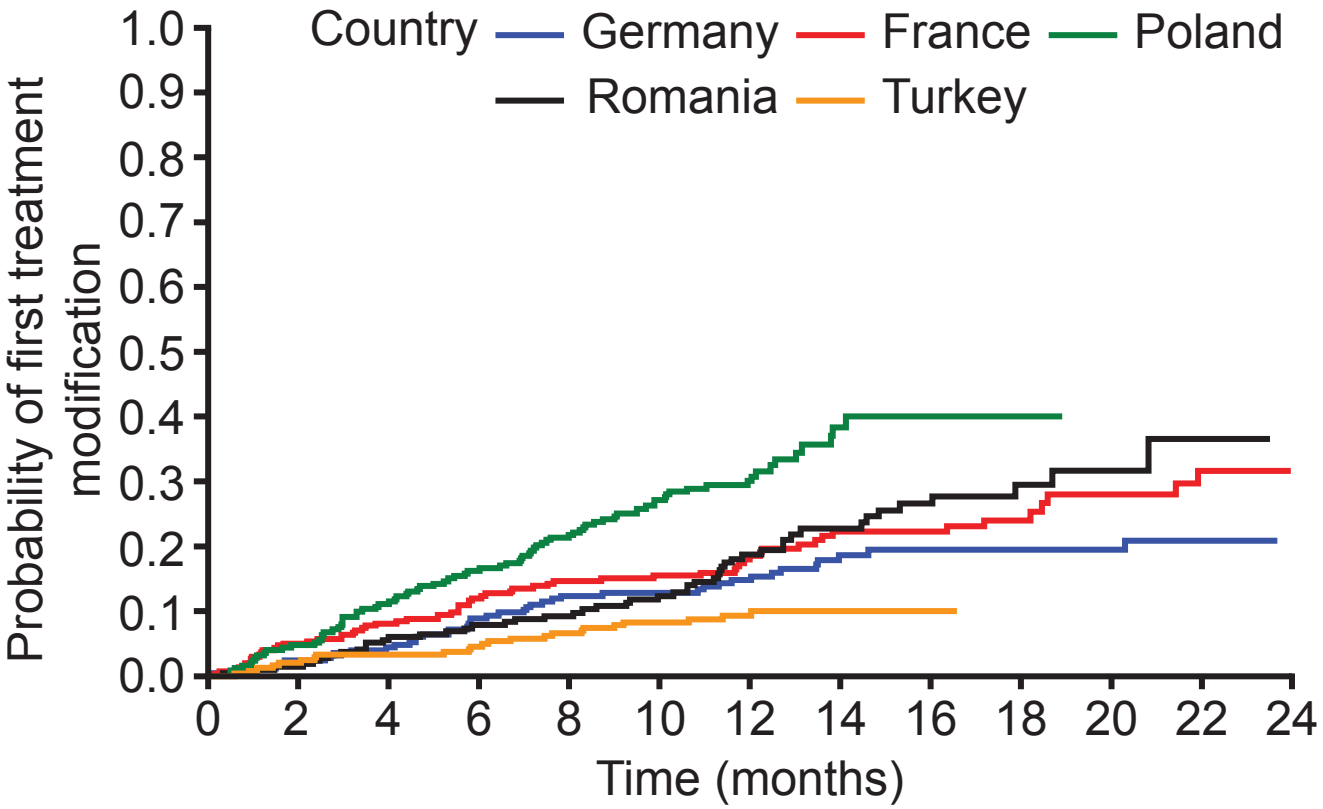
Table 4. Treatment modifications during follow-up according to post-hoc analysis

		Germany, N=255	France, N=300	Poland, N=253	Romania, N=218	Turkey, N=241
Treatment-naïve patients[a], n		80	157	143	156	130
Treatment modifications during follow-up, n (%)[b]		9	17	38	29	9
Initiation		9 (100)	16 (100)	38 (80.9)	29 (93.5)	9 (100)
Switch		1 (11.1)	2 (12.5)[c]	9 (19.1)[d]	2 (6.5)[d]	-
Add-on		-	-	-	-	-
Stop		-	2 (12.5)	14 (29.8)	1 (6.5)	-
Probability of treatment initiation at Month 12 (95% CI)[e]		10.5 (3.6, 17.5)	9.3 (4.6, 14.0)	24.7 (17.6, 31.8)	12.9 (7.3, 18.5)	7.0 (2.6, 11.4)
Treatment-experienced patients[f], n		175	143	110	62	111
Treatment modifications during follow-up, n (%)[b]		34	48	45	21	14
Switch		24 (70.6)	40 (83.3)	13 (36.1)	6 (31.6)	4 (28.6)
Add-on		6 (17.6)	7 (14.6)	1 (2.8)	-	2 (14.3)
Stop		5 (14.7)	9 (18.8)	25 (69.4)	14 (73.7)	9 (64.3)
Probability of treatment modification at Month 12 (95% CI)[e]		16.4 (10.7, 22.1)	27.2 (9.9, 35.5)	36.7 (27.5, 46.0	33.3 (20.8, 45.7)	12.1 (5.9, 18.3)
Investigator acknowledged reasons for treatment modification[g]						
Number of patients for whom a reason was provided		n=39	n=65	n=70	n=39	n=16
% of responses	HBV DNA level	91.1	55.4	75.7	43.6	43.8
	Insufficient HBV DNA response	10.5	4.6	-	10.3	12.5
	HBV viral rebound	-	10.8	1.4	2.6	12.5
	Undetectable HBV DNA	2.6	56.9	7.1	5.1	62.5
	ALT level	5.3	23.1	14.3	43.6	12.5
	HBeAg seroconversion	5.3	-	2.9	-	6.3
	Liver disease progression	-	4.6	4.3	-	6.3
	Drug side effects	2.6	6.2	2.9	-	-
	Tolerability	7.9	16.9	18.6	-	6.3
	HBsAg seroconversion	2.6	3.1	-	-	6.3
	Other	18.4	43.1	52.9	87.2	50.0

[a]Treatment-naïve patients are patients Untreated at baseline with no history of treatment during the 12 months prior to baseline. [b]Patients may have received more than one treatment modification during the follow up period. [c]One 'switch' was a treatment re-initiation. [d]All were treatment reinitiation. [e]Kaplan-Meier analysis. [f] Treatment-experienced patients are patients Treated at baseline and patients Untreated at baseline with a history of treatment during the 12 months prior to baseline. [g]Patients may have undergone several changes and multiple reasons could be indicated at each instance.

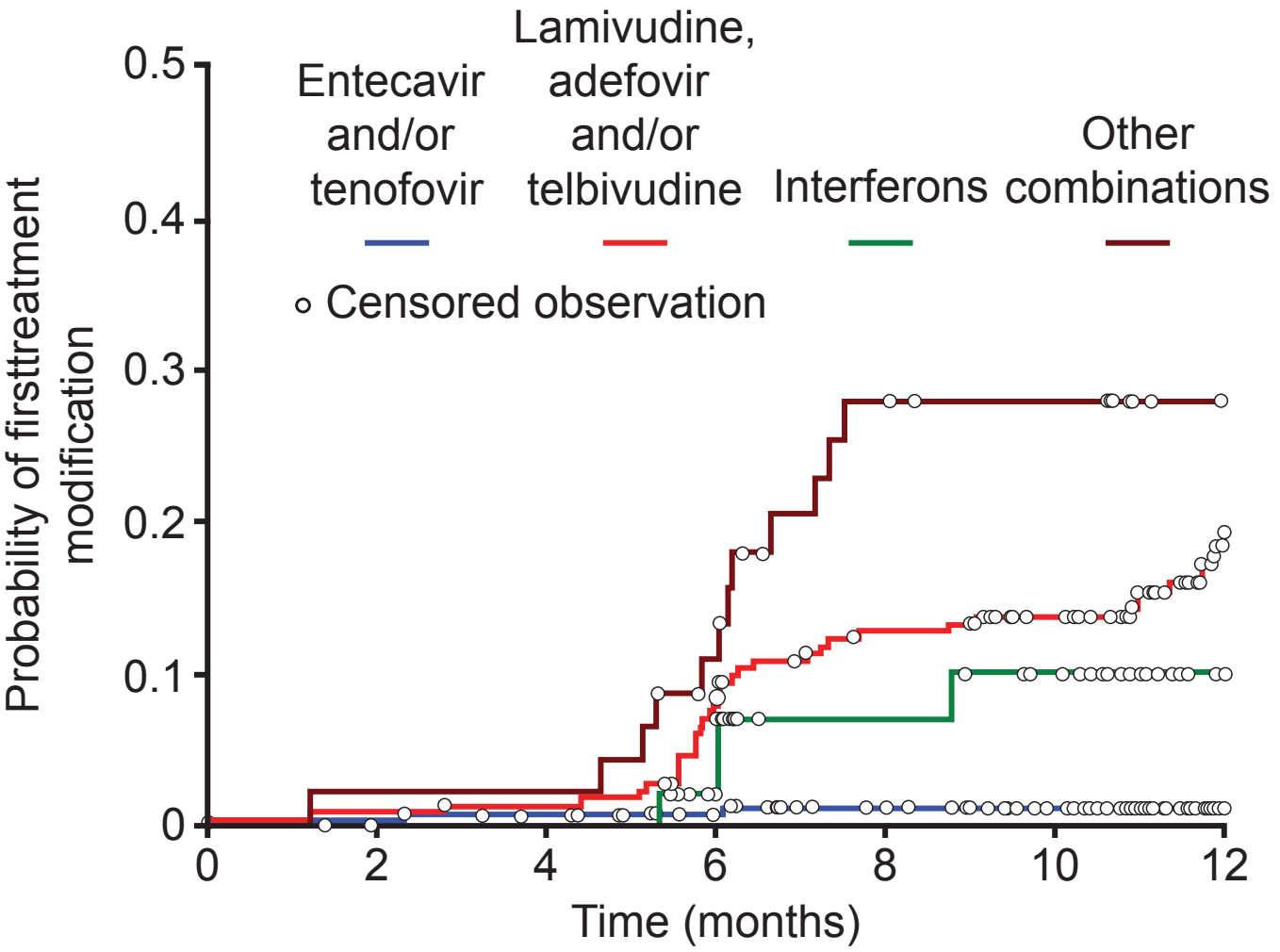
ALT, alanine transaminase; CI, confidence interval.

(A)



Number at risk Probabilty (95% CI)	6 months	12 months	18 months	24 months
Germany (N=255)	219 8.9% (5.3;12.4)	160 14.8% (10.2;19.3)	85 19.4% (14.0;24.9)	6 20.9% (14.8;27.0)
France (N=300)	242 12.0% (8.2;15.7)	144 18.5% (13.8;23.2)	62 24.1% (18.3;29.9)	18 31.6% (23.4;39.9)
Poland (N=253)	212 16.2% (11.7;20.7)	103 30.1% (24.3;35.9)	6 40.0% (32.0;48.0)	0 40.0% (32.0;48.0)
Romania (N=218)	194 7.9% (4.3;11.4)	121 18.7% (13.2;24.2)	37 29.6% (21.7;37.5)	2 36.6% (24.3;48.8)
Turkey (N=241)	228 4.6% (1.9;7.2)	139 9.4% (5.6;13.1)	0 10.0% (6.1;13.9)	0 10.0% (6.1;13.9)

(B)



Number at risk **Probabilty (95% CI)**	**6 months**	**12 months**
Entecavir and/or tenofovir (N=248)	232 0.4% (0;1.2)	162 0.8% (0;1.9)
Lamivudine, adefovir and/or telbivudine (N=216)	194 7.9% (4.3;11.6)	126 19.1% (13.5;24.6)
Interferons (N=53)	39 2.1% (0;6.2)	11 10.0% (0.6;19.4)
Other combinations (N=46)	38 10.9% (1.9;20.1)	19 27.9% (14.4;41.4)