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NON-INTERVENTIONAL STUDY AI463-12 OF REAL-WORLD CHRONIC HBV INFECTION MANAGEMENT - BASELINE CHARACTERISTICS AND TREATMENT PATTERNS OF POLISH PATIENTS KOHORT

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ABSTRACT

AIM. This longitudinal non –interventional study aims to describe the demographics data disease characteristics and clinical management of a cross-sectional CHB patient population in Poland treated in regional medical centers.
MATERIAL AND METHODS. Between March 2008 and December 2010 we observed patients with HBV related liver disease from 5 medical centers in Poland, both sexes ,>18 years old . At baseline, we used a case report form to extract data from patient charts, comprising: sociodemographic data; disease characteristics, HBeAg/ antiHBeAg status, genotype HBV; co-morbidities; viral load, liver biopsy and ALT levels in previous 12 months; treatment history in previous 12 months; current CHB treatment; changes in disease characteristics and CHB management; time from diagnosis to the therapy and resource utilization and any reasons for termination of follow-up. Written informed consent was obtained from all participants
RESULTS. The analysis population included 253 patients (94 treated and 159 non-treated at baseline) mostly male (69.1vs.56.6). Patients in treated group compared with untreated group were: significantly older (mean 42.6 vs. 37.5 years respectively, $p<0.001$), observed longer since diagnosis(3.9 vs.2.9 years), with higher rate of HBeAg(+)(42.6% vs.5.1%), lower ALT activity, and higher VL HBV DNA PCR .
Of the 53% of treated patients, the most frequently prescribed anti-HBV drugs were: Lamivudine (53%), Entecavir (23.7%), Pegylated IFN-alfa2a (23.7%), Adefovir(11.1%). During 24 months of follow-up in treated group 13(36.1%) patients underwent a treatment switch to another nucleosi(-ti)de analogue, in one (2.8%) patient another analogue was added, and in 25 (69.4%)patients the therapy was stopped. The proportion of all patients treated with monotherapy at the end of follow-up was 99.4%, unfortunately mostly with Lamivudine-49.3%.
SUMMARY. 1.Despite the several methodological limitations usually associated with this type of observation, the collected data does characterize the demographics of polish patients chronically infected with HBV well, provides some insights into the determinants of treatment initiation and the clinical management of patients in real-word settings.
2. These results indicate that in clinical practice in 5 medical non-academic centers in Poland, European guidelines regarding the qualification to HBV treatment were followed, but there were discrepancies between the initial treatment decisions in real-life current clinical practice and guideline recommendations

Key words*: HBV infection, interferon alfa, nucleoti(-zi)de analogues*

INTRODUCTION

The epidemiological situation of HBV infections in Europe and Poland during the past 30 years has improved considerably. The incidence rate in 2011 was ca. 3.1/100 thousand inhabitants (as compared to 40/100 thousand at the end of the 1970s), but the number of chronically infected HBV patients is estimated at 320 thousand. Unfortunately, indicators of past HBV infections are found among ca. 15% of the population (presence of anti-HBc antibodies, which does not rule out mini HBV replication, with all of its consequences) (1, 2, 3, 4). Each year, 1.3-5.9% of CHB patients develop cirrhosis (in total, this applies to 25-40% of infected); ca. 4%/year of cirrhosis patients develop primary liver cancer (5 ,6, 7). Qualification for treatment and available therapies for HBV-infected patients with chronic liver disease and/or forms of infection outside the liver is a complicated process, requiring both extensive knowledge and proper experience, and, above all, access to current diagnostics and treatment methods (2,8-12).

The primary aim of HBV infection therapy is improving the patient's quality of life; increasing survivability by preventing the progression of the disease into cirrhosis and hepatic encephalopathy, or the development of hepatocellular carcinoma; and minimising the spread of HBV infections. This goal may be achieved by long-term suppression of HBV replication.

According to current therapeutic standards in treating HBV infections, developed by groups of experts in the field of liver disease [e.g. the European Association for the Study of the Liver, or Polish HBV Expert Group (Polska Grupa Ekspertów Leczenia HBV)], children and adult patients meeting the below criteria should be subjected to etiotropic treatment (12-14):

1. the HBsAg, with or without the HBeAg are present;
2. the number of HBV DNA copies in the blood plasma exceeds 2000 IU/ml (10000 copies/ml). With unfortunate exceptions, a lower number of copies in the blood plasma usually does not carry a serious risk of the development of cirrhosis or hepatocellular carcinoma, or any pathology at all;
3. biochemical markers of disease activity – at least a single, above-average activity spike of aminotransferase (AspAT, AlAT) in the blood plasma within the past 3 months;
4. chronic hepatitis in various stages of infection, cirrhosis caused by chronic hepatitis, symptoms outside the liver (regardless of the presence or absence of symptoms in the liver), and with comorbid HCC;

Two different groups of drugs for treating the causes of CHB were registered: immunomodulatory drugs, i.e. interferon alfa, and drugs that directly prevent HBV replication – nucleoside/ nucleotide analogues.

Therapy is not given to patients who do not grant written, informed consent, have contraindications (which are especially numerous in the case of interferon alfa), are HBV carriers or are infected with HBV in the immune-tolerant phase. Nevertheless, not every patient must meet all of the listed criteria for qualification simultaneously (3, 8, 9, 14, 15).

AIMS OF THE STUDY

There exists a lack of well-documented, longitudinal observational studies regarding the modes of qualification, therapy and means of monitoring the treatment of chronically infected HBV patients in clinical practice. The study was designed and supervised by the Study Steering Committee: *Prof. Stefan Zeuzem (SZ*), *Prof. Hakan Leblebicioglu (HL), Prof. Krzysztof Simon (KS), Prof. Jean-Pierre Zarski (JPZ), Dr. Stefan Arama (SA), Dr. Mihaela Radulescu (MR), Benedicte Lescrauwaet (BL), Samuel Gwed (SG), Nathalie Schmidely (NS), Damien Ponsonnet (DP), Annelore le Maux (ALM), Valérie Taillieu (VT), Cristina Ivanescu (CV)*

The aims of this study were to: describe the demographics data disease characteristics and clinical management of a cross-sectional CHB patient population treated in non-regional medical centres; evaluating the rules and factors deciding about treatment initiation; monitoring treatment and reasons for modifying it, ways of modifying therapy and the probability of this occurring. This latter point was the subject of a separate publication. The study comprised patients from: Germany, France, Turkey, Romania and Poland. The results of the joint research were accepted for publication in the Journal of Viral Hepatitis. This paper presents the results of the Polish patient cohort.

MATERIALS AND METHODS

The study took place between March 2008 and December 2010. The observed patients came from 5 centres in Poland that declared the willingness to participate in the study. These were patients of both sexes, >18 years of age, in which a retrospective analysis of documentation revealed the presence of the HBsAg twice within a minimum period of 6 months, as well as biochemical and histological features of chronic hepatitis or hepatitis-induced cirrhosis. The study excluded patients with HCV and HIV comorbidity, currently included in randomised research grants, patients with decompensated cirrhosis and primary liver cancer (HCC).

The following data was gathered at baseline, using case report forms and after obtaining the patients' written consent: basic demographic data, characteristics

of the disease, HBeAg/anti-HBeAg status, HBV genotypes, HBV comorbidities, initial viral load, liver biopsy, ALT levels, CHB treatment in the past 12 months, and the time elapsed between confirming the diagnosis and beginning treatment. Subsequently, patients were subjected to a prospective 24 month observation, analysing CHB management, resource utilization, reasons for termination of follow-up, frequency and location of consultations with physicians. A statistical analysis was carried out on the achieved results using the t-Student test, while the probability of changing therapy was measured with the Kaplan-Meier estimator.

RESULTS

In Poland, 253 patients were observed, of which 94 were undergoing treatment and 159 were untreated at baseline. The higher number of untreated patients is particularly conspicuous, although both groups were dominated by middle-aged men (69.1 vs. 56.6), who were older in the group of treated patients (42.6 vs. 37.5 years). The group of treated patients was characterised by a longer mean period of observation between diagnosis and treatment (3.9 vs. 2.9 years), a lower percentage of patients with negative HBeAg (57.4% vs. 94.9%), lower percentage of normal ALT levels (58.1% vs. 76.1%) and higher HBV DNA values in the period leading up to our study. In addition, 12 months before the baseline visit, seroconversion of HBeAg into anti-HBeAg was noted in 9 patients. Unfortunately, HBV genotyping was not performed on any of the patients (7). A similar percentage of patients in both groups (25%) had significant comorbidities requiring constant treatment: hypertension and diabetes.

Among the tests qualifying for antiviral treatment, 25% of patients from the treated group and 20.1% of patients from the non-treated group underwent liver biopsy and 37% of all the patients under observation had abdominal USG performed. Before the study, 98.0% of the treated patients and 88.1% of the untreated patients were tested for ALAT levels which for the majority of them were within ≤1x the upper-normal limits. Markedly, the treated patients had significantly less detectable HBV viraemia and higher HBV DNA at baseline in comparison to the untreated group.

In the lead-in and observation period, due to being qualified for therapy or because of the treatment itself: 16.2% of patients from both groups were hospitalised – the mean period of hospitalisation was 1,812 days (chiefly due to the lack of possibilities for performing or settling accounts for certain tests for monitoring treatment under ambulatory conditions); 50.6% of patients consulted their doctor (due to the appearance of symptoms suggesting adverse effects caused by the therapy or a deterioration of their overall health). This adds up to ca. 3.198 visits per patient, including 1.220 visits to a specialist. Table I shows data about antiviral treatment before and during the study. More than 13.9% (31/218, no available data for the others) of patients from both the treated and untreated groups (although more often in the former group) declared undergoing anti-HBV therapy that ended according to the rules of managing antiviral treatment and the NFZ guidelines at some point in the past. At baseline, the majority of the treated patients were prescribed with lamivudine (51.6%), with entecavir, PEGIFNalfa 2a and adefovir being less common.

Table I. Monotherapies at baseline, treatment modifications during follow-up and monotherapies at end of follow-up of Polish HBV-infected patients cohort

Number of patients n=253	T n=94	
Monotherapy at baseline, %		
Entecavir	23.7%	
Lamivudin	51.6%	
Adefovir	11.1%	
Peg-IFN-α 2a	23.7%	
Others	-	
Every treatment modification (%)	T n=94 36 (38.3%)	nT n=159 47 (29.6%)
Type of modification (%)		
Beginning	-	38/47 (80.9%)
Changing	13/36 (36.1%)+	9/47 (19.1%)‡
Adding a second drug	1/36 (2.8%)	-
Ending treatment	25/36 (69.4%)	-
Monotherapy at follow-up %	T n=116	
Entecavir	25.0%	
Lamivudin	49.3%	
Adefovir	2.1%	
Peg-IFN-α 2a	23.6%	
Others	-	

T, treated patients ; nT- patients not treated at baseline * Treatment modification: beginning, changing, adding a second drug or ending therapy in treated patients; † in one case, the modification consisted of „re-initiating therapy";‡ cases of re-initiating treatment that ended several years ago

During the 24 month observation, therapy was modified in 38.3% of the treated patients. In the group of patients untreated at baseline 29.6% changed therapy. The overall percentage of patients on monotherapy at the end of the study was 99.4% (115/116) and for as many as 49.3% this consisted of lamivudine (the mean period of therapy during observation was 12 months). In the period between the baseline visit and the end of the study, seroconversion of HBeAg into anti-HBeAg was noted in 7.4% of patients.

DISCUSSION

From the data gathered in this study, it appears that all of our patients met the criteria for confirmed

chronic hepatitis connected with HBV (2, 3, 6); most of the evaluated patients were middle-aged (ca. 40 years old), HBeAg-negative men (with the majority of them in the untreated group), although patients in the group undergoing treatment were slightly older than the untreated patients. All of the patients had a similar number of comorbidities at the beginning of treatment. HBeAg is a surrogate marker of increased HBV replication, which explains the high percentage of HBeAg-negative patients in the untreated group. This data resembles the observations of other authors conducting HBV infection therapy under standard clinical conditions (4, 5, 10). The low number of patients in the Polish cohort who underwent liver biopsy is particularly noticeable, corresponding with general trends around the world and indicating that the ever-more prevalent non-invasive liver disease testing methods were used, or that the qualification for treatment was based on only two markers (HBV DNA value and ALAT levels). Nevertheless, while the ALAT levels measured in the blood plasma were standard for cirrhosis, the reasons for elevated levels of this enzyme may be varied (e.g. fatty liver disease, muscle damage and others) (3); therefore, when doubts arise as to the reasons for, or the stage of liver pathology, it is always advisable to consider the validity of performing a biopsy.

Worrisome in the data are the results of quantitative HBV DNA tests and elevated ALAT levels (in 41.9% of the treated patients) in the lead-in period – these are the key elements in evaluating the efficacy of therapy. This may point to the inefficacy of antiviral nucleotide/nucleoside analogue therapy, but it may also be connected with a high percentage of patients treated with pegylated interferon alfa2a, which yields results several years after treatment ends(11, 17-19). On the other hand, the high percentage of treated patients who had quantitative HBV DNA and ALAT level tests performed, along with the frequency of these tests points to a proper treatment monitoring in the group of HBV-infected Poles. What was incomprehensible for some of the members of the Steering Committee were the hospitalisations of patients in the Polish cohort and the frequent interruption of nucleotide/nucleoside analogue therapy. Unfortunately, this is connected with the way therapy is initiated, interrupted and funded in the NFZ programme, as well as the distribution of drugs through hospitals/medical centres. The gathered data also indicate that a number of patients undergoing therapy frequently used hospital/specialist care (every 5.26± 0.62 months). Additionally, despite undergoing treatment or having confirmed chronic HBV infection, almost half of the patients in the period before and during our observations did not use medical care at all, for unknown reasons. This may result in a low quality of treatment or initiating treatment too late (advanced stages of liver disease, complications).

In accordance to the NFZ programme, which was already out of date with European standards at the time of the study, the majority of patients were treated with only one drug. This was usually lamivudine (51.6%) or pegylated interferon alfa2a, and rarely the far more effective entecavir (12-16). None of the patients were treated with tenofovir. At the time, tenofovir therapy was not refunded by the NFZ (it is refunded at present, although only as a second-line drug). The use of lamivudine and adefovir as first-line therapy drugs has been anachronistic for several years, and is not recommended in most European countries (currently, first-line drugs, both for HBeAg-positive and HBeAg-negative patients, include pegylated interferon alfa2a and the powerful nucleotide/nucleoside analogues, entecavir and tenofovir) (6, 12-19). This publication has its methodological limitations, stemming from the fact that it was not a randomised study, which is particularly relevant for methods of treatment.

SUMMARY

1. Despite some methodological limitations, the gathered data characterises the demographics of Polish HBV-infected patients that are qualified for anti-viral therapy, points to the methods of qualifying for anti-viral treatment and the ways in which therapy is conducted at a standard infectious diseases ward.
2. Although the criteria for qualifying HBV-infected patients for anti-viral treatment are generally in line with European standards, the therapy itself unfortunately does not meet the standards proposed by the European Association for the Study of the Liver or the 2010 and 2013 guidelines of the Polska Grupa Ekspertów HBV (Polish HBV Expert Group).

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