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Missed treatment in an Italian HBV infected patients cohort: HBV RER

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ABSTRACT

Background and aims: Very little is known about the access to treatment for Chronic Hepatitis B in the real clinical practice and the characteristics of the patients who do not receive antiviral therapy.
Methods: HBV-RER is an observational multicenter network that collected data of patients with HBV infection during a 3 years observational period (2009–2012).
Results: Among 2527 HBsAg positive patients, 1099 were never treated (NT); only 280 were included in the analysis due to different exclusion causes A minority was HBeAg-positive. The median age was 42. At liver biopsy most patients had Metavir score of F0-F1. Univariate analysis between 280 NT patients and the 290 naïve to treatment showed that NT patients were mostly female ($P = 0.002$), not Italian ($P = 0.044$), younger ($P < 0.001$). Metavir score was lower in NT (P0.002), such as the Fib4 score ($P < 0.001$). HBV DNA level was significantly higher in NT. At multivariate analysis, independent variables associated with no-treatment were younger age, female gender, Metavir score F0-F1, Fib4 lower than 1.6 and lower blood level of HBV-DNA.
Conclusions: There is a large number of patients eligible to treatment who do not receive it. A younger age and a less severe disease seem to be associated to deferral of treatment.

1. Introduction

Chronic Hepatitis B virus (HBV) infection is a worldwide spread disease. It can present in different patterns such as HBV inactive carrier and progressive Chronic Hepatitis B (CHB), that may evolve in liver cirrhosis and hepatocellular carcinoma (HCC) [1].

At present, six treatments are available for hepatitis B: interferon (pegylated or not) and five nucleotide/nucleoside analogues (NUCs): lamivudine, telbivudine, adefovir, entecavir and tenofovir. National and international guidelines suggest the use in first line treatment of both pegylated interferon (PEG-IFN) or nucleot(s)ide analogues (entecavir or tenofovir). The use of PEG-INF is indicated from a stage of minimal liver fibrosis up to a stage of a well compensated cirrhosis [2,3]. The use of NUCs is allowed in all the stages of the HBV disease up to decompensated cirrhosis. The ideal goal of therapy is the HBsAg loss and seroconversion to HBsAb, but this end-point is obtained in a very low percentage of patients treated with the different available drugs [4]. Therapeutic intervention is currently aiming at suppression of HBV replication, that is key to decrease liver injury and disease progression, in order to prevent cirrhosis, decompensation and to reduce the risk of HCC [5]. Very little is known about the access to treatment for CHB in the clinical practice and mainly of the epidemiological and clinical characteristics of the patients who do not receive any antiviral therapy. Aim of our study was to analyze the clinical and epidemiological features of the "missing treatments" in a multicenter observational study conducted on an Hepatitis B surface antigen (HBsAg) positive cohort of patients.

2. Patients and methods

HBV-RER is an observational multicenter Italian network that collects clinical and virological data of patients with CHB coming

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[1] See Appendix A

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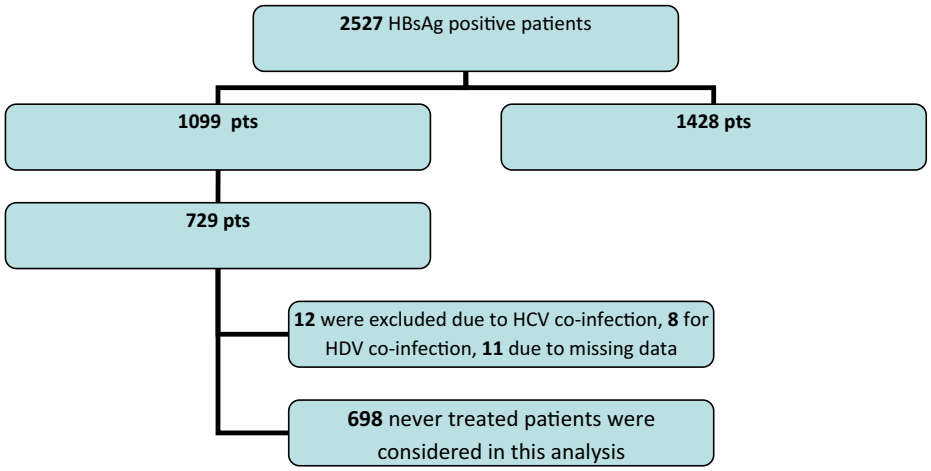

Fig. 1. Flowchart for the selection of patients.

from 33 different medical units (infectious diseases, gastroenterology, hepatology, internal medicine) of the Emilia-Romagna region. The main purpose of the study group was to improve the best clinical practice in HBV infection using a standard protocol of diagnosis and treatment of HBV infected patients in all clinical centres of the Region. All patients with HBsAg positivity, who underwent at least one medical visit in one of the centres involved in the study from 1st January 2009 to 31st December 2012 were considered included in the study. All patients were tested for HBsAg, HBsAb, HBeAg, HBeAb, HBcAB, HCVAb, HDVAb, HIVAb. HIV positive patient were excluded. Other data collected were: 1-demographic, haematologic and virologic parameters (transaminase, HBV viral load at baseline and during follow-up), 2-stage of fibrosis if liver biopsy was performed, 3-therapy (previous or during follow-up, Interferon or NUCs, type of NUC, first line or rescue therapy). An ALT level > 40 UI/ml was considered to be upper the normal level. The FIB4 score, a non-invasive scoring system based on several laboratory tests that help to estimate the amount of fibrosis in the liver using the following formula: (Age × AST)/(Platelets × (sqr(ALT)) was used. Age of the patient was the age at the time of enrolment. A FIB4 value <1.6 was considered as null fibrosis, between 1.6 and 3.6 as mild fibrosis, and >3.6 as cirrhosis. Patients were enrolled in the observational study independently from the stage of HBV infection (Inactive carrier, CHB, cirrhosis compensated or not, HCC) or from the presence of co-infections (HDV, HCV). We defined as missing treatments patients who underwent at least 3 visits during the observational period. (We supposed that 3 visits are necessary and sufficient to define the clinical status and to evaluate the therapeutic options.) We excluded from the analysis patients with other viral co-infections (HIV, HCV, HDV).

Statistical analysis was made by the use of median and interquartile range (IQR) for summarize continuous variables and frequency for categorical variables. At univariate analysis between different groups continuous variables were compared using non-parametric analysis (Mann Whitney), categorical variables were compared using Chi-square test. A *P*-value less than 0.05 was considered to be statistically significant. Multivariate analysis was performed using stepwise logistic regression method. All the statistical data were collected using IBM SPSS version 22.

3. Results

A total of 2527 HBsAg positive patients were enrolled in the study during the four years of observation (Fig. 1 shows the flowchart for the selection of the patients): 1325 of them where never treated before (52.4%), while 1202 (47.6%) had been treated previously or were on treatment at the moment of the inclusion in the cohort. 1099 (43.5%) patients continued to be not treated at the end of the period of observation; 177 (16.1%) of them attended only one medical visit, 193 (17.6%) two. 729 patients were seen at least 3 times, thus were considered as "missing treatment"; of these, 12 were excluded due to HCV co-infection, 8 for HDV co-infection, 11 due to missing data. A total of 698 never treated patients were considered in this analysis. Table 1 summarizes the demographic and clinical characteristics of the patients not treated. They were mostly

Table 1
General characteristics of never treated patients.

Characteristics	Never treated Num.: 698
Gender	
Male	431 (61.7%)
Strangers	326 (46.7%)
Ethnicity	
Caucasian	556 (79.7%)
Asian	67 (9.6%)
Black	71 (10.1%)
Hispanic	4 (0.6%)
Age (median)	42 (18–83)
HBeAg	
Positive	92 (13.2%)
Negative	606 (86.8%)
HBV DNA, IU/ml (median)	2165 (0–10,000,000)
ALT/HBV DNA level	
HbeAg +	
>ALT < 20,000	23 (3.4%)
>ALT > 20,000	55 (7.9%)
NALT < 20,000	11 (1.6%)
NALT > 20,000	3 (0.4)
HbeAg −	
>ALT < 2000	233 (33.4%)
>ALT > 2000	225 (32.2%)
NALT > 2000	57 (8.2%)
NALT < 2000	91 (13%)
Biopsy	
Performed	181 (25.9%)
Not performed	517 (74.1%)
Fibrosis	
F0-F1	141 (77.9%)
F2	15 (8.3%)
F3-F4	9 (5%)
NC	16 (8.8%)
FIB4	
<1.6	545 (78.1%)
≥1.6 to <3.6	81 (11.6%)
≥3.6	16 (2.3%)
NC	56 (8%)