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Original article

Current practice of chronic hepatitis B treatment in Southern Italy

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ABSTRACT

Background: Treatment choice for chronic HBV infection is a continuously evolving issue, with a wide range of options. We aimed to evaluate the current practice of HBV therapies in the real world in Southern Italy.
Methods: A prospective study enrolling over a six month period (February–July 2010) all consecutive HBsAg positive subjects, never previously treated, referred to 16 liver units in two Southern Italy regions (Calabria and Sicily).
Results: Out of 247 subjects evaluated, 116 (46.9%) had HBV-DNA undetectable or lower than 2000 UI/ml. There were 108 (43.7%) inactive carriers, 103 (41.7%) chronic hepatitis, and 36 (14.6%) liver cirrhosis. Antiviral treatment was planned in 94 (38.0%) patients (26 cases with Interferon or Pegylated Interferon and 68 with nucleos(t)ides analogues). As many as 49.5% of subjects with chronic hepatitis did not receive antiviral treatment.
Discussion: The majority of chronic HBsAg carrier referring centres for evaluation were not considered suitable for antiviral treatment. Nucleos(t)ides analogues are the preferred first choice for therapy. A long-lasting period of observation may be needed to make appropriate therapeutic decisions in several cases.

1. Introduction

Growing attention has been addressed to hepatitis B virus (HBV) during the last few years. Current treatment of chronic hepatitis B infection represents an evolving challenge due to the introduction of several new and effective antiviral agents. There are currently four major treatment guidelines for therapy of chronic hepatitis B, published by the American Association for the Study of the Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL), the Asian Pacific Association for the Study of the Liver (APASL) and

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Table 1
Treatment criteria for the four major guidelines for therapy of chronic hepatitis B.

Guidelines	HBV-DNA (IU/ml)	ALT (U/L)
AASLD		
HBeAg +ve	≥20,000	>2×ULN
HBeAg −ve	≥20,000	>2×ULN
EASL		
HBeAg +ve	≥2000	>ULN
HBeAg −ve	≥2000	>ULN
APASL		
HBeAg +ve	≥20,000	>2×ULN
HBeAg −ve	≥20,000	>2×ULN
AISF, SIMaST, SIMIT		
HBeAg +ve	>20,000	>ULN
HBeAg −ve	>2000	>ULN

ASSLD: American Association for the Study of Liver Diseases.
EASL: European Association for the Study of the Liver.
APASL: Asian-Pacific Association for the Study of the Liver.
AISF : Italian Association for the Study of The Liver.
SIMaST, Italian Society for the Study of Sexually Transmitted Diseases.
SIMIT Italian Society of Infectious and Tropical Diseases.
ULN: upper limit of normal.

three Italian scientific societies [1–4]. The key difference between these guidelines is the adoption of a different threshold of HBV-DNA and ALT levels for treatment (Table 1).

Treatment choice is a continuously evolving issue with a wide range of options. Seven drugs are now available for the treatment of chronic hepatitis B in Italy. They include recombinant Alpha Interferon (rIFN), Pegylated Alpha Interferon (PEG-IFN), nucleoside analogues, Lamivudine (LAM), Telbivudine (LdT), and Entecavir (ETV), and nucleotide analogues, Adefovir dipivoxyl (ADV) and Tenofovir (TDF).

However, information on the current practice of HBV treatment in the real world is lacking. Recently, we have evaluated the effectiveness of hepatitis C virus (HCV) treatment in Southern Italy [5]. It has allowed us a good opportunity to evaluate in the same area even the current practice of HBV infection treatment.

2. Methods

2.1. Study population

During a six month period (February–July 2010) all consecutive HBsAg positive subjects, who never had previously received antiviral therapies, referred to 16 liver units located in two southern Italian Regions (Calabria and Sicily) were recruited. Patients were eligible for the study if they were older than 18 years of age, had a positive HBsAg test by ELISA, regardless of HBV-DNA titre. Those that were found to have decompensated liver cirrhosis or hepatocellular carcinoma (HCC) were excluded.

At the time of enrolment, all patients received comprehensive counselling by a treating clinician, including natural history and prognosis of chronic HBV infection and treatment options. The treating physician at each centre was a gastroenterologist, hepatologist, or infectious disease specialist who was experienced in the management of patients with chronic HBV infection. Patients were evaluated for HBV therapies by the clinician using standardised criteria based on the current international treatment guidelines.

There is a common way, among the different centres, to manage HBV naive patients, as all are referral centres members of the Italian Association Study Liver Diseases (AISF).

Demographic information and results of laboratory testing were recorded on standardised data collection sheet. Diagnostic criteria for inactive carrier, chronic hepatitis and liver cirrhosis were used according to the American guideline [6]. An inactive carrier was defined as a person with persistent HBV infection of the liver without significant necroinflammation at liver biopsy; chronic hepatitis and liver cirrhosis as chronic necroinflammatory hepatic disease caused by persistent infection with HBV.

2.2. Laboratory assay

HBV markers, anti-hepatitis C virus (HCV), anti-hepatitis D virus (HDV), and anti-human immunodeficiency virus (HIV) were determined by ELISA tests. Serum HBV-DNA levels were determined by a commercial Real Time PCR assay (Abbott, Realtime, USA) with a sensitivity threshold of 10 IU/ml. Laboratory assays were performed in the various hospitals participating in the investigation.

2.3. Statistical analysis

Continuous variables were expressed as mean and standard deviation (SD), and Student's *t* test was used. Categorical variables were reported as absolute and percentage values, and compared by using chi-squared test. A p value<0.05 was considered to be significant. All reported p values were two sided.

3. Results

During the study period 247 HBsAg positive subjects were enrolled. Their mean age was 48.9 years, with a male preponderance (55.5%). The majority of subjects (53.0%) reported more than 5 years of awareness of HBsAg positivity. The proportion of HBeAg positive patients was 13.4%. Co-infection with HDV, or HCV or HIV was reported in 6.1%, 6.1%, and 3.6% respectively. The majority of cases (46.9%) had HBV-DNA undetectable or lower than 2000 UI/ml. Half of cases (49.0%) had normal transaminases values and one-fifth had >2 normal value. As many as 43.7% of subjects were labelled as inactive carriers and 14.6% had liver cirrhosis. Antiviral treatment was planned in 94 (38.0%) subjects. rIFN or PEG-IFN and nucleoside or nucleotide analogues were given in 10.5% and 27.5% of cases,

Table 2
Baseline characteristics of 247 HBsAg positive subjects.

Characteristic	
Age (years) (mean ± S.D.)	48.9 ± 13.8 (19–82)
Gender	
Male	137 (55.5%)
Female	110 (44.5%)
Years of awareness of HBsAg positivity[a]	
≤1	50 (23.3%)
1–5	51 (23.7%)
>5	114 (53.0%)
HBeAg positive	33 (13.4%)
Anti-HDV positive	15 (6.1%)
Anti-HCV positive	15 (6.1%)
Anti-HIV positive	9 (3.6%)
HBV-DNA (IU/ml)	
Undetectable	5 (2.0%)
<2000	111 (44.9%)
2000–20,000	43 (17.4%)
>20,000	88 (35.6%)
ALT (ULN)	
<1	21 (49.0%)
1–2	64 (25.9%)
2–5	51 (20.6%)
>5	11 (4.5%)
Diagnostic category	
Inactive carrier	108 (43.7%)
Chronic hepatitis	103 (41.7%)
Liver cirrhosis	36 (14.6%)
Treatment received	
No drug	153 (62.0%)
rIFN/PEG-IFN	26 (10.5%)
Nucleos(t)ide analogues	68 (27.5%)

[a] Some data are missing. ULN: upper limit of normal.

Table 3
Comparison of 247 chronic HBsAg according to decision for treatment.

	No treatment (n = 153)	Treatment (n = 94)	p
Age (years) (mean ± S.D.)	45.9 ± 13.3	53.8 ± 13.4	<0.001
Age (years)			
≤30	20 (13.1%)	4 (4.3%)	0.002
31–40	38 (24.8%)	13 (13.8%)	
41–50	35 (22.9%)	19 (20.2%)	
>50	60 (39.2%)	58 (61.7%)	
Gender			
Male	80 (52.3%)	57 (60.6%)	0.2
Female	73 (47.7%)	37 (39.4%)	
Years of awareness of HBsAg positivity[a]			
≤1	34 (26.0%)	16 (19.0%)	0.001
1–5	40 (30.5%)	11 (13.1%)	
>5	57 (43.5%)	57 (67.9%)	
HBeAg positive	20 (13.1%)	13 (13.8%)	0.8
Anti-HDV positive	12 (7.8%)	3 (3.2%)	0.1
Anti-HCV positive	9 (5.9%)	6 (6.4%)	0.9
Anti-HIV positive	8 (5.2%)	1 (1.1%)	0.09
HBV-DNA (UI/ml)[a]			
Undetectable	4 (2.6%)	1 (1.1%)	<0.001
<2000	96 (62.7%)	15 (16.0%)	
2000–20,000	30 (19.6%)	13 (13.8%)	
>20,000	23 (15.0%)	65 (69.1%)	
ALT (ULN)			
<1	110 (71.9%)	11 (11.7%)	<0.001
1–2	27 (17.6%)	37 (39.4%)	
2–5	15 (9.8%)	36 (38.3%)	
>5	1 (0.7%)	10 (10.6%)	
Diagnostic category			
Inactive carrier	99 (64.7%)	9 (9.6%)	<0.001
Chronic hepatitis	51 (33.3%)	52 (55.3%)	
Liver cirrhosis	3 (2.0%)	33 (35.1%)	

[a] Some data are missing. ULN: upper limit of normal.

respectively (Table 2). Presence of comorbidities, in untreated patients, that could influence the decisions of a physician was lacking.

Compared to untreated subjects, those who received therapy were more likely older (mean age 53.8 years vs. 45.9 years, p<0.01), with longer duration of awareness of HBsAg positivity (67.9% vs. 43.5%, p<0.01), with altered transaminase values and with highest proportion of HBV-DNA values at >20,000 UI/ml (69.1% vs. 15.0%, p<0.01). Note that 51 (49.5%) out of the 103 subjects labelled as having chronic hepatitis did not receive treatment. In contrast, 9 out of the 108 inactive carriers received treatment (Table 3). Thirty-two (62.7%) out of the 51 untreated chronic hepatitis cases had an HBV-DNA titre higher than 2000 UI/ml (data not shown).

Subjects treated with rIFN or PEG-IGN had a more likely mean younger age (44.3 years vs. 57.9 years, p<0.01) and they were more likely with chronic hepatitis (76.9% vs. 45.1%, p<0.01) as compared to those treated with nucleos(t)ide analogues (Table 4).

4. Discussion

Treatment of chronic hepatitis B has greatly changed over the last few years. Despite the availability of several effective drugs, areas of uncertainty exist and often therapeutical choices are made on the basis of evidence that is not fully mature. Moreover, information on current practice of HBV treatment in the real world is lacking. The present prospective survey, including patients never previously treated from several units (thus avoiding the single centre effect) may provide representative and valuable findings on this topic.

The large number of centres participating in this study may raise some concern for the homogeneity with which HBV patients have been evaluated and treated by the different involved centres. However, it should be taken into account that all were referral centre members of the Italian Association Study Liver (AISF), which adopts the same protocol in the management of HBV patients.

Nearly half of HBsAg carriers referring centres for evaluation have undetectable HBV-DNA or viral load below the threshold (2000 IU/ml) considered suitable for treatment. This figure likely underestimates the true proportion of inactive carriers in the general population, because subjects were selected and referred to participating centres by their general practitioners in order to potentially be treated. The majority (61.9%) of HBsAg carriers were not considered suitable for treatment. Among those treated nucleos(t)ide analogues are the preferred first choice as two-thirds of them receive these drugs. As expected, subjects treated with rIFN/PEG-IFN are more likely to be younger and without liver cirrhosis. Co-infection with other viruses (i.e. HDV, or HCV, or HIV) does not affect the choice.

Some pitfalls in treatment practice emerge. Treatment was provided to 9 (8.3%) out of the 108 inactive carriers. In contrast, and more importantly, as many as 51 (49.5%) out of the 103 chronic hepatitis cases did not receive any treatment despite EASL guidelines recommend to treat most of these cases [2]. The latter point represents a major pitfall. In fact, under treatment of chronic hepatitis cases limits the effectiveness of efficacious drugs currently available for treatment of chronic hepatitis. However, it should be considered that a limited period of observation cannot be exhaustive to take appropriate decision regarding timing and type of treatment as changes or fluctuation of viral load over time may occur [7]. It may explain why in some chronic hepatitis cases therapy was not provided during the study period.

Even if we are aware that the short period considered (6 months) may represent a source of bias that could affect the findings, this real world survey may provide the possible, even if not the best, picture of current treatment practice for HBV infection in Southern Italy.

Table 4
Comparison of chronic HBsAg carriers according to drug received.

	rIFN/PEG-IFN (n = 26)	Nucleos(t)ide analogue (n = 68)	p
Age (years) (mean ± S.D.)	44.3 ± 11.2	57.4 ± 12.1	<0.001
Age (years)			
≤30	2 (7.7%)	2 (2.9%)	<0.001
31–40	11 (42.3%)	2 (2.9%)	
41–50	6 (23.1%)	13 (19.1%)	
>50	7 (26.9%)	51 (75.1%)	
Gender			
Male	17 (65.4%)	40 (58.8%)	0.56
Female	9 (34.6%)	28 (41.2%)	
Years of awareness of HBsAg positivity[a]			
≤1	4 (17.4%)	12 (19.7%)	0.3
1–5	5 (21.7%)	6 (9.8%)	
>5	14 (60.9%)	43 (70.5%)	
HBeAg positive	6 (23.1%)	7 (10.3%)	0.1
Anti-HDV positive	1 (3.8%)	2 (2.9%)	0.8
Anti-HCV positive	2 (7.7%)	4 (5.9%)	0.7
Anti-HIV positive	0	1 (1.5%)	0.5
HBV-DNA (UI/ml)[a]			
Undetectable	0	1 (1.5%)	0.7
<2000	3 (11.6%)	12 (17.6%)	
2000–20,000	5 (19.2%)	8 (11.8%)	
>20,000	18 (69.2%)	47 (69.1%)	
ALT (ULN)			
<1	5 (19.2%)	6 (8.8%)	0.5
1–2	8 (30.8%)	29 (42.6%)	
2–5	10 (38.5%)	26 (38.2%)	
>5	3 (11.5%)	7 (10.3%)	
Diagnostic category			
Inactive carrier	5 (19.2%)	4 (5.8%)	<0.001
Chronic hepatitis	20 (76,9%)	32 (47.1%)	
Liver cirrhosis	1 (3.9%)	32 (47.1%)	

[a] Some data are missing. ULN: upper limit of normal.

Despite some limitations, this study may contribute to critically review therapeutic choices in actual clinical practice.

The majority of HBsAg carriers don't receive antiviral treatment. Nucleos(t)ide analogues are the preferred first choice for treatment. A long-lasting period of observation may be needed to make appropriate therapeutic decisions in several cases.

Learning Points

- Treatment choice of chronic HBV infection is a continuously evolving issue due to the introduction of several new and effective antiviral agents
- Information on the current practice of HBV treatment in the real world is lacking.
- The majority of HBsAg carriers don't receive antiviral treatment.
- Nucleos(t)ide analogues are the preferred first choice for treatment.

Conflict of interest

The authors declare that they have no conflict of interest.

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