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The burden of HBV infection in HCV patients in Italy and the risk of reactivation under DAA therapy

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ABSTRACT

Background: There is increasing awareness of HBV reactivation in HCV-RNA-positive/HBV-coinfected patients with chronic liver disease (CLD) treated with oral direct-acting antivirals (DAAs).
Aim: To provide figures on the prevalence of HBV markers in HCV-RNA-positive subjects in Italy, where these findings are lacking.
Methods: All subjects aged ≥18 years with CLD consecutively referring to Italian liver units located throughout country were prospectively enrolled in two national surveys in 2001 and 2014.
Results: The total number of HCV-RNA-positive cases was 6984; 356 (5.1%) subjects vaccinated against HBV were excluded. A total of 6628 cases were evaluated. The prevalence rates of HBsAg, isolated anti-HBc and anti-HBc/anti-HBs-positivity were 2.9%, 8.1% and 14.7%, respectively. Among the estimated one million HCV-RNA-positive subjects in Italy, a substantial number of subjects are at risk of HBV reactivation due to DAA therapy. The prevalence of liver cirrhosis was higher than that of CLD in HBsAg-positive subjects (4.4% vs. 2.6%, $p < 0.01$) but not in those positive for other HBV markers.
Conclusions: These findings outline the burden of HBV markers among HCV-RNA-positive subjects in Italy, where in 2017 reimbursement for DAA therapy by the National Health System became universal for all patients with chronic HCV infection. HBV vaccination coverage should be greatly extended, since nearly two thirds of subjects in this study resulted negative for any HBV marker.

1. Introduction

Recent papers have shown that Interferon-free hepatitis C virus (HCV) therapies with direct-acting antiviral agents (DAAs) can induce a reactivation of hepatitis B virus (HBV) in HCV-treated patients with a concomitant overt or occult HBV infection. This has raised growing interest in the prevalence of HBV serum markers among HCV-RNA-positive subjects, namely hepatitis B surface antigen (HBsAg), antibody to HBsAg (anti-HBs) and antibody to HBV core antigen (anti-HBc). DAA-induced HBV reactivation occurs more frequently in HBsAg-positive individuals than in persons with a resolved HBV infection (HBsAg-negative/anti-HBc-positive with or without anti-HBs) [1,2].

Several studies have reported the prevalence figures of chronic HCV infection among patients with chronic HBV infection [3–8], whereas little is known on the prevalence of HBV markers in patients with HCV infection. A study performed in the U.S.A. showed that among 1257 HCV-RNA-positive subjects, 5.8% were HBsAg-positive and 58.8% had evidence of prior exposure to HBV [9].

The burden of HCV-RNA positive subjects at risk of HBV reactivation is currently lacking in Italy, where in 2017 reimbursement for DAA therapy by the National Health System (NHS) became universal for all patients with chronic HCV infection.

By pooling the data of two prospective national surveys performed in 2001 [10] and 2014 [11] on subjects referring to several

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liver units for evaluation of chronic liver disease (CLD), we herein provide figures on the prevalence of HBV markers among HCV-RNA-positive subjects in Italy.

2. Material and methods

2.1. Patients

The two national surveys have been previously described [10,11]. Briefly, the first enrolled 9997 subjects with CLD consecutively referring to 79 liver units in 2001 and the second 2408 CLD cases consecutively referring to 15 Italian liver units in 2014. In both studies all patients aged 18 years or older referring to the participating liver units for altered hepatic biochemistry or positivity for hepatitis viral markers were prospectively enrolled as inpatients or outpatients only once at their first observation over a six-month period. These liver units were located all over the country. Most of the 15 units participating in the second survey had also taken part in the first. Subjects that participated in the first survey were excluded from the second survey in order to avoid the same patients being counted twice in the prevalence estimates. Access procedures, clinical approach and analytical methods were similar in both surveys. For each patient, a pre-coded questionnaire containing demographic, epidemiological and clinical data was filled out. No patient refused to participate in the studies.

2.2. Ethics statement

This study (extensive protocol, participating centres and summary grid) was formally and definitively approved by the Ethics Committee of the Coordinating Center (Prof. Piero Luigi Almasio), Ethics Committee of the University Hospital (Azienda Ospedaliera Universitaria Policlinico P. Giaccone" of Palermo, Italy) on December 9, 2015 (Protocol number 11/2015, point 18). All procedures applied in the study were in accordance with the international guidelines, with the standards of human experimentation of the local Ethics Committees and with the Helsinki Declaration of 1975, revised in 1983.

At the time of enrolment in the two surveys, each patient signed an informed consent for the collection of personal data, as designated by the Ethics Committee of the coordinating centre.

Patients who agreed to undergo liver biopsy signed an appropriate informed consent before biopsy was performed.

2.3. Diagnostic criteria

The diagnosis of chronic hepatitis was based on liver histology when available, or, in the absence, on the persistence (>6 months) of abnormal ALT in the absence of clinical, biochemical and ultrasound (US) evidence of liver cirrhosis [12]. The diagnosis of liver cirrhosis was based on liver histology or on the characteristic clinical, biochemical, and US signs [12]. The diagnosis of hepatocellular carcinoma (HCC) was based on histological and/or imaging findings and alpha-1-fetoprotein serum levels [13].

2.4. Serological assays

Serum HBV markers (HBsAg, anti-HBc, anti-HBs) and antibody to HCV were sought using commercial immune enzymatic assays. HCV RNA was detected and quantified by a real-time PCR in a Light cycler 1.5 with a detection limit of 40 IU/mL.

2.5. Statistical analysis

The data were collected in a pre-established electronic CRF database (web-based data collection, e-CRF provided by Air-TelR, Airon Telematica, Milan, Italy). Continuous variables were summarized as means and standard deviation, and categorical variables were summarized as absolute and relative frequencies. Differences in means and in proportions were evaluated by the Student t-test and by a Chi-squared test, respectively. A p value <0.05 was considered significant. All p values were two-tailed.

3. Results

Of the 12,405 subjects enrolled, 8304 resulted anti-HCV-positive, and, of these, 6984 (84.1%) were HCV-RNA-positive. After the exclusion of 356 subjects vaccinated against hepatitis B (presence of isolated anti-HBs positivity), the total number of HCV-RNA-positive subjects evaluated in the present study was 6628. The proportion of chronic hepatitis cases was 76.5%, that of liver cirrhosis 19.9%, and that of HCC 3.7% (data not shown). Of these subjects, 191 (2.9%) resulted HBsAg-positive, 540 (8.1%) HBsAg/anti-HBs-negative and anti-HBc-positive, 972 (14.7%) HBsAg-negative and anti-HBc/anti-HBs-positive, 1703 (26.0%) positive for any HBV marker. All HBV markers showed a decreasing prevalence over time, reaching a statistically significant level only for HBsAg-negative subjects with a presence of both antibodies, and for those positive for any HBV marker (Table 1). None of the 191 subjects with an overt infection (HBsAg positive) was a carrier without HBV induced liver disease.

HBsAg-positive subjects were significantly younger (51.7 vs. 56.6 and 54.4 years; $p < 0.01$) and with a higher male to female sex ratio (3.5 vs. 1.3 and 1.4; $p < 0.01$) compared to those with isolated anti-HBc or those with a presence of both antibodies. The prevalence of liver cirrhosis was significantly higher than that of chronic hepatitis in subjects positive for HBsAg (4.4% vs. 2.6%, $p < 0.01$), but not in those positive for other HBV markers. A statistically significant difference ($p < 0.01$) in educational level and area of birth was observed only in subjects with isolated anti-HBc positivity (Table 2).

Applying the observed prevalence rates to the estimated one million HCV-RNA-positive subjects living in Italy, a number recently provided by a survey among the general population in five Italian metropolitan areas [13], we can hypothesize the potential number of subjects with HBV markers among HCV-RNA-positive subjects in Italy: nearly 30,000 subjects with overt HBV infection (i.e. presence of HBsAg), almost 80,000 with isolated anti-HBc positivity, and 145,000 with a resolved HBV infection (HBsAg-negative and anti-HBc/anti-HBs-positive) (Table 3).

Table 1
Prevalence of HBV markers among 6628 HCV-RNA-positive subjects with chronic liver disease in Italy.

Markers	All patients (No. = 6628)	2001 study (No. = 5808)	2014 study (No. = 820)	p-Value
HBsAg-positive, No. (%)	191 (2.9%)	175 (3.0%)	16 (2.0%)	n.s.
Isolated Anti-HBc-positive, No. (%)	540 (8.1%)	488 (8.4%)	52 (6.3%)	n.s.
Anti-HBc/Anti-HBs-positive, No. (%)	972 (14.7%)	869 (15.0%)	103 (12.6%)	0.01
Any positive HBV marker, No. (%)	1703 (26.0%)	1532 (26.4%)	171 (20.9%)	<0.01

Table 2
Prevalence of HBV markers among 6628 HCV-RNA-positive subjects with chronic liver disease in Italy.

Variables	HBsAg positive (No. = 191)	p	Isolated anti-HBc positive (No. = 540)	p	Anti-HBs/anti HBs-positive (No. = 972)	p
Age (years) (mean ± SD)	51.7 ± 14.5		56.6 ± 14.4		54.4 ± 15.1	<0.01
Male to female sex ratio	3.5		1.3		1.4	<0.01
Diagnosis, No. (%)						
- Chronic hepatitis (n = 5070)	123 (2.6%)	<0.01	412 (8.1%)	n.s.	742 (14.6%)	n.s.
- Liver cirrhosis/HCC (n = 1558)	68 (4.4%)		128 (8.2%)		230 (14.8%)	
Level of schooling, No. (%)						
- Low/medium (n = 4722)	146 (3.1%)	n.s.	413 (8.7%)	<0.01	706 (15.0%)	n.s.
- High (n = 1906)	45 (2.4%)		127 (6.7%)		266 (14.0%)	
Area of birth in Italy, No. (%)						
- North/center (n = 2670)	76 (2.8%)	n.s.	184 (6.9%)	<0.01	362 (13.6%)	n.s.
- South/islands (n = 3958)	115 (2.9%)		356 (9.0%)		610 (15.4%)	

Table 3
Number of subjects positive for HBV markers among the estimated one million HCV-RNA-positive subjects in Italy (Ref. No. 16).

Marker	Number
HBsAg-positive	29,000
Isolated anti-HBc-positive	82,000
Anti-HBc/anti-HBs-positive	145,000
Any positive HBV marker	256,000

4. Discussion

The 2001 and the 2014 nationwide prevalence surveys were structurally similar. Both studies were cross-sectional and prospectively enrolled over a six-month period inpatients and outpatients aged 18 years or more with CLD of any etiology consecutively referring for altered hepatic biochemistry or positivity of hepatitis virus serum markers at one of the participating liver units. The same clinical approach, analytical methods and facilities to access the participating liver units were adopted; several of these liver units had participated in both the 2001 and 2014 surveys. For these reasons pooling and comparison of the two studies raised no concern. In addition, the large number of patients investigated and the geographical distribution of the liver units throughout the country supports a generalization of the findings for the whole of Italy.

The availability of DAA therapy for chronic HCV infection is a milestone in the cure of this disease. These drugs can eliminate the virus in more than 95% of subjects treated, including those with liver cirrhosis and those with HIV co-infection [15].

There is increased awareness of HBV reactivation in chronic HCV/HBV co-infected patients treated with DAAs [1,2]. The recent emergence of this adverse event of DAA therapy is due to the exclusion of HBV co-infected subjects from registration clinical trials evaluating the safety of these treatments. A likely explanation for this adverse event is that the clearance of HCV infection due to effective anti-HCV therapy may remove the suppression exerted by HCV over HBV replication [16], thus inducing HBV reactivation [17]. Spontaneous fluctuations of HBV replication or of the immunological changes after HCV clearance have also been suggested rather than a direct HBV/HCV interference [18]. The severity of hepatic damage may range from HBV reactivation without hepatitis to fulminant hepatic failure requiring liver transplantation [1]. The risk of HBV reactivation differs according to the HBV infection status: high in subjects with an overt infection, but low in those with an occult infection [1,2]. The European Association for the Study of the Liver (EASL) guidelines focus on the management of subjects with HBV/HCV coinfection [18]. The EASL guidelines recommend testing for HBV markers before starting DAAs for HCV. HBsAg positive patients should be considered for concomitant NA prophylaxis, while the HBsAg-negative/anti-HBc-positive should be monitored and tested for HBV reactivation in the case of ALT elevation [18].

In Italy, oral DAA therapy became available in 2015; the reimbursement criteria by the NHS provided prioritized access to treatment to cover the urgent necessities based on the severe liver disease. In 2017 reimbursement by the NHS became universal for all patients with HCV chronic infection. The present findings, collected just before the start of this policy for HCV infection, estimate the potential burden of subjects at risk of HBV reactivation.

HBsAg positivity is found in nearly 3% of HCV-RNA-positive subjects, a rate more than three-fold higher than that observed in the general population [19]. This figure is not surprising because HBV and HCV share several modes of transmission. This proportion means that among the estimated one million HCV-RNA-positive subjects living in Italy, nearly 30,000 could be HBsAg-positive subjects at risk of DAA-induced HBV reactivation. Careful monitoring should also be addressed to the nearly 80,000 subjects with isolated anti-HBc also at risk of reactivation, albeit to a lesser extent. However, it should be considered that the real population target eligible for antiviral treatment is less as only part of these individuals will be identified and will have access to HCV therapy.

Some concern exists for subjects negative for any HBV marker still not vaccinated for HBV, representing nearly three quarters of the enrolled HCV-RNA-positive cases, despite the fact that immunisation has been strongly recommended and offered free of charge for this population.

The significantly higher male to female sex ratio in HCV-RNA/HBsAg-positive subjects compared to those with positivity for other HBV markers may suggest a more likely HBV clearance in females, once infected.

Among the HCV-RNA-positive subjects investigated, the prevalence of liver cirrhosis resulted significantly higher than that of chronic hepatitis in HBsAg-positive subjects, but not in those positive for other HBV markers, confirming that overt HBV infection speeds up HCV chronic hepatitis to a more severe outcome [7–9,16,20].

In conclusion, these findings outline the burden of HBV markers among the HCV-RNA-positive subjects in Italy, where reimbursement of oral DAA therapy by the NHS has become universal for all subjects with HCV infection. HBV vaccination coverage requires greater effort by the Italian Healthcare Authorities to reach the nearly two thirds of HCV-RNA-positive subjects at risk of acquiring HBV infection.

Conflict of interest
None declared.

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