Low risk of HBV reactivation in a large European cohort of HBV/HCV coinfected patients treated with DAA

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1 INTRODUCTION

In recent years many IFN-free therapies with direct acting antivirals (DAA) were introduced for successful treatment of HCV infection. Effective elimination of HCV may increase the risk of the shift in the immune control in treated patients and reactivation of chronic viral infections including *Herpesviridae* and HBV [1]. Several cases of HBV reactivation during DAA for hepatitis C were described in both HBsAg(+) and HBsAg(-)/anti-HBc IgG(+) patients [2]. However the exact rate of HBV-reactivation in HBV/HCV coinfection is poorly defined, especially in large European cohorts.

2 AIM

The aim of study was to characterize HBV/HCV coinfection and evaluate the prevalence HBV-reactivation during DAA in a large European cohort.

3 METHODS

EpiTer-2 is an investigator-initiated study, supported by the Polish Association of Epidemiologists and Infectiologists and includes 22 Polish centers involved in treatment of hepatitis C [3].

- Studied population consisted of 6228 chronic hepatitis C patients (52% female, mean age 54yo, 82% HCV-GT1b, 34% with liver cirrhosis) included in a large national database EpiTer-2.
- All patients included received DAA therapy between 1 July 2016 and 31 December 2017. DAA regimen f was selected without fibrosis restrictions, based on the physician's judgement among reimbursed therapeutic options
- Treatment was administered according to the current protocol of the NHF and product characteristics by the European Medicines Agency.
- DAA combinations consisted mainly of OBV/PTV/r±DSV±RBV (53%) and LDV/SOF±RBV (28%). Prior to the DAA all subjects had HBsAg testing and ALT-activity evaluated every 4 weeks during DAA. Anti-HBc IgG testing was available in 742 patients without HBsAg.

4 RESULTS

- **70 of 6228 patients (1.1%) had detectable HBsAg.** In the HBsAg negative group 742 patients were HBcAb positive, although this parameter was not tested in every patient.
- **HBV/HCV patients were significantly younger** and more often infected with HCV-GT3 and 4 than HCV-group (Table 1). They were also **less often diagnosed with arterial hypertension** (26% vs 38%, P=0.04), **diabetes** (6% vs 15%, P=0.03) **and had lower BMI** (24.5 vs 26.0, P<0.01). On the other hand, proportion of liver cirrhotics, ALT activity, MELD and Child-Pugh were comparable.
- **HIV co-infection was much more prevalent in the HBsAg** positive group comparing to the HbsAg negative group (10% vs 3%, P<0.001). There were 142 cases of liver transplant prior to or during the anti-HCV treatment in the studied population, including 1 in the HBsAg positive group
- Prior of DAA only 21 (30%) of HBV/HCV required NA-therapy
- In HBsAg negative group patients were treated with: OBV/PTV/r+-DSV based regimes (n=3307; 54%), SOF based regimes (n=2237; 35%), GZR/EBR based regimes (n=413; 7%), ASV+DCV based regimes (n=134, 2%) and other (n=67; 1%).
- In HBsAg positive group patients were treated with: OBV/PTV/r+-DSV based regimes (n=33; 47%), SOF based regimes (n=34; 49%), GZR/EBR based regimes (n=3; 4%).
- In both groups **DAA-therapy was continued according to plan in 96% (HBV/HCV) vs 95% (HCV)** and number of adverse events was comparable. **SVR rates were similar in HBV/HCV and HCV in overall group (mITT 97% vs 95%, P=0.7)** and for specific HCV-genotypes (Figure 1).
- 151 cases of **hepatocellular carcinoma (HCC)** were reported before or during the anti-HCV therapy, although only 1 in the HBsAg positive group. 37 deaths occurred during treatment, although none of them were related to the DAA side effects.
- **In HBsAg(+) subjects 3 (4.3%) HBV reactivations were observed.** All 3 subjects with reactivation were HBeAg(-), infected with HCV-GT1 and had advanced liver disease (F3-F4). One reactivation was clinically significant with HBV-DNA increase (from 1.3 to 7.6 log10 IU/mL at wk5) and ALT-flare (1337 IU/m) requiring DAA discontinuation and NA therapy, while 2 remaining were subclinical with HBV-DNA increase form negative to 1.3 (wk12) and 3.2 log10 IU/mL (wk8). All subjects with HBV-reactivation reached SVR. Table 2.
- **No reactivations were observed in HBsAg(-) / anti-HBc(+) subjects**

Table 1. Characteristics of HBV/HCV vs HCV-monoinfected subjects

Serologic status	HBsAg – (n=6158)	HBsAg + (n=70)	p
n	6158 (99%)	70 (1%)	
Age [years]	56	42,5	<0,001
Sex	M=2967 (48%), F=3191 (52%)	M=43 (61%), F=27 (39%)	0,03
HCV genotype	1=124 (2%); 1a=154 (2%); 1b=5089 (83%); 2=5 (0,1%); 3=544 (9%); 4=242 (4%)	1=1 (1,5%) 1a=3 (4%); 1b=50 (71%); 2=0 (0%) 3=10 (14%); 4=6 (9%)	<0,001
Previous treatment	yes = 2622 (43%) no = 3536 (57%)	yes = 30 (43%) no = 40 (57%)	0,96
Fibrosis [Metavir]	0=40 (1%); 1=1701 (27%); 2=1021 (17%); 3=1086 (18%); 4=2096 (34%); not tested=214 (3%)	0=1 (2%) 1=18 (26%); 2=11 (16%); 3=14 (20%); 4=24 (34%); not tested=2 (2%)	0,91
Entecavir	-	11 (16%)	
Tenofovir	-	10 (14%)	
HIV coinfection	166 (3%)	7 (10%)	<0,001
OLTx	141 (2%)	1 (1%)	
Comorbidities	Hypertension = 2318 (38%) Chronic kidney disease = 329 (5%) Diabetes = 939 (15%) Autoimmune disease = 138 (2%)	Hypertension = 18 (26%) Chronic kidney disease = 7 (10%) Diabetes = 4 (6%) Autoimmune disease = 0	0,04 0,08 0,03
BMI	26,03 (21.2-32.1)	24,49 (19.6-30.8)	0,008

Figure 1. Treatment efficacy in mITT analysis for HBV/HCV vs HCV-monoinfected subjects

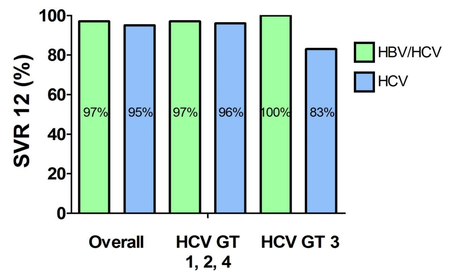

Table 2. Characteristics and outcomes of HBsAg(+) patients with HBV-reactivation during DAA-therapy

	Age	Sex	HCV GT	DAA regimen	Fibrosis	HBsAg	HBeAg	HBV-DNA BL	BL AN-therapy	Reactivation time on DAA	HBV-DNA at reactivation (IU/mL)	ALT at reactivation (IU/mL)	DAA / NA	SVR	HBV outcome
Pt 1	28	M	1a	OBV/PTV/r+DSV+RBV	4	Pos	Neg	25 IU/mL	No	Week 5	7.6 log10	1337	Stopped ETV	Yes	ETV HBV-DNA(-)
Pt 2	59	M	1b	LDV/SOF+RBV	4	Pos	Neg	Neg	Yes LAM	Week 8	3.2 log10	<ULN	Cont. LAM	Yes	LAM resist. Switch to TDF
Pt 3	30	M	1b	OBV/PTV/r+DSV+RBV	3	Pos	Neg	Neg	No	Week 12	1.3 log10	<ULN	Cont. No NA	Yes	No AN HBV-DNA(-)

5 CONCLUSIONS

- **Data form a large European cohort suggest that the risk of HBV reactivation during therapy with DAA seems to be low in HBsAg(+) HBV/HCV subjects (<5% subclinical, ~1% clinical), while probably neglectable in HBsAg(-)/anti-HBc IgG(+).**
- **Subjects with HBV/HCV coinfection seem to less often present symptoms and complication of metabolic syndrome.**

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