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Evaluation of intracellular and plasma pharmacokinetics, pharmacogenetics and clinical features in HBV e antigen-negative patients treated with entecavir.

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Stampa a cura della S.C. Relazioni Esterne ASL TO 2

BACKGROUND

Hepatitis B infection affects two billion people worldwide and 350 million of these are chronically infected. Chronic hepatitis B virus is one of the most important cause of mortality and morbidity worldwide (1). Treatment options include currently available pegylated interferon and nucleos(t)ide analogues: among these, entecavir is currently the most used (2). Despite this, not many information are currently available about its plasma pharmacokinetics and its intracellular disposition.
Vitamin D is an important immunomodulator and it has a role in inflammatory and metabolic liver diseases, including infection with hepatitis C virus (HCV) (3). The relationship between vitamin D metabolism and chronic HBV infection remains unknown, but its levels result low in patients affected by this virus.

OBJECTIVES

Our aim was to study entecavir plasma/intracellular pharmacokinetics and the impact of single nucleotide polymorphisms (SNPs) related to its metabolism/distribution and vitamin D pathway.

	UNIVARIATE *p;OR (IC 95%)*	*MULTIVARIATE* *p;OR (IC 95%)*
Age	0,228; 0,064 (0.007; 0.120)	
Sex	0,996; 0-005 (-1946; 1.957)	0,089; 172 (-28; 372)
Metavir score	**0,193; 0.511 (-0,271; 1,292)**	0,616; 0,187 (-0,571;0,946)
ALT	0,409; -0,006 (-0,021; 0,009)	
Cirrhosis	0,661; 0,472 (-1,699;2,643)	
Genotype	0,402; 0,207 (-0,208; 0,702)	
ΔHBsAg 1 month	**0,150; 2,008 (-0,764; 4,779)**	0,159; 1,674 (-0,694;4,041)
PEPT2 rs1143670 AA	0,750; 0,173 (-0,917; 1,263)	
UGT1A3 rs1983023 TT	0,434; 0,378 (-0,592; 1,348)	
CNT2 -146 TT	0,905; -0,070 (-1,267; 1,126)	
CNT2 124 TT	0,518; -0,345 (-0,729; 1,418)	
CNT2 225 CA/AA	0,538; 0,319 (-0,723; 1,632)	0,008; 160 (-35; 356)
CNT3 338 TT	0,823; -0,825(-2,865; 2,294)	
ENT1 rs747199 GG	0,740; 0,258 (-1,308; 1,823)	
ENT1 rs760370 GG	0,834; 0,109 (-0,937; 1,154)	
AK1 rs1109374 TT	**0,180; -0,790 (-1,964; 0,383)**	0,627; -0,256 (-1,322;0,810)
NT5C2 rs1083841 CC	0,519; -0,500 (-2,159; 1,058)	
HNF4α rs1884613 GG	0,491; -0,402 (-1,576; 0,771)	
OAT1 rs4149170 AA	**0,148; -1,057 (-2,509; 0,396)**	0,646; -0,310 (-1,675;1,056)
OCT1 rs683369 GG	0,682; 0,380 (-1,489; 2,249)	
CYP27B1 +2838 TT	**0,065; 1,318 (-0,084;2,720)**	0,889; 0,201 (-2,736;3,139)
CYP27B1 -1260 GT/TT	**0,035; -1,488 (-2,869;-0,107)**	**0,006; -1,072 (-2,316; 0,172)**
CYP24A1 rs2248359 TC/CC	**0,078; -0,929 (-1,968; 0,110)**	0,389; -0,419 (-1,399;0,561)
CYP24A1 rs927650 CT/TT	0,287;-0,729 (-2,098;0,640)	
CYP24A1 rs2585428 GG	0,370; -0,537 (1,740;0,665)	
VDR ApaI AA	0,671; 0,218 (-0,817;1,253)	
VDR TaqI CC	0,242; 0,678 (-0,479;1,836)	
VDR FokI TC/CC	0,238; -0,734 (-1,375; 0,578)	
VDR BsmI AA	**0,152; 0,800 (-0,312; 1,911)**	0,824; -0.117 (-1,201; -0,966)
VDR Cdx2 AG/GG	0,486; -0,335 (-1,301;0,632)	
ESR1 rs2234693 TT	0,411; 0,496 (0,713;1,705)	
VDBP rs7041 GG	0,705; -0,183 (-1,155;0,789)	
CYP27A1 rs4674343 GG	0,604; -0,288 (-1,408; 0,832)	
IL28B rs12979860 CC	0,279; -0,655 (-1,865;0,555)	
IL28B rs12980275 AA	0,273; -0,700 (-1,978;0,578)	
IL28B rs8099917 TT	0,312; 0,844 (-0,828;1.516)	

Table 1. Factors, in univariate and multivariate analyses able to predict the ΔHBV DNA at three months of therapy (drop of HBV DNA at three months of therapy compared to HBV DNA at baseline).

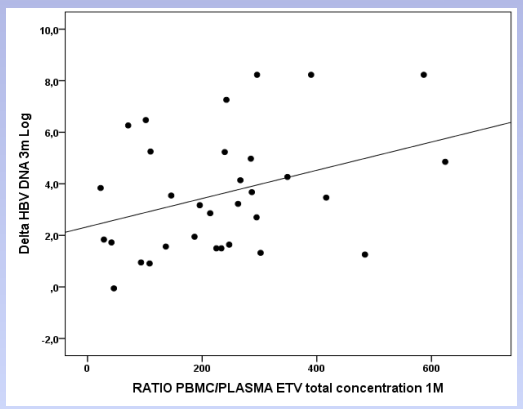

Figure 1. Direct correlation between ΔHBV DNA Log at 3rd month and RATIO PBMCs/plasma entecavir total concentration at 1 month.

MATERIALS AND METHODS

We have enrolled HBV e antigen-negative chronically infected adult patients treated with the standard dose of 0.5 mg/die of entecavir; we have evaluated plasma and peripheral blood mononuclear cells (PBMCs) entecavir exposure according to SNPs in the following genes: *CYP27A1, CYP27B1, CYP24A1, VDR, VDBP, UGT1A3, SLC28, SLC29, OAT1, OCT1, AK1, NT5C2, HNF4, IL28, NT5C2, AK1, PEPT2, hENT1, UGT1A3, ESR1* with real-time PCR analyses. Drug plasma and intracellular concentrations were measured through an UPLC-MS/MS validated method.

RESULTS

36 patients infected with different HBV genotypes were enrolled; pharmacogenetic results suggested that plasma concentrations were influenced by *AK1 rs1109374 CC* (p=0.041), *CYP24A1 rs2248359 TC/CC* (*p*=0.028), *CNT2 124 rs11854484 CT/TT* (*p*=0.037), *CNT2 225 rs1060896 CA/AA* (p=0.037) genotypes; a significant association between *CYP24A1 rs927650 CT/TT* (*p*=0.020) and entecavir PBMCs levels was found. In the logistic regression analysis, *CNT2 225 CA/AA* (*p*=0.008) and *CYP27B1-1260 GT/TT* (*p*= 0.006) genotypes were factors able to predict the ΔHBV DNA at three months of therapy (drop of HBV DNA at three months of therapy compared to HBV DNA at baseline, table 1).
Concerning pharmacokinetics, according to the efficacy marker of HBV DNA reduction of 2 Log at three months of therapy, a PBMC/plasma ratio cut-off value of 276 was identified (*p*=0.028, sensitivity 50%, specificity 87%; AUROC= 0.741, figure 1).

CONCLUSIONS

Pharmacogenetics and therapeutic drug monitoring could contribute to improve therapy optimization on the basis of interindividual genetic variability. Our work provides a new overview of entecavir pharmacogenetics and it adds information concerning intracellular exposure, which actually lacks in literature.

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