VDR gene polymorphisms impact on anaemia at 2 week of anti-HCV therapy: a possible mechanism for early RBV-induced anaemia.

Jessica Csusato1, Sarah Allegra1, Lucio Boglione1, Amedeo De Nicolò1, Giuseppe Cariti1, Giovanni Di Perri1 and Antonio D’Avolio1.

BACKGROUND

Vitamin D receptors (VDR) binds the active form of calcitriol and modulates several physiological systems, through genomic and non-genomic pathways. Calcitriol stimulates store-operated channels Ca2+ influx by translocation of the caveolar VDR to the plasma membrane. An increase in intracellular Ca2+ concentration can deregulate erythrocytes membrane composition, cell volume, glycolytic enzymes regulation, redox state and cell clearance1.

OBJECTIVES

Our aim was to retrospectively evaluate the role of individual single nucleotide polymorphisms (SNPs) in ITPA, CYP27B1, CYP24A1 and VDR genes in the prediction of ribavirin (RBV) and pegylated-interferon-alpha (pegIFN-α) therapy-induced anaemia in a cohort of HCV mixed genotypes monoinfected patients at 2 and 4 weeks of treatment.

MATERIALS AND METHODS

Allergic discrimination for ITPA rs7207010 A>C, rs6051702 A>C and rs1127354 C>A, CYP27B1 rs6446536 (+2388) C>T and rs10877012 (-1260) G>T, CYP44A1 rs2298359 T>C, rs2585428 A>G and rs927650 C>T, VDR rs795232 (Apol) G>A, rs731236 T>C (TaqI), rs1544110 G>A (BsmI), rs7053810 T>C (FokI) and rs11568820 A>C (Cdx2) SNPs was performed by real-time PCR.

RESULTS

Two hundred and twenty five patients were included in the study. The linkage disequilibrium (LD) analysis was shown in figure 1. At week 2, CYP24A1 rs6051702 (p=0.025), Apal (p=0.042) and BsmI (p=0.004) SNPs were associated with anaemia. The univariate analysis identified the following factors: gender, body mass index (BMI) at baseline > 30 Kg/m², ALT at baseline > 37 IU/L, steatosis, ITPA rs6051702 AC/CC, CYP24A1 rs927650 TT, CYP27B1 +2838 TT, Apal CC and BsmI AA profiles. All the patients developing early anaemia at week 2 have CC genotype for ITPA rs1127354 SNP. In multivariate analysis only BMI at baseline > 30 Kg/m² (p=0.013), ALT at baseline > 37 IU/L (p=0.020) and BsmI AA profile (p=0.003) were statistically significant (table 1).

At week 4, ITPA rs6051702 (p=0.002) and rs1127354 (p=0.003) SNPs were associated with anaemia in the univariate analysis among 4 years, diabetes, insulin resistance, peg-type, FokI TCC and ITPA rs6051702 AC/CC profiles remained in the model. Also in this case, all the anemic patients were CC for ITPA rs1127354 SNP. In the multivariate analysis ITPA rs6051702 AC/CC genotype (p=0.001) was the only retained factor (table 2).

CONCLUSIONS

BsmI AA genotype is a predictive factor of anaemia at 2 weeks and could be related to an enhanced activity of the VDR, thus an increased calcium influx, resulting in the deregulation of the Ca2+-dependent signaling. These results indicate for the first time the strong, significant and ITPA-independent role of VDR in the early development of RBV-induced anaemia and confirm the VDR function in the prediction of anaemia at week 42,3.

REFERENCES