The Association of vitamin D metabolic pathway related genes polymorphisms with virologic response in HBeAg-negative patients treated with pegylated interferon: Multicenter study

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Background/aims:In chronic hepatitis B (CHB)-infected patients, low serum vitamin D levelare associated with high level of hepatitis B virus (HBV) replication.From GWAS data, the number of single nucleotide polymorphisms (SNPs) within the 7-dehydrocholesterol reductase (*DHCR7*), 1-α-hydroxylase (*CYP27B1*), Cytochrome P450, family 2, subfamily R, polypeptide 1 (*CYP2R1*), vitamin D binding protein (*GC*) and vitamin D receptor (*VDR*) of the vitamin D synthetic pathway is related with vitamin D level and function. This study aimed to determine the association between the SNPs of vitamin D cascade and response to peginterferon (PegIFN) therapy in patients with HBeAg-negative CHB infection.

Methods:115 patients with HBeAg-negative CHB infection treated for 48 weeks with PegIFN-alfa 2a from 13 hospitals were prospectively enrolled. Thirteen SNPs across the vitamin D cascade related genes, including *DHCR7* (rs12785878), *CYP27B1* (rs10877012), *CYP2R1* (rs2060793, rs12794714), *GC* (rs4588, rs7041, rs222020, rs2282679) and *VDR* (*Fok*I, *Bsm*I, *Tru9*I, *Apa*I, *Taq*I) were genotyped.The virologic response was defined as HBV-DNA < 2,000 IU/ml.

Results: Majority of patients (81.7%) had HBV genotype C and 5.3% (n=5) had liver cirrhosis. At 24 weeks after therapy, 55.7%(n=54) achieved sustained virologic response (SVR) and 6.3% (n=6) cleared HBsAg. Seventy-two patients (79.1%) gained end-of-therapy virologic response (ETVR).The non-CC allele of *Fok*I(85.3%) wassignificant associated with higher ETVR than CC allele of *Fok*I(60.9%)($p<0.05$).Patients who had non-CC allele of *Fok*Itended to have lower mean HBsAg level during therapy than CC allele. The *Fok*Ipolymorphism had no impact on decline of HBV DNA during therapy and 24 weeks of follow-up.All of the studying SNPs in vitamin D pathway were not associated with SVR and HBsAg lost at 24 weeks after therapy. In multivariate analysis, pre-treatment.HBsAg level < 10,000 IU/ml (OR=13.71, 95%CI=1.34-140.08, p=0.03) and pre-treatment HBV DNA < 4 log IU/ml

(OR=5.00, 95% CI=1.31-19.08, p=0.02) predicted SVR at 24 weeks after therapy.Pre-treatment HBV DNA < 4 log IU/ml and pre-treatment HBsAg level < 10,000 IU/ml predicted 81% and 61.7% SVR after PEG-IFN treatment.

Conclusions:This study suggested that inHBeAg-negative CHB patients treated with PegIFN, genetic variations of *DHCR7*, *CYP27B1*, *CYP2R1*,GC and *VDR* gene on vitamin D pathway had no impact on sustained response after therapy. However, the non-CC allele of *Fok*I was related with trend of lower HBsAg level during and off-treatment and associated with more virologic response at end-of-therapy than CC allele.

Figure: Mean change in serum HBsAg level from baseline, during treatment and 6 months of off-treatment follow-up across *Fok*I polymorphism.