HBV DNA level at 6-months is the best predictor of virologic response to adefovir add-on therapy in patients with lamivudine resistance

**Background:** Although clevudine is a potent antiviral drug for the management of chronic hepatitis B (CHB), emergence of drug resistance is the one of the major drawbacks. Still, optimal management of clevudine resistance needs to be elucidated.

**Methods:** On March 2010, we retrospectively reviewed the medical records and registered clevudine-resistant CHB patients to the cohort. Prospective follow-ups were done until March 2011. Antiviral efficacy of each rescue regimen was evaluated.

**Results:** A total of 118 patients were registered. Patients received adefovir (n=15, group 1), adefovir plus clevudine (n=23, group 2), adefovir plus lamivudine (n=37, group 3), or entecavir (n=43, group 4) over 48 weeks. Baseline characteristics were not different between the groups. Mean HBV DNA were 6.4, 5.8, 5.3, 5.7 log copies/mL at baseline, p=0.816), respectively. Mean degrees of HBV DNA reduction from baseline were -1.7, -3.2, -2.0, -2.4 log copies/mL at week 24 (p=0.017), -3.2, -3.0, -1.9, -2.7 log copies/mL at week 48 (p=0.401), respectively. HBV DNA undetectability (<60 IU/mL) was 0%, 33.3%, 16.7%, 22.9% at week 24 (p=0.131) and 30.3%, 31.3%, 23.1%, 31.3% (p=0.95), respectively. HBV DNA reduced significantly from baseline to week 24 and week 48 in all groups (p<0.05, Wilcoxon signed rank test). Levels of mean ALT and rate of ALT normalization were not statistically different between the groups through 48 weeks. HBsAg loss (22.2%, 14.3%, 15.8%, 16.0%, respectively, p=0.964) and HBsAg seroconversion (11.1%, 10.0%, 20.0%, 14.3%, respectively, p=0.920) rates were not different, either. Elevations of CPK (>3×ULN) were noted in 2 patient from group 2 and 1 patient from group 3.

**Conclusions:** Although adefovir monotherapy showed slow decline of HBV DNA until week 24, HBV DNA significantly decreased in most of groups through 48 weeks of rescue therapy.

**Keyword:** Clevudine, Lamivudine, Adefovir, Entecavir, resistance
TDF alone or in combination with lamivudine (LAM) for ≥6 months due to suboptimal response (11 patients) or development of resistance (17 patients) to two or more previous NA therapy were included. Complete virologic response (CVR) was defined as serum hepatitis B virus (HBV) DNA ≤ 60 IU/mL.

Results: Ten patients had a history of treatment with LAM and adefovir (ADV), and 18 patients were exposed to LAM, ADV and entecavir (ETV). The median age was 52 years (range 22 to 64) and 20 patients were male (71.4%). Eleven patients had compensated liver cirrhosis (39.3%) and 26 patients (92.9%) were hepatitis B e antigen (HBeAg) positive. Eighteen patients (64.3%) had elevated level of alanine aminotransferase. The median treatment duration of TDF was 15.4 months (range 6-26). During the period of TDF treatment, 26 patients (92.9%) showed CVR and HBeAg loss occurred in 4 patients (15.4%). The cumulative incidence of CVR at 3,6,9,12 months were 38.5%, 69.2%, 88.4%, 93.2%, respectively. The mean viral reduction at 3,6,9,12 months were 3.09±1.19, 3.86±1.15, 4.00±1.40, 4.23±1.46 log IU/mL, respectively. No patients developed serum creatinine elevation more than 0.5 mg/dL from the baseline or hypophosphatemia. Although two patients failed to show CVR, serum HBV DNA levels decreased more than 4log from baseline and the last serum HBV DNA levels were 100 IU/mL and 272 IU/mL, respectively. No patients showed viral breakthrough during the observation period.

Conclusions: Tenofovir can be an effective and safe rescue therapy in chronic hepatitis B patients after failure to multiple NAs.

Keyword: Multiple drug resistance hepatitis B virus, Tenofovir disoproxil fumarate

Free Paper Session: Hepatitis B 2

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0-013

The mutations in the enhancer 1/X promoter and X gene region increased risk for hepatocellular carcinoma in patients with chronic hepatitis B infection

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Background: Specific mutations in X gene of the hepatitis B virus (HBV) genome have been reported to be associated with the development of hepatocellular carcinoma (HCC). Enhancer 1 (Enh 1)/X promoter play a role in regulation to production of X protein. The aim of this study was to determine whether mutations in HBV X gene and Enh 1/X promoter are associated with HCC development in patients with chronic hepatitis B infection.

Methods: 69 patients infected with HBV genotype C2 with HCC were compared to 93 patients with non-HCC. Enh 1/X promoter and X gene mutations were determined by direct sequencing in all patients.

Results: The HCC and non-HCC groups were similar with respect to clinical characteristics. However, HCC group was significantly elderly (p=0.001) compared to non-HCC group. The T1753V mutation in the X gene (p=0.001) and G1229A mutation in the Enh 1/X promoter (p=0.001) were associated significantly with HCC, respectively. In the multivariate analysis, advanced age (50yr <), (p=0.001, odds ratio [95% confidence interval], 3.07 [1.60-6.60]), T1753V mutation (p=0.002, OR [95% CI], 4.343 [1.73-10.8]), G1229A mutation (p=0.002, OR [95% CI], 3.07 [1.54-6.23]) were an independent predictive factor for HCC. The addition of the V1753 mutation to G1229A mutation increased the risk of HCC (OR: 5.96, P=0.01).

Conclusion: In conclusion, age factor, G1229A and/or T1753V mutation are associated with HCC in Korean patients with HBV genotype C2. This result suggest that mutations of Enh 1/X promoter as well as X gene may be associated with hepatocarcinogenesis.

Keyword: Hepatocellular carcinoma, Enhancer 1, X gene, Hepatitis B Virus

0-014

HBV-specific T cell response of HCV-infected persons with isolated anti-HBc and combined anti-HBc/anti-HBs antibody response

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Background: Anti-HBc in HBsAg-negative persons suggests prior HBV infection with subsequent virus control. However, unlike anti-HBs, anti-HBc is generally not associated with protective immunity to HBV, raising questions about HBV vaccination for chronic hepatitis C (CHC) with isolated anti-HBc. Since T cells play a critical role in HBV clearance, we examined the T cell responses to HBV in anti-HBc+ CHC with and without anti-HBs.

Methods: Among our cohort of CHC, 20 HBsAg-, anti-HBc+ were identified, including 9 with isolated anti-HBc and 11 with combined anti-HBc/ anti-HBs. Peripheral blood mononuclear cells isolated from these subjects were examined for T cell responses to HBV peptides ex vivo and after 7days in vitro expansion using IFNγ-ELISPOT. Antigenic peptides included 155 overlapping 15-mer peptides in pools derived from HBV preS, S, preC, Core and Polymerase regions. Positive responses in 7day IFNγ-ELISPOT were confirmed with intracellular cytokine staining with T cell markers.

Results: IFNγ response to HBV was weak ex vivo in HBsAg- anti-HBc+ CHC. However, a positive response to HBV regions was detected in 15/20 (75%) anti-HBc+ and 2/7 (29%) anti-HBc-. Ex vivo, HBV core (55%) and polymerase (45%)