Virological Response and Clinical Events in Patients with Chronic Hepatitis B Treated with Nucleos(t)ide Analogue

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- **Backgrounds:** Nucleos(t)ide analogue (NUC) is a potent inhibitor of viral replication for chronic hepatitis B (CHB). Prolonged antiviral treatment may result in regression of fibrosis. Long term therapy has improved the overall outcome.
- **Aims:** No empirical evidence is yet available to confirm effect of NUC therapy on viral suppression as well as giving value in prevention of clinical events (CE) among patients with severity of liver disease in Ping-Tung. This study was to investigate the effect and value of NUC as first line monotherapy.
- **Methods:** One hundred and four consecutive patients with CHB were classified as chronic hepatitis without cirrhosis (N=64), compensated cirrhosis (N=25), and decompensated cirrhosis (N=15). All patients were treated with NUC. We compared a virological response (VR) and CE among patients according to the severity of liver disease at baseline. Risk factors and predictors of CE were identified.
- **Results:** During a median follow-up of 51 weeks (IQR 1-172), the overall VR rate was 97.1% (101/104). The proportion of developing CE was 21.2% (22/104). A VR rate was not significantly influenced by severity of liver disease (p=0.592). The accumulative probability of developing CE was similar among groups with different severity (p=0.944). A VR did not affect the probability of CE (p=0.965). The proportion of CE was higher in patients with decompensated cirrhosis than in those with compensated cirrhosis or with CHB only (45% vs. 36.4% vs.18.2%, p<0.001). In multivariate Cox models including VR, factors with age (HR: 1.066; 95% CI: 1.010-1.124; p=0.020), Child-Tucotte-Pugh (CTP) classification (HR: 48.871; 95% CI: 2.032-1175.287; p= 0.017), CTP score (HR: 4.280; 95% CI: 1.259-14.553; p=0.020) were independently associated with developing CE.
- **Conclusions:** NUC therapy provides a comparable effect on a VR and probability of developing CE among groups with different severity of disease. Long term NUC use does not eliminate risk of CE. A VR does not prevent probability of CE. The risk of CE is higher in patients with old age, active disease. A careful surveillance of these patients is warranted even effective therapy.

Table 1 Baseline characteristics of 104 patients with chronic hepatitis B treated with nucleos(t)ide analogue(s) therapy according to the severity of liver disease

	CHB without cirrhosis (N=64)	Compensated cirrhosis (N=25)	Decompensated cirrhosis (N=15)	p Value
Gender (% male)	49 (76.6%)	18 (72.0%)	12 (80.0%)	**0.835**
Age (years)	52.98±10.97	61.52±9.10	59.20±9.69	**0.01**
<50	21 (32.8%)	1 (4.0%)	1 (6.7%)	**0.002**
50-60	28 (43.8%)	9 (36.0%)	9 (60.0%)	
>60	15 (23.4%)	15 (60.0%)	5 (33.3%)	
ALT (IU/L)	457.80±582.38	88.52±98.86	197.60±299.24	**0.003**
AST (IU/L)	259.67±270.11	78.20±77.66	246.80±373.60	**0.012**
ALT (xULN)	10.82±13.31	2.12±2.27	4.91±7.85	**0.003**
Bilirubin (mg/dl)	2.13±2.97	1.01±0.57	6.01±5.26	**<0.001**
PT INR	1.09±0.24	1.09±0.09	1.28±0.30	**0.014**
Platelet count (10^4/μl)	20.56±7.71	11.30±6.14	10.07±6.73	**<0.001**
APRI score	4.18±6.38	2.31±3.38	8.14±12.65	**0.043**
HBV DNA (log_{10} IU/ml)	5.92±1.48	5.74±1.03	5.04±1.64	**0.097**
HBeAg-positive	23 (35.9%)	5 (20.0%)	2 (13.3%)	**0.118**
Previous treatment with PEG-IFN or NUCs	20 (31.2%)	3 (12.0%)	3 (20.0%)	**0.151**
Total VR	61 (60.4)	25 (24.8)	15 (14.9)	**0.381**
Accumulative at year 1	41 (59.4)	17 (24.6)	11 (15.9)	**0.864**
Accumulative at year 2	56 (61.5)	22 (24.2)	13 (14.3)	
Accumulative at year 3	61 (60.4)	25 (24.8)	15 (14.9)	
VR time (week)	47.87±31.74	45.44±35.35	40.07±29.73	**0.701**
Total CE	4 (18.2)	8 (36.4)	10 (45.5)	**<0.001**
Accumulative at year 1	2 (15.4)	5 (38.4)	6 (46.2)	**0.983**
Accumulative at year 2	3 (16.7)	7 (38.9)	8 (44.4)	
Accumulative at year 3	4 (18.2)	8 (36.4)	10 (45.5)	
CE time (week)	**77.00±53.60**	**65.00±48.84**	**62.50±53.62**	**0.893**

CHB, chronic hepatitis B; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal; INR, international normalized ratio; APRI, aspartate aminotransferase to platelet ratio index; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; VR, virological response; CE, clinical event; PEG-IFN, peginterferon; NUCs, nucleos(t)ide analogues

Table 2 Multivariate Cox model including virological response and different baseline variables on cumulative probability of clinical events in all patients

	HR (95% CI) virological response	P Value
VR and age	1.066 (1.010-1.124)	**0.020**
VR and CTP score	4.280 (1.259-14.553)	**0.020**
VR and CTP classification	**48.871 (2.032-1175.287)**	**0.017**

VR, virological response; CTP, Child-Turcotte-Pugh; Generated from Cox proportional hazards regression models. Virological response was included as a time-dependent covariate.

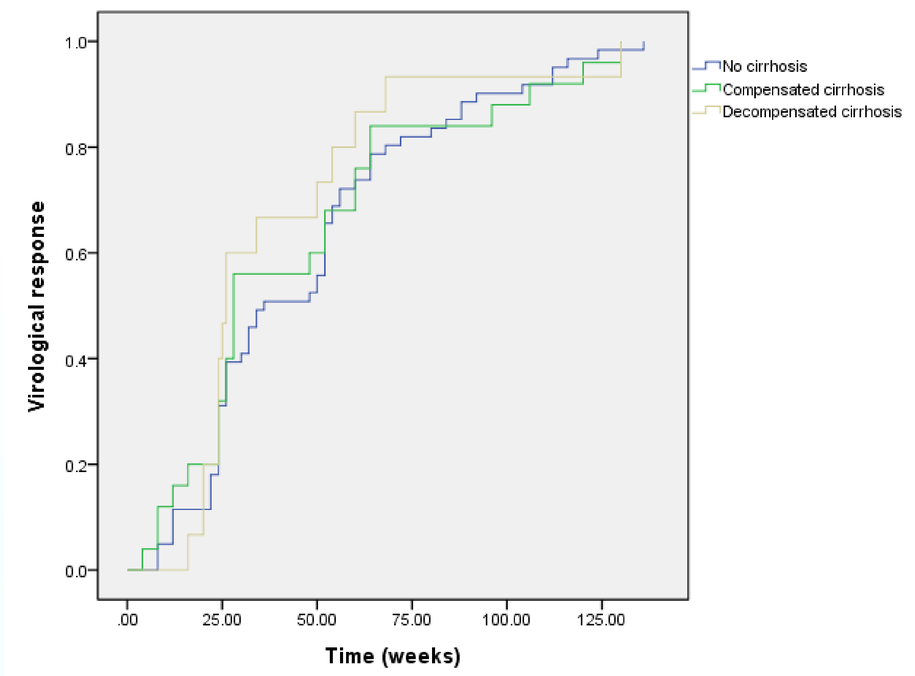

Figure 1 Kaplan-Meier curve for the cumulative probability of achieving a virological response in patients with chronic hepatitis B treated with nucleos(t)ide analogue(s) stratified according to severity of the liver disease at baseline. Virological response was defined as serum HBV levels undetectable.

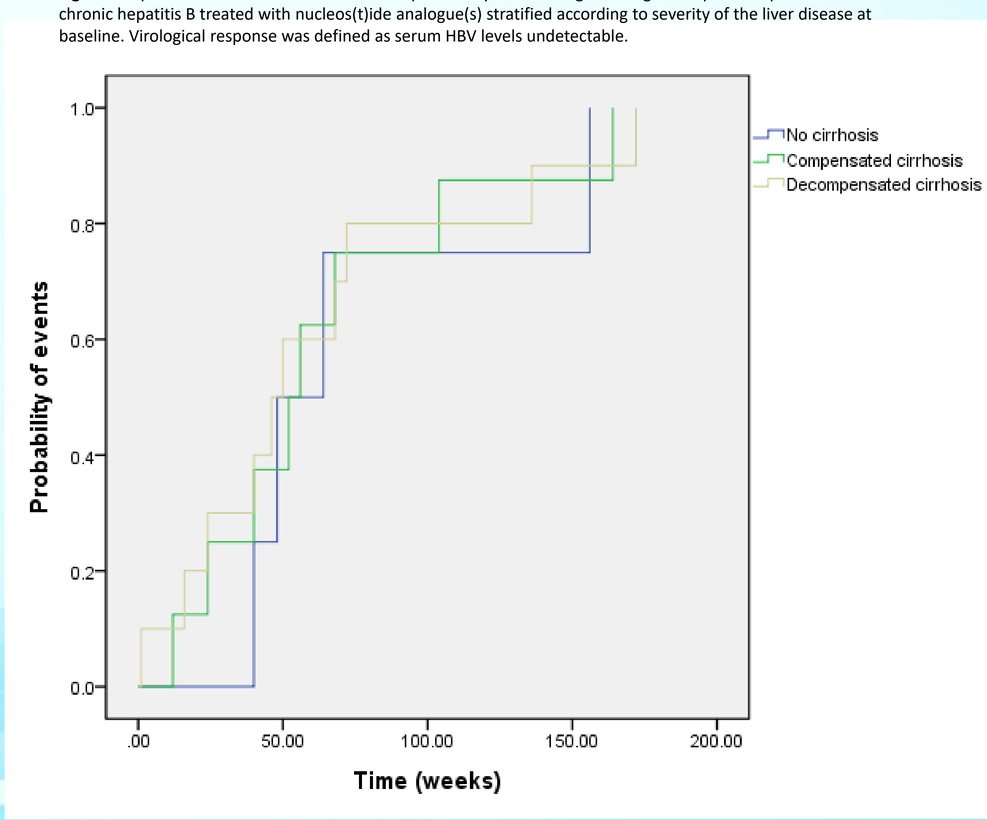

Figure 2 Kaplan-Meier curve for the cumulative probability of developing a clinical event in patients with chronic hepatitis B on nucleos(t)ide analogue(s) treatment stratified according to the presence of no cirrhosis, compensated cirrhosis and decompensated cirrhosis at baseline. Clinical event was defined as developing hepatocellular carcinoma, hepatic decompensation or death.