Randomized double-blind study of Nitazoxanide for virologically suppressed HBeAg negative Chronic Hepatitis B

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Background

- Nitazoxanide (NTZ) is a potential HBV therapeutic agent.
- NTZ disrupts Hepatitis B x protein (HBx) and host DNA-binding protein 1 (DDB1) interaction and prevents the formation of HBx-DDB1 protein complex responsible for the degradation of host restriction factor – structural maintenance of chromosomes 5/6 (SMC5/6). Restoration of SMC5/6 level after NTZ treatment suppresses Hepatitis B covalently closed circular DNA expression *in vitro*. [1]
- A subsequent pilot study demonstrated good anti-viral efficacy with 33% of patients (3 of 9 patients) achieving HBsAg loss [2].
- Consequently, this randomized controlled trial was designed to test NTZ efficacy.

Methods

- We conducted a phase 2, double-blinded, placebo-controlled, dose-finding, randomized control trial for Hepatitis B e antigen (HBeAg) negative Chronic Hepatitis B patients on long-term (>1 year) nucleos(t)ide analogues (NUCs) (Tenofovir disoproxil fumarate, Tenofovir alafenamide, or Entecavir).
- Participants were randomized (1:1:1:1) to receive either placebo (Group 1), NTZ 600mg once daily (Group 2), NTZ 600mg twice daily (Group 3), or NTZ 900mg twice daily (Group 4), in addition to their NUC therapy.
- Primary efficacy endpoint was defined by the mean change in quantitative Hepatitis B surface antigen (qHBsAg) from baseline to week 48. Secondary endpoints included sustained off-treatment Hepatitis B surface antigen (HBsAg) loss, qHBsAg reduction, HBsAg seroconversion, Hepatitis B DNA suppression, and change in baseline Fibroscan and/or Fibrosis-4 score

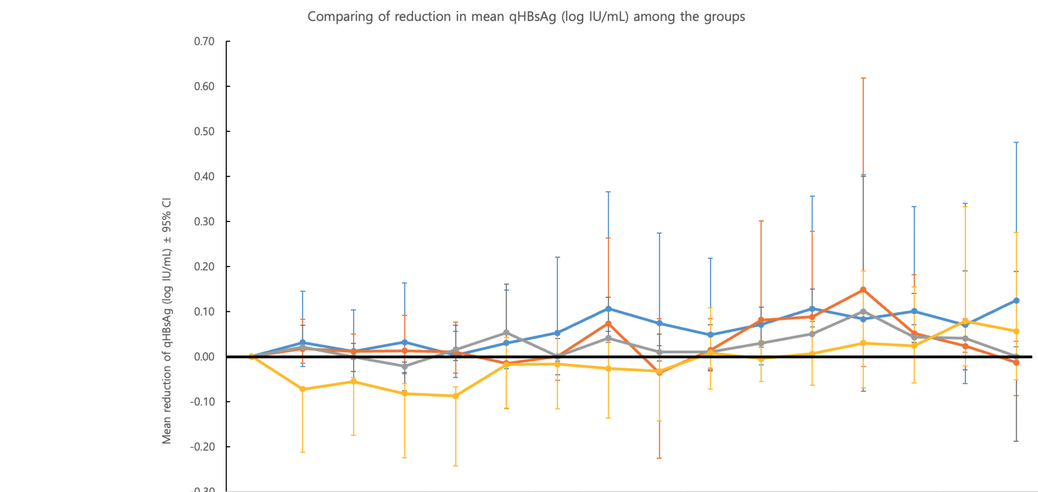
Results

- In total, 48 patients were enrolled. 12, 13, 10, and 13 patients were randomized to Group 1, 2, 3, and 4 respectively.
- There were no statistical differences in the key baseline patient characteristics (age, gender, presence of fatty liver, cirrhosis, Fibroscan score, Fibrosis-4 score, previous PEG-IFN exposure) between treatment groups.
- Overall, 4 patients who received NTZ and 1 patient who received placebo experienced severe adverse events (SAEs). 4 cases of grade 3 SAEs were deemed to be unrelated to NTZ (hepatocellular carcinoma (n=2); gastroesophageal reflux (n=1); perianal abscess (n=1)). Grade 4 SAE for alanine transaminase and aspartate aminotransferase elevation occurred in 1 patient (group 4) before resolving uneventfully with NTZ dose reduction (Figure 1).
- The primary and secondary efficacy endpoints were not met in all groups (Figure 1). No statistical difference in qHBsAg reduction or mean qHBsAg was detected between groups at all study time-points.
- Analysis of individual patient quantitative HBsAg kinetics did not identify any NTZ responder. The study was terminated early because of the lack of efficacy.

Table 1. Summary of Severe Adverse Events

	Grade 3 SAE	Grade 4 SAE	Relatedness
Placebo	HCC (n=1)	-	No
NTZ	HCC (n=1) GERD (n=1) Perianal abscess (n=1)	-	No
	-	ALT and AST elevation (n=1)	Yes. Resolved uneventfully with NTZ dose reduction

Figure 1. Mean reduction of qHBsAg across groups 1 to 4 over various study time-points.



	BL	D3	W1	W2	W4	W8	W12	W16	W20	W24	W36	W48	W60	FUW4	FUW8	FUW12
Group 1: Placebo (n=12)	0.00	0.03	0.01	0.03	0.00	0.03	0.05	0.11	0.07	0.05	0.07	0.11	0.08	0.10	0.07	0.12
Group 2: 600 mg NTZ Once (n=13)	0.00	0.02	0.01	0.01	0.01	-0.02	0.00	0.07	-0.04	0.01	0.08	0.09	0.15	0.05	0.02	-0.01
Group 3: 600 mg NTZ Twice (n=10)	0.00	0.02	0.00	-0.02	0.02	0.05	0.00	0.04	0.01	0.01	0.03	0.05	0.10	0.04	0.04	0.00
Group 4: 900 mg NTZ Twice (n=13)	0.00	-0.07	-0.06	-0.08	-0.09	-0.02	-0.02	-0.03	-0.03	0.01	-0.01	0.01	0.03	0.02	0.08	0.06

Conclusions

- NTZ is safe and tolerable in CHB
- Addition of Nitazoxanide to Nucleos(t)ide analogue therapy did not increase anti-viral efficacy

References

[1] Sekiba K, Otsuka M, Ohno M, Yamagami M, Kishikawa T, Suzuki T, et al. Inhibition of HBV Transcription From cccDNA With Nitazoxanide by Targeting the HBx-DDB1 Interaction. Cell Mol Gastroenterol Hepatol 2019;7:297-312.

[2] Rossignol JF, Brechot C. A Pilot Clinical Trial of Nitazoxanide in the Treatment of Chronic Hepatitis B. Hepatol Commun 2019;3:744-747.

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