Oral Prenylation Inhibition with Lonafarnib in Chronic Hepatitis D Infection: A Randomized, Double-Blinded, Placebo Controlled Proof-of-Concept Study

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Introduction

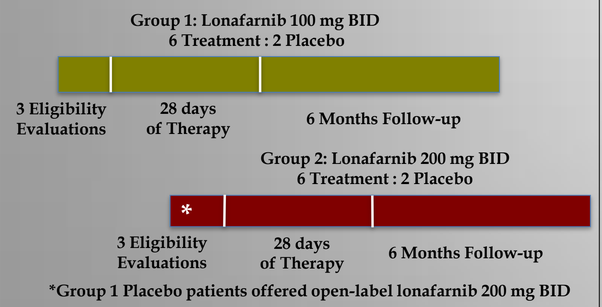
- 15-20 million people are infected worldwide with chronic hepatitis D (HDV).
- Up to 80% of patients with HDV may develop cirrhosis within 5-10 years.
- Interferon-based therapy is unsatisfactory, <30% achieve HBsAg loss and become HDV RNA negative.
- Nucleos/tide analogues are ineffective.
- Prenylation inhibition has demonstrated effectiveness against HDV in in vitro & in vivo models.

Aims

- To assess the antiviral effect and safety of the prenylation inhibitor, lonafarnib, in patients with chronic HDV infection.

Methods

- 14 chronically infected HDV patients were sequentially enrolled into 2 groups in a phase 2a double-blinded, randomized, placebo-controlled study.



*Group 1 Placebo patients offered open-label lonafarnib 200 mg BID

- Serial measurements of safety parameters, liver tests, virologic (HDV RNA & HBV DNA) markers and symptom questionnaires were performed.

Results

Table 1: Patient Demographics

Feature	Result
Males	71%
Median Age	38
Nucleoside Analogues	31%
Race	
Caucasian	43%
Asian	50%
African	7%
Median Baseline Histology	
Ishak Fibrosis	3

Figure 1: Study Flow

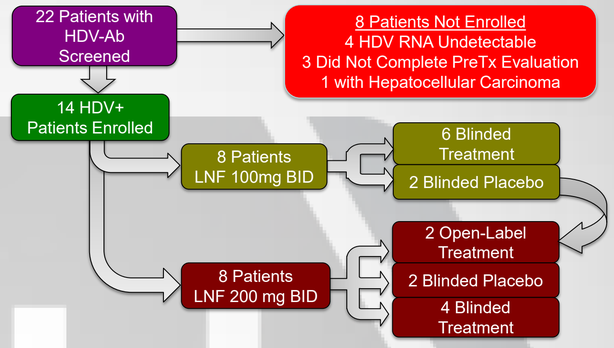


Table 3: Baseline Lab Values

Feature	Placebo	Group 1		Group 2	
	Median	Median	P Value	Median	P Value
Log HDV RNA (IU/mL)	6.14	6.05	0.8	5.93	1.0
HBV DNA (IU/mL)	17.0	25.7	0.45	123.0	0.4
AST (U/L)	72	61	0.6	42	0.8
ALT (U/L)	101	125	0.7	63	0.6
T. Bili (mg/dL)	0.4	0.35	0.9	0.4	1.0

Table 4: Change at End of Therapy

Finding	Placebo vs Group 1		Placebo vs Group 2	
	Group 1 Mean Δ	P Value	Group 2 Mean Δ	P Value
Log HDV RNA (IU/mL)	-0.73	0.04	-1.54	0.002
Log HBV DNA (IU/mL)	0.08	0.1	1.12	0.05
AST (U/L)	12	0.7	-2.7	0.6
ALT (U/L)	4	0.96	29	0.6
T. Bili (mg/dL)	-0.05	1.0	-0.08	0.1

Fig 2: HDV RNA Decline After 28 Days of Therapy

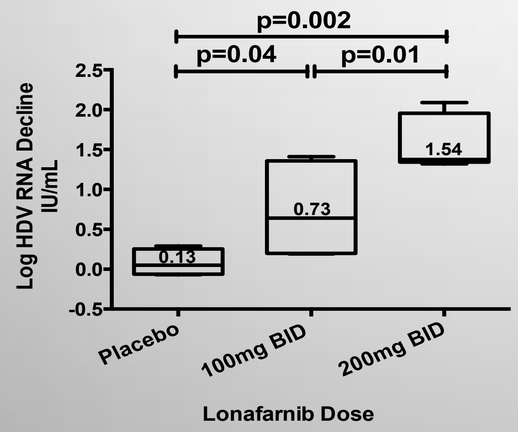
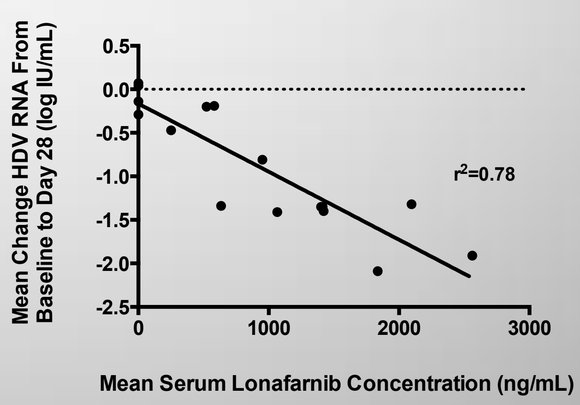


Fig 3: Serum Drug Levels Correlate With Change in HDV RNA



Discussion

- After 28 days of therapy with lonafarnib, serum HDV RNA was significantly lower in both treatment groups compared to placebo
- A dose dependent reduction in serum HDV RNA was seen with lonafarnib therapy
- Serum lonafarnib concentrations correlate with HDV RNA decline
- No HDV resistance was identified
- Lonafarnib was safe and generally well tolerated at the prescribed doses for 28 days.

Conclusion

- This is the first demonstration that treatment of chronic HDV with the prenylation inhibitor lonafarnib significantly reduces virus levels in patients.
- The decline in virus levels significantly correlated with serum drug levels, providing further evidence for the efficacy of prenylation inhibition in chronic HDV.

References

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Disclosures

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- All patients provided informed consent for IRB approved studies.
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