Prenylation Inhibition with Lonafarnib Decreases Hepatitis D Levels in Humans

Christopher Koh[1], Cihan Yurdaydin[2], Stewart Cooper[3], David Cory[4], Harel Dahari[5], Vanessa Haynes-Williams[1], Mark A Winters[6], Matthew Bys[4], Ingrid Choong[4], Ramazan Idilman[2], Onur Keskin[2], Laetitia Canini[5], Peter Pinto[7], Erin Wolff[8], Rachel Bishop[9], David E Kleiner[7], Jay H Hoofnagle[1], Jeffrey Glenn[6], and Theo Heller[1]

National Institute of Diabetes & Digestive & Kidney Diseases[1], Ankara University[2], California Pacific Medical Center[3], Eiger Biopharmaceuticals[4], Loyola University Medical Center[5], Stanford School of Medicine[6], National Cancer Institute[7], National Institute of Child Health and Human Development[8], National Eye Institute[9].

Introduction

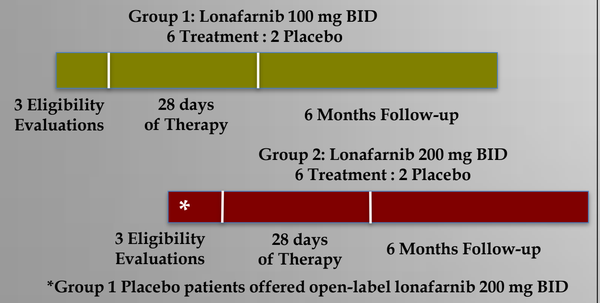
- 15-20 million people are infected worldwide with chronic hepatitis D (HDV).
- Up to 80% of patients with HDV may develop cirrhosis within 5-10 years.
- Interferon-based therapy is unsatisfactory, <30% achieve HBsAg loss and become HDV RNA negative.
- Nucleos/tide analogues are ineffective.
- Prenylation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

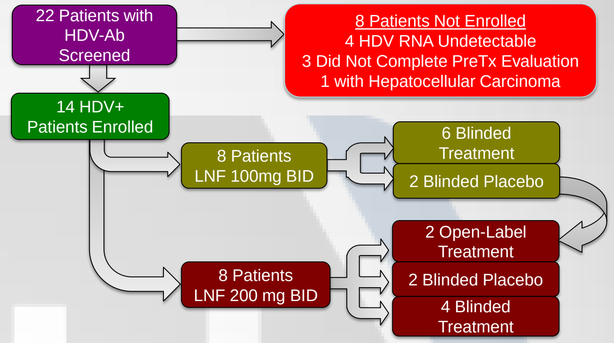


Table 3: Baseline Lab Values

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

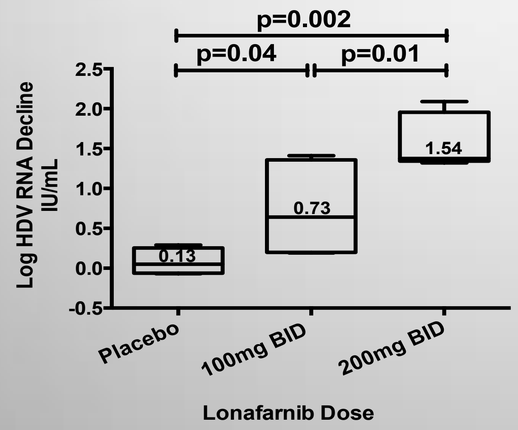
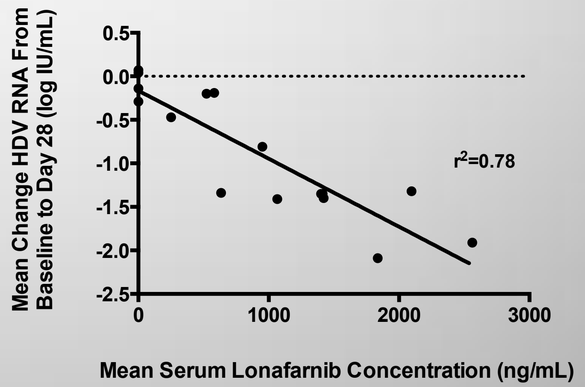


Fig 3: Serum Drug Levels Correlate With Change in HDV RNA



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

1. Hughes SA, et al. Lancet 2011;378
2. Colombo M, et al. Gastroenterol 1983;85
3. Manesis EK, et al. J Hep 2013;59
4. Wedemeyer H, et al. Hepatology 2013; 58
5. Heller T, et al. Aliment Pharmaol Ther 2014; 40
6. Bordier BB, et al. J Clin Invest 2003;112

Disclosures

- This work was supported by the intramural research programs of the NIDDK, NCI & NICHD, NIH.
- All patients provided informed consent for IRB approved studies.
- D. Cory, I. Choong & M. Bys: Eiger Biopharmaceuticals;
- J. Glenn: Eiger Biopharmaceuticals, Riboscience, LLC Consulting: Gilead, Janssen, Sundise, Genentech, Merck, Roche, Romark Industries, StemCells Inc.
- All other authors have no financial disclosures.