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Retreatment of HCV Genotype-1 with Sofosbuvir and Ledipasvir after Relapse with Sofosbuvir and Ribavirin: A Pilot Study

Anu Osinusi, M.D.[1,2], **Anita Kohli, M.D.**[3,4], **Miriam M Marti, B.S.**[2], **Amy Nelson, R.N.**[3], **Xiaozhen Zhang**[2], **Eric G Meissner**[2], **Rachel Silk, R.N.**[4], **Kerry Townsend**[2], **Phillip S Pang, M.D., Ph.D.**[5], **Mani Subramanian, M.D., Ph.D.**[5], **John G. McHutchison, MD.**[5], **Anthony S Fauci, M.D.**[2], **Henry Masur, M.D.**[3], and **Shyam Kottilil, M.D., Ph.D**[2]

[1]Div. of Infectious Diseases, Institute of Human Virology, University of Maryland, MD, USA

[2]Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, MD, USA

[3]Critical Care Medicine Department, NIH Clinical Center, National Institutes of Health, MD, USA

[4]Clinical Research Directorate/Clinical Monitoring Research Program, Leidos Biomedical Research, Inc. (formerly SAIC-Frederick, Inc.), Frederick National Laboratory for Cancer Research

[5]Gilead Sciences Inc, CA, USA

Abstract

Background—The interferon (IFN)-free regimen of sofosbuvir and ribavirin for 24 weeks was recently approved to treat chronic hepatitis C virus (HCV), genotype-1 (GT-1) infection for interferon-ineligible patients . However, sofosbuvir/ribavirin therapy is associated with treatment relapse in 15-30% of HCV GT-1 study subjects. Neither the mechanism of relapse nor the optimal retreatment strategy for these subjects is defined.

Objective—To assess the safety and efficacy of sofosbuvir and ledipasvir in chronic HCV GT-1 infected subjects who relapsed following sofosbuvir/ribavirin therapy.

Design—Phase 2a, open-label study (ClinicalTrials.gov, number NCT01805882).

Setting—Single U.S site.

Subjects—Fourteen HCV, GT-1 subjects who relapsed following treatment with 24 weeks of sofosbuvir/ribavirin were treated with 12 weeks of sofosbuvir/ledipasvir.

Measurments—HCV RNA concentration and population sequencing to detect NS5B S282T mutations.

Correspondence to: Shyam Kottilil, M.D., Ph.D., Immunopathogenesis Section, Laboratory of Immunoregulation, NIAID, NIH, Bldg10, Rm.11N204, Bethesda, MD 20892, Phone: (301) 435-0936, Fax: (301) 435-3339, skottilil@niaid.nih.gov.

The data from this study was presented at the 49th annual congress of European Association for the Study of the Liver (EASL), The International Liver Congress in London, UK on April 2014.

Declaration of Interest: Phillip S Pang, G. Mani Subramanian and John G McHutchison are employed by Gilead Sciences Inc.

Results—All 14 subjects treated with sofosbuvir/ledipasvir for 12 weeks achieved a sustained virologic response, including seven with advanced liver disease (HAI-fibrosis 3-4) and one with a detectable NS5B S282T mutation post sofosbuvir/ribavirin therapy. Sofosbuvir/ledipasvir was well tolerated with few adverse events. Four grade 3 events (elevated serum creatinine in a subject with baseline renal insufficiency, hypercholesterolemia and hypophosphatemia (n=2)) occurred. There were no grade 4 events or treatment discontinuations.

Limitations—Small sample size.

Conclusions—The fixed-dose combination of sofosbuvir/ledipasvir was efficacious in a small cohort of subjects with HCV GT-1 infections who relapse following sofosbuvir/ribavirin therapy, even in the setting of advanced liver disease. Larger studies are needed to confirm these preliminary efficacy results.

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Introduction

Chronic HCV infection is a major cause of chronic liver disease and hepatocellular carcinoma, and is the leading indication for liver transplantation in Western countries (1, 2). Until recently, HCV treatment consisted of combination therapy with pegylated interferon (IFN) and ribavirin, and in recent years addition of an HCV protease inhibitor (boceprevir or telaprevir). In 2013, the Food and Drug Administration approved sofosbuvir/ribavirin as the first IFN-free treatment for HCV GT-2, 3 infected subjects and GT-1 interferon-ineligible subjects (3-7). While sofosbuvir/ribavirin is well tolerated and effective with sustained virologic response (SVR) rates ranging from 68% - 76% in HCV GT-1 subjects (8, 9), modest rates of treatment relapse in subjects with advanced liver disease and transplant recipients have been observed (8, 10, 11). Recent studies utilizing sofosbuvir combined with ledipasvir (NS5A inhibitor) for 12 weeks demonstrated high SVR rates (95-99%) in treatment naïve HCV GT-1 subjects (12-15). Ledipasvir has potent antiviral activity against the S282T resistance associated variant (RAV), known to reduce susceptibility to sofosbuvir *in vitro* (16).

As previously reported, 17 of 54 subjects treated with 24 weeks of sofosbuvir/ribavirin in the NIAID SPARE study relapsed post-treatment (8). We hypothesized that combination of a second potent DAA with sofosbuvir could result in SVR, even in sofosbuvir/ribavirin relapsers who may harbor the S282T mutation. To test this hypothesis, we retreated sofosbuvir/ribavirin relapsers with sofosbuvir/ledipasvir for 12 weeks.

Methods

Design Overview

All subjects who relapsed after 24 weeks of treatment with sofosbuvir/ribavirin on the NIAID SPARE study (8) were offered retreatment with sofosbuvir/ledipasvir in the ongoing, phase 2a, open-label NIAID SYNERGY study (Clinical Trials.gov number NCT01805882).

Of the 17 eligible subjects, 3 did not participate in the study.. Fourteen subjects enrolled and were treated for 12 weeks with sofosbuvir 400 mg and ledipasvir 90 mg, administered daily as a single combination tablet.

Setting and Participants

The trial was conducted at the National Institutes of Health (NIH) in Bethesda, Maryland and at community clinics that are part of the Washington, D.C. Partnership for AIDS Progress (DC-PFAP). Written informed consent approved by the NIAID Institutional Review Board was obtained from all study participants. Eligibility criteria included documented HCV GT-1 infection and treatment relapse in the NIAID SPARE study (8). Liver fibrosis stage was determined by biopsy within 3 years of enrollment in the NIAID SPARE study

Outcomes and Follow-up

Efficacy Assessments—Plasma HCV RNA levels were measured using the Abbott real-time HCV Assay, with a lower limit of quantification (LLOQ) of 12 IU/mL and a lower limit of detection (LLOD) of 3 IU/mL and/or the COBAS TaqMan HCV RNA assay, version 2.0 (Roche), with an LLOQ of 43 IU/mL and an LLOD of 15 IU/mL.

Safety Assessments—Subjects were closely monitored for adverse events. Clinical laboratory results were assessed on therapy (weeks 4, 8 and 12) and afterwards (2, 4, 8, 12 weeks post-treatment). Adverse events were graded from 1 (mild) to 4 (severe) according to the NIAID Division of AIDS toxicity table (version 1.0).

IL-28B Genotyping—*IL-28B* genotype (rs12979860) was determined as previously described (8).

Clinical End Points—The primary end point was the proportion of participants with unquantifiable plasma HCV viral load 12 weeks after treatment completion (SVR_{12}). Safety end points included frequency and severity of adverse events, discontinuations due to adverse events, and safety laboratory changes.

Statistical Analysis

Primary safety and efficacy data were analyzed by intention-to-treat (all subjects who initiated study medication). Missing virologic data were imputed if data from preceding and succeeding time points were obtained. Baseline demographics were described using frequency statistics. Comparisons were calculated using either non-parametric tests or t-tests using Prism v6.0 (GraphPad Software).

Results

Baseline Characteristics of Participants

Most study participants were African American males with unfavorable *IL-28B* non-CC genotype (Table 1). There was high representation of subjects with HCV GT-1a infection,

elevated baseline HCV viral load (>800K), elevated BMI (>30), and advanced liver disease (HAI fibrosis 3-4).

Presence of S282T Mutation

At the time of relapse after sofosbuvir/ribavirin treatment in the SPARE trial, 13 of 14 participants had wild-type virus by population sequencing (Supplemental Table 1). The one exception achieved unquantifiable HCV RNA levels by week 2 of therapy in SPARE, and remained undetectable through the end of treatment. He missed his week 26 (post-treatment week 2) visit, but at week 28 (post-treatment week 4), his HCV viral load was 374 IU/mL and the S282T mutation was readily detected by population sequencing. By week 36 (post-treatment week 12), his HCV viral load was 81,286 IU/mL and the S282T mutation was no longer detectable. He initiated sofosbuvir/ledipasvir treatment 50 weeks after relapse.

Virologic Response

All participants (14/14) treated with sofosbuvir/ledipasvir had HCV RNA levels below LLOQ by week 4 (Roche Assay), which was maintained through the end of treatment (week 12). All subjects achieved SVR12.

Changes in Hemoglobin

No significant change in hemoglobin levels during sofosbuvir/ledipasvir treatment was observed, in contrast to the decline observed with sofosbuvir/ribavirin. The mean hemoglobin change was + 0.0071 g/dL vs -1.17 g/dL at week 4 (p=0.01), -0.046 g/dL vs -1.26 g/dL at week 8 (p=0.01), and -0.31 g/dL vs -1.21 g/dL at week 12 (p=0.06) with sofosbuvir/ledipasvir and sofosbuvir/ribavirin, respectively. No subject had ≥ 1.5g/dL drop with sofosbuvir/ledipasvir compared to 8/14 (57%) with sofosbuvir/ribavirin.

Changes in Renal Function

There were no significant changes in renal parameters over the course of treatment although a single subject with grade 2 renal insufficiency at baseline (estimated glomerular filtration rate (eGFR) of 54 ml/min) developed a grade 3 event. After 6 weeks of receiving study medications, he initiated amoxicillin in the context of a dental procedure, and continued pre-enrollment medications (benazepril, telmisartan and simvastatin). In this context his eGFR declined to 29 ml/min (grade 3 toxicity), but within a week of stopping amoxicillin his eGFR improved (grade 2), and within 3 weeks returned to baseline and remained stable thereafter. He received study drugs without interruption..

Safety

All subjects completed treatment and no grade 4 adverse events or laboratory abnormalities occurred. The most common adverse events were myalgia and hypophosphatemia, and most adverse events were mild (Table 2). Four grade 3 events occurred (elevated creatinine described above (n=1), hypercholesterolemia (n=1), hypophosphatemia (n=2)).

Discussion

In this study, we demonstrate that HCV infected, GT-1 subjects who experience viral relapse following sofosbuvir/ribavirin therapy can be successfully retreated with sofosbuvir/ledipasvir. Seven (50%) of the patients in this study had advanced liver disease, which has been shown to be associated with treatment relapse with sofosbuvir/ribavirin therapy. (8, 10, 11).In addition to having a high prevalence of traditionally poor predictive factors for successful IFN-based treatment outcome, this cohort included one patient with a detectable S282T mutation after sofosbuvir/ribavirin treatment.

This trial is the first to evaluate the use of alternative IFN-free DAA therapy in patients who relapsed after receiving a DAA-only regimen. Presence of the S282T mutation confers resistance to sofosbuvir *in vitro* (17, 18). In clinical trials to date, most treatment failures after sofosbuvir-based treatment experience post-treatment relapse rather than on-treatment breakthrough, and only rarely have S282T mutants been detectable, consistent with the results reported here (1/14 with detectable S282T). Although rarely detected *in vivo*, it remains possible that S282T mutants are causally associated with relapse, and inability to commonly detect the mutation may relate to reduced viral fitness with replacement by wild-type virus as the predominant species by the time relapse is detected at follow-up (19-21). In this regard, the ideal management strategy for patients who have relapsed after receiving sofosbuvir-containing regimens is unclear. There are few published studies on retreatment of subjects harboring HCV variants resistant to DAAs, and thus far all retreatment strategies included use of pegIFN and ribavirin. Encouragingly, the favorable treatment outcome in the subject harboring the S282T mutation suggests that prior detection of S282T does not necessarily preclude future successful use of a sofosbuvir-containing regimen.

The major limitations of this study are the small sample size and the lack of in-depth viral sequencing, which could have identified more subjects with S282T mutations after sofosbuvir/ribavirin relapse. We also did not assess NS5A baseline variants, and naturally occurring RAVs conferring decreased ledipasvir susceptibility have been reported in 4 – 12% of HCV-infected individuals at baseline (15, 22-24). Whether the presence of these RAVs will impact treatment outcome in the setting of previous relapse with sofosbuvir requires testing in larger studies. Finally, the retreatment occurred a year after initial relapse and whether retreatment earlier would have resulted in similar SVR rates is unknown.

In conclusion, our study suggests that subjects who relapse following sofosbuvir/ribavirin can be successfully retreated with sofosbuvir plus ledipsavir for 12 weeks. The low incidence of adverse events, low pill burden, shorter treatment duration, and high efficacy demonstrated in this group and other populations, make this drug combination attractive in a real life setting.. This new paradigm in the management of HCV subjects should be further tested in larger clinical trials for sofosbuvir relapsers of all HCV genotypes, including subjects with comorbidities such as transplantation and cirrhosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Anu Osinusi MD and Shyam Kottilil MD had full access to all data in the study and take responsibility for the integrity and accuracy of the data analysis. Shyam Kottilil , Anu Osinusi, Miriam Marti and Henry Masur had unrestricted access to the data and wrote the manuscript. Subsequent drafts of the manuscript reflect comments from all coauthors. All authors reviewed and approved the final manuscript.

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Table 1
Baseline Characteristics of Study Participants

	Sofosbuvir [+] LedipasvirN=14
Median age (range)	59 (48 – 70)
Male gender – number (%)	13 (93)
Median body mass index – (range)	28.5 (19.8 – 38.4)
BMI ≥ 30 – number (%)	5 (36)
Black race or ethnicity – number (%)	13 (93)
IL28B genotype – number (%)	
CC	2 (14)
CT	7(50)
TT	5(36)
Knodell HAI Fibrosis – no (%)	
0 -1	7 (50)
3 - 4	7 (50)
HCV genotype 1 subtype – no (%)	
1a	8 (57)
1b	6 (43)
Median baseline HCV RNA–log10IU/ml (range)	6.31(5.50 – 6.76)
HCV RNA > 800,000 IU/ml – no (%)	11 (79)
Median creatinine mg/dL (range)	0.97 (0.71 – 1.61)

Continuous variables are shown as median (IQR), Categorical variables are expressed as frequencies (%)

[+]Race was self-reported. Body mass index is the weight in kilograms divided by the height in meters squared.

Table 2
Treatment Discontinuations, Adverse Events and Laboratory Abnormalities

	Sofosbuvir/ledipasvirfor 12 weeks(n=14)
Discontinuation of sofosbuvir/ledipasvir due to adverse events – n (%)	0
Serious adverse event – n (%)	0
Adverse events - n (%)	
Loose stool	1 (7)
Constipation	1 (7)
Headache	1 (7)
Myalgia	2 (14)
Nasal congestion	1 (7)
Pruritic rash	1 (7)
Dry cough	0
Dry mouth	0
Nausea	0
Light headedness	0
Fatigue	0
Dyspnea	0
Upper respiratory infection	0
Acid reflux (esophageal)	0
Pruritus	0
Laboratory Abnormalities	
Absolute neutrophil count 750 – 1000/mm^3	1 (7)
Absolute neutrophil count 500 – 749/mm^3	0
Blood glucose 40 - 54mg/dL	1 (7)
Fasting blood glucose 126 – 250 mg/dL	0
Serum phosphate 1.0 – 1.9mg/dL	2 (14)
Fasting cholesterol > 240mg/dL	2 (14)
Elevated ALT (SGPT) 2.6 – 10.0 × ULN	0
Elevated AST (SGOT) 2.6 – 10.0 × ULN	0
Elevated serum bilirubin 1.6 – 2.5 × ULN	0
Serum creatinine 1.4 × 3.4 × ULN	1 (7)