Research Article

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Sofosbuvir (GS-7977) plus peginterferon/ribavirin in treatment-naïve patients with HCV genotype 1: A randomized, 28-day, dose-ranging trial

Maribel Rodriguez-Torres[1,*], Eric Lawitz[2], Kris V. Kowdley[3], David R. Nelson[4], Edwin DeJesus[5], John G. McHutchison[6], Melanie T. Cornpropst[7,†], Michael Mader[6,†], Efsevia Albanis[6,†], Deyuan Jiang[6], Christy M. Hebner[6], William T. Symonds[6,†], Michelle M. Berrey[8,†], Jay Lalezari[9]

[1]*Fundacion de Investigacion, San Juan, Puerto Rico;* [2]*Alamo Medical Research, San Antonio, TX, USA;* [3]*Digestive Disease Institute, Virginia Mason Medical Center, Seattle, WA, USA;* [4]*University of Florida, Gainesville, FL, USA;* [5]*Orlando Immunology Center, Orlando, FL, USA;* [6]*Gilead Sciences, Foster City, CA, USA;* [7]*BioCryst, Durham, NC, USA;* [8]*Independent Consultant, San Francisco, CA, USA;* [9]*Quest Clinical Research, San Francisco, CA, USA*

Background & Aims: Sofosbuvir (formerly GS-7977) is a pyrimidine nucleotide analog inhibitor of the hepatitis C virus (HCV) NS5B polymerase. We assessed the safety, tolerability, antiviral activity, and pharmacokinetics of sofosbuvir plus pegylated-interferon (PegIFN)/ribavirin (RBV) in a 28-day, dose-ranging trial in treatment-naïve patients infected with genotype 1 HCV.

Methods: In this double-blind study, 64 patients were randomized (1:1:1:1) to receive one of three once-daily doses of oral sofosbuvir (100, 200, or 400 mg) or placebo plus PegIFN/RBV for 28 days, after which all patients continued to receive PegIFN/RBV alone for a further 44 weeks.

Results: Patients in the sofosbuvir/PegIFN/RBV groups experienced mean reductions in HCV RNA >5 $\log_{10}$ IU/ml (−5.3 for 100 mg, −5.1 for 200 mg and −5.3 for 400 mg) *vs.* −2.8 $\log_{10}$ IU/ml for placebo/PegIFN/RBV after 28 days. Rapid virologic response (RVR) rates were markedly higher after sofosbuvir treatment (88–94%) than placebo (21%), as were rates of sustained virologic response (SVR) at post-treatment Week 24 (56%, 83%, and 80% for sofosbuvir 100, 200, and 400 mg, respectively, *vs.* 43% for placebo). The number of patients experiencing virologic breakthrough and post-treatment relapse was higher in the sofosbuvir 100 mg group than sofosbuvir 200 and 400 mg groups. Sofosbuvir was well tolerated; the most frequent adverse events were fatigue and nausea.

Conclusions: These results support further studies with sofosbuvir at 200 mg and 400 mg to determine the optimal dose and treatment duration of sofosbuvir in HCV genotype 1.

Keywords: Sofosbuvir; Hepatitis C virus; Antiviral; Rapid virologic response; Sustained virologic response.

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* Corresponding author. Address: Fundacion de Investigacion, 555 Munoz Rivera Avenue San Juan, PR 00927, USA. Tel.: +1 787 722 1248; fax: +1 787 721 6098.
E-mail address: mrodrigueztorres@fdipr.com (M. Rodriguez-Torres).

† Employed by Pharmasset, Inc., Princeton, NJ, USA at the time the study was conducted.

Abbreviations: HCV, hepatitis C virus; PegIFN, pegylated interferon; RBV, ribavirin; RVR, rapid virologic response; SVR, sustained virologic response; IL, interleukin; LOD, limit of detection; MedDRA, Medical Dictionary for Regulatory Activities; ECG, electrocardiogram; AUC_{0-tau}, area under the concentration–time curve from time 0 to the end of dosing interval; C_{max}, maximum plasma concentration; t_{max}, time to C_{max}; $t_{½}$, elimination half-life; HOMA-IR, homeostasis model assessment of insulin resistance; CI, confidence interval.

Introduction

The recent approval of the hepatitis C virus (HCV) protease inhibitors telaprevir and boceprevir has inaugurated a new era in the treatment of HCV infection. These agents have raised the rates of sustained virologic response (SVR) for patients with genotype 1 HCV by as much as 30% in comparison with the former standard-of-care, pegylated-interferon (PegIFN) combined with ribavirin (RBV) [1,2]. However, the current protease inhibitor-based regimens are limited by lower rates of response in non-responders to prior therapy, the emergence of resistant mutations, and significant adverse events [2–4]. Thus, there remains a significant unmet need for potent antiviral agents with pangenotypic sensitivity, a high barrier to resistance, and fewer side effects for patients with HCV.

There are currently a large number of agents in development across a variety of classes for the treatment of HCV. One class for which promising *in vitro* results have been reported is represented by the nucleoside/nucleotide analogs [1,5]. These compounds share properties with the intracellular nucleoside substrates of the target HCV enzymes involved in the transcription of the viral genome and, when phosphorylated to the nucleoside-triphosphate, lead to premature termination of the growing HCV RNA chain during viral replication [6,7]. Sofosbuvir (formerly GS-7977) is a phosphoramidate prodrug of beta-D-2′-deoxy-2′-fluoro-2′-C-methyluridine 5′-monophosphate with enhanced antiviral potency compared with earlier nucleoside analogs [8]. Sofosbuvir was initially studied as one of the two isomers of GS-9851 [9].

In the present study, we assess the safety, tolerability, antiviral activity, and pharmacokinetics of three different doses

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of sofosbuvir in combination with PegIFN/RBV in treatment-naïve patients infected with genotype 1 HCV.

Materials and methods

Study population

We enrolled 64 treatment-naïve patients with chronic HCV genotype 1 infection (HCV RNA levels ⩾100,000 IU/ml at screening), 18–65 years of age with a body mass index of 18–36 kg/m^2. Females of childbearing potential were required to use a protocol-approved method of contraception. A liver biopsy within 3 years of dosing was required to exclude cirrhosis. Patients were otherwise in good health, with no significant co-morbidities. Other key exclusion criteria included positive test for hepatitis B surface antigen, anti-hepatitis B core protein IgM antibodies and anti-human immunodeficiency virus antibodies.

Informed consent was obtained from each patient included in the study. Local Ethics Review Committees provided approval for the study, which was conducted in accordance with Good Clinical Practice and the ethical guidelines of the 1975 Declaration of Helsinki.

Study design

This randomized, placebo-controlled, double-blind dose-ranging study (Clinicaltrials.gov: NCT01054729) was conducted from 18 January, 2010 to 25 August, 2011, at seven sites in the United States (and Puerto Rico). Oral sofosbuvir or matching placebo (both manufactured by Metrics Inc., NC, USA on behalf of Gilead Sciences, Inc.) was administered with PegIFN alfa-2a (Pegasys®, Genentech, San Francisco, CA, USA) and RBV (Copegus®, Genentech, San Francisco, CA, USA). Both PegIFN and RBV were administered according to the package insert for patients with genotype 1 infection.

Eligible patients were randomized in a ratio of active:placebo of 1:1:1:1 to receive one of three once-daily doses of sofosbuvir (100, 200, or 400 mg) or placebo plus PegIFN/RBV for 28 days, after which patients continued treatment with PegIFN/RBV alone for a further 44 weeks. Both investigators and patients were blinded to the treatment assignment. Randomization was stratified by interleukin (IL) 28B status (rs12979860) for CC or CT/TT allele. The randomization schedule was provided by PharStat, Inc. (NC, USA). Patients were randomized by a central web-based system using permutated blocks. Patients attended regular visits until the end of the 48-week period and follow-up took place 12 and 24 weeks after the last dose of PegIFN/RBV to assess for SVR.

Patients were to have all therapy discontinued if there is inadequate response to therapy with PegIFN and RBV according to the following stopping rules (note to typesetters: please ask author to check this text): if HCV RNA is still detectable at Week 12, therapy should be continued until Week 24; if HCV RNA is still detectable at Week 24, therapy with PegIFN and RBV should be discontinued. The subject should then have an early termination visit approximately 30 days after all therapy is discontinued.

Assessment of efficacy

Efficacy end points included change in circulating HCV RNA over 28 days of dosing, rates of rapid virologic response (HCV RNA below the limit of detection at Week 4), and rates of sustained virologic response at 12 (SVR12) and 24 (SVR24) weeks following completion of 48 weeks of treatment.

Blood samples to quantify plasma HCV RNA were collected at screening and in the morning (pre-dose on dosing days) on Days 1, 2, 4, 8, 15, 22, 28 and 29 and Weeks 6, 8, 12, 24, 48, 52, 60 and 72 (SVR24 visit). Blood samples for NS5B genotypic and phenotypic monitoring were collected (pre-dose on dosing days) at Days 0, 7, 14, 21 and 28 and Weeks 12, 20, 24, 28, 32, 36, 40, 44, 48, 52, 60 and 72 (SVR24 visit).

Hepatitis C virus genotyping and genotypic monitoring were performed as previously described [9]. Resistance monitoring was completed in all patients who received sofosbuvir and were classified as non-responders or rebounders, had virologic breakthroughs, or those with a plateau in HCV viral load between Day 1 and Day 28. Sequencing and phenotypic analyses were performed at 4-week intervals (for up to 48 weeks), in patients who had mutations leading to sofosbuvir resistance, in order to determine the time for the resistant virus to return to background levels. Phenotypic assays to monitor resistance to sofosbuvir were performed on baseline (pre-dose on Day 1) and end-of-treatment samples.

All patients were assessed for rapid virologic response (RVR) (defined as HCV RNA <limit of detection, LOD [15 IU/ml] at Day 28) and viral breakthrough (defined as HCV RNA increase >LOD in two or more consecutive visits after an initial drop to below detection). Efficacy assessments included sustained virologic response, defined as HCV RNA below the LOD at 12 (SVR12) and 24 weeks (SVR24) following the last dose of study medication, and viral relapse, defined as HCV RNA >LOD after an initial drop to below detection by the end of treatment visits.

Safety analysis

The primary end points were safety and tolerability of 28 days of treatment with sofosbuvir/PegIFN/RBV. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (note to typesetters; please ask authors whether dictionary could read terminology) [10]. Vital signs were measured at screening and Days 1, 2, 4, 8, 15, 22, and 28. Twelve-lead electrocardiograms (ECGs) were recorded at screening and pre- and post-dose on Days 1 and 28. Clinical laboratory samples (for serum chemistry, hematology and urinalysis) were obtained at screening and Days 1, 4, 8, 15, 22 and 28.

Pharmacokinetic sample collection and analysis

Blood samples for pharmacokinetic analysis were collected on Day 1 at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 hours post-dose; pre-dose on Days 2, 4, 8, 15 and 22 and pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 hours post-dose on Day 28.

Plasma concentrations of sofosbuvir and GS-331007 (beta-D-2′-deoxy-2′-fluoro-2′-C-methyluridine 5′-monophosphate) were determined using a validated high-performance liquid chromatography-tandem mass spectroscopy method (QPS, LLC Newark, DE, USA). The linear range of the plasma assay was 5–5000 ng/ml for sofosbuvir and 10–5000 ng/ml for GS-331007. Pharmacokinetic parameters were derived from the time–concentration data by standard non-compartmental analysis using WinNonLin Version 5.2 (Pharsight Corporation, Mountain View, CA, USA). Derived plasma pharmacokinetic parameters for sofosbuvir and GS-331007 included: area under the concentration–time curve from time 0 to the end of dosing interval (AUC_{0-tau}), maximum plasma concentration (C_{max}), time to C_{max} (t_{max}) and elimination half-life ($t_{½}$).

Statistical analysis

No formal analysis was performed to determine sample size or to assess safety data. HCV RNA values (IU/ml) were transformed to the logarithmic (base 10) scale (log_{10} IU/ml) and summary statistics were performed on log_{10} transformed data for each treatment by visit. The efficacy end points, RVR rates and proportion of patients with HCV RNA levels lower than LOD at end-of-treatment, SVR4, SVR12 and SVR24 rates, were analyzed for the following subgroups: HCV genotype (1a, 1b), *IL28B* genotype (CC, CT/TT), gender (male, female), race (black, non-black), ethnicity (Hispanic or latino, not Hispanic or latino), homeostasis model assessment of insulin resistance (HOMA-IR) score (⩽3, >3), baseline HCV RNA level (⩽800,000 IU/ml, >800,000 IU/ml).

Pharmacokinetic parameters were log_{10}-transformed before analysis. Accumulation was determined by comparing AUC_{0-tau} on Day 28–Day 1. Accumulation was analyzed by mixed effects model with day as a fixed effect and patient as a random effect. A 90% confidence interval (CI) for the true difference on the log-scale across all patients was estimated.

Results

Study population disposition and demographics

The demographic characteristics of the study population were similar across treatment groups (Table 1); patients in the placebo/PegIFN/RBV treatment group had higher mean weight and body mass index than those in the sofosbuvir/PegIFN/RBV treatment groups. There were no notable differences between the treatment groups for any disease characteristic (Table 1). Of the 64 randomized patients, 63 received at least one dose of study medication and were included in the safety analysis: sofosbuvir