Research Article

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Generic ledipasvir-sofosbuvir for patients with chronic hepatitis C: A real-life observational study

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Background & Aims: Few patients from developing countries can afford brand name direct-acting antiviral agents for treating hepatitis C virus (HCV) infection, and controversy regarding the bioequivalence of generics exists. This study aimed to observe the safety and efficacy of 8 or 12 weeks of generic ledipasvir-sofosbuvir with or without ribavirin for Chinese genotype 1b HCV-infected patients.

Methods: In this open-labelled observational study, 63 cirrhotic (group 1) and 65 non-cirrhotic (group 2) patients were administered generic ledipasvir-sofosbuvir plus 1000–1200 mg of ribavirin daily for 12 and 8 weeks, respectively; and 64 non-cirrhotic patients (group 3) received ledipasvir-sofosbuvir for 8 weeks. The primary efficacy endpoint was undetectable HCV RNA at week 12 (SVR12) after cessation of therapy. Safety and pharmacokinetic data were collected.

Results: One hundred and eighty-seven patients completed treatment, and the latest undetectable HCV RNA was observed in three patients with cirrhosis at week 5 during treatment. Intention-to-treat analysis revealed 96.8% (61/63), 96.9% (63/65), and 96.9% (62/64) of SVR12 rates in groups 1, 2, and 3, respectively. One patient in group 3 relapsed at post-treatment week 4. The regimens were generally well-tolerated. The most common adverse events were fatigue (17.8%), diarrhea (10.9%), and headache (9.9%). Four patients discontinued therapy due to diarrhea and vomiting. One patient from group 2 discontinued treatment on day 29 because of drug-unaffordability; fortunately, she achieved SVR12.

Conclusion: This study demonstrated that 8 or 12 weeks of generic ledipasvir-sofosbuvir with or without ribavirin are safe and effective for patients with genotype 1b HCV infection.

Lay summary: The price of Harvoni® has led to restrictions and access limitations in many developing and even developed countries with limited healthcare budgets. Gilead approved generic ledipasvir-sofosbuvir costs far less than Harvoni® and presents a similar cure rate for patients with chronic hepatitis C.

Introduction

Chronic hepatitis C virus (HCV) infection is a major global health problem that affects 130–170 million people worldwide and represents a major cause of liver cirrhosis and hepatocellular carcinoma (HCC) [1–3]. In China, the overall prevalence of HCV infection is estimated to be 2.2% [1]. In Henan province, the incidence is 9.6% owing to a higher infection rate via blood transmission [1,2,4]. Genotype 1 is the most common in China, as it accounts for 58.4% of all HCV-infected persons, principally genotype 1b [1,2]. Many studies have demonstrated that genotype 1 HCV infection is difficult to treat compared to genotypes 2 and 3 in the era of the pegylated interferon-α plus ribavirin (PegIFN + RBV) regimen [1,5]. A recent study revealed that patients with genotype 1b HCV infection are at a higher risk at developing HCC than those infected with non-genotype 1b subtypes [6]. Genotype 1b HCV infection is thus a serious healthcare problem in China.

Currently, the PegIFN + RBV regimen remains the standard of care in China. Worldwide, this former standard of care for chronic hepatitis C (CHC) is associated with a sustained virologic response (SVR) in approximately 40% of patients with genotype 1 infection and 75% of patients infected with genotypes 2 or 3 [5,7]. Fortunately, an SVR to a PegIFN + RBV regimen is higher for Chinese patients with chronic genotype 1 HCV infection than for Caucasian patients [1–3]. Several host, viral, and disease factors have been found to influence the response to PegIFN + RBV treatment [5,8]. Polymorphism in the interleukin (*IL*)-*28B* gene is a major reason [9]. A favorable *IL-28B* genotype (rs12979860 CC and rs8099917 TT) is associated with a 2- to 3-fold greater SVR rate to PegIFN + RBV treatment for HCV genotype 1 [9], and 91.75% of

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Chinese CHC patients have the rs12979860 CC genotype [10]. However, it is well known that PegIFN + RBV has some contraindications and several side effects, and thus, this regimen may be poorly tolerated and adhered to in some patients. The combination of an unfavorable SVR rate and poor tolerance and adherence warrant the development of new antiviral agents.

As an eliminator of HCV and a leader of direct-acting antiviral agents (DAAs), sofosbuvir has revolutionized the treatment of CHC since 2013 [11]. Sofosbuvir is a nucleotide analogue HCV NS5B polymerase inhibitor, and ledipasvir is an inhibitor of HCV NS5A [12–16]. These two DAAs have complementary mechanisms of action. A fixed-dose combination tablet composed of ledipasvir-sofosbuvir is approved in Western countries based on the results of three phase III studies (ION-1, ION-2, and ION-3) [14–16]. The European Association for the Study of the Liver (EASL) Recommendations on Treatment of Hepatitis C 2016 suggested that non-cirrhotic patients infected with HCV genotype 1 can be treated with a fixed-dose combination tablet of ledipasvir and sofosbuvir once daily for 12 weeks, and treatment may be shortened to 8 weeks in treatment-naïve patients without cirrhosis if their baseline HCV RNA level is below 6 million (6.8 $\log_{10}$) IU/ml [17]. Patients with cirrhosis should be treated with this fixed-dose combination for 12 weeks with daily weight-based RBV (1000 mg or 1200 mg in patients <75 kg or ≥75 kg, respectively), or for 24 weeks of ledipasvir-sofosbuvir without RBV [17].

China is a developing country with the largest amount of HCV-infected individuals worldwide [1]. However, brand name DAAs are unaffordable. Fortunately, Gilead Sciences, Inc. approved generic ledipasvir-sofosbuvir with a very low price in many neighboring countries of China, and patients can go to these countries to purchase the drug and for treatment. For example, on December 15 2015, Indian Natco Pharma Limited announced that it received approval for the generic version of ledipasvir-sofosbuvir (Hepcinat LP) after signing a non-exclusive licensing agreement with Gilead Sciences earlier in 2015; and ledipasvir-sofosbuvir was previously sold globally by Gilead Sciences, Inc., under its brand name Harvoni®. However, there has been some controversy concerning the bioequivalence of generics when compared to brand name agents [18,19], and the safety and efficacy data for generic ledipasvir-sofosbuvir are lacking. Herein, we report the safety and efficacy of 8 weeks or 12 weeks of generic ledipasvir-sofosbuvir for Chinese patients with chronic genotype 1b HCV infection.

Patients and methods

Inclusion and exclusion criteria

In a current open-label study, enrolled patients met all of the following inclusion and exclusion criteria at baseline: (1) age 30–70 years; (2) a history of chronic HCV infection; (3) HCV genotype 1b; (4) with or without cirrhosis, including compensated and decompensated cirrhosis (without esophagogastric varices or hepatic encephalopathy); (5) treatment-naïve; (6) albumin >30 g/L, hemoglobin >85 g/L, platelet >50 × 10^9/L, prothrombin time activity percentage >60%; and (7) negative test results for hepatitis A, B, and E viruses, Epstein–Barr virus, cytomegalovirus, and human immunodeficiency virus, as well as antinuclear, anti-smooth muscle, and antimitochondria autoantibodies.

Patient assessments at baseline

The following clinical tests were completed for all patients during the period of initial visits: electrocardiography; anti-hepatitis A and E antibodies, serum hepatitis B surface antigen, anti-human immunodeficiency virus, anti-HCV, HCV RNA, and HCV genotype tests; thyroid function, blood glucose levels, prothrombin time activity percentage, autoantibodies, alpha-fetoprotein, and serum biochemistry; abdominal imaging examinations; and tests of liver stiffness.

Serum HCV RNA was monitored using a Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Test (Roche Molecular Systems, Branchburg, NJ, USA; V.3.0, cut-off value, 15 IU/ml). Anti-HCV reactivity was detected using a VITROS® enhanced electrochemiluminescence immunoassay (Ortho-Clinical Diagnostics, Raritan, NJ, USA). The HCV genotype was analysed using a gene sequencing assay.

Cirrhosis was diagnosed based on the results of at least two imaging tools (i.e., abdominal ultrasonography, FibroScan®, computed tomography or magnetic resonance imaging) plus clinical evidence of manifestations. The liver stiffness cut-off >12.5 kPa indicates cirrhosis in patients without ascites [20]. HCC was screened for by at least two imaging tools, or by one imaging diagnostic modality plus a serum alpha-fetoprotein level of at least 400 ng/ml [21].

Treatment regimens

A total of 192 patients who purchased the generic version of ledipasvir-sofosbuvir through medical tourism by themselves from neighboring countries of China were divided into three groups (Fig. 1). Cirrhotic hepatitis C patients in group 1 (n = 63) were treated with a fixed-dose combination tablet containing 90 mg of ledipasvir and 400 mg of sofosbuvir (once daily), and RBV (1000 mg or 1200 mg daily divided into three doses in patients who weighed <75 kg or ≥75 kg, respectively) for 12 weeks. CHC patients in group 2 (n = 65) were administered a generic ledipasvir-sofosbuvir tablet once daily plus ribavirin for 8 weeks. CHC patients in group 3 (n = 64) received a ledipasvir-sofosbuvir tablet once daily without ribavirin for 8 weeks. The generic version of ledipasvir-sofosbuvir (Hepcinat LP) was approved by Gilead Sciences earlier in 2015 and is produced by Indian Natco Pharma Limited.

Evaluations during antiviral therapy

HCV RNA levels, electrocardiography, serum biochemistry and routine blood test parameters were measured weekly until HCV RNA was undetectable; and then every 4 weeks through week 12 (group 1) or week 8 (groups 2 and 3); and again at weeks 4, 8, and 12 after the end of the treatment period.

Efficacy and safety evaluations

The primary efficacy endpoint was the SVR, which was defined as an undetectable HCV RNA level at 12 weeks (SVR12) after the cessation of therapy. Adverse events that occurred both during and after therapy were also reported. HCC was screened at the end of therapy and 12 weeks after the therapy.

Sample size estimation

One of the aims of this study was designed to demonstrate that the difference in the SVR rate (generic ledipasvir-sofosbuvir – historically controlled brand name counterpart) is no less than '– non-inferiority margin' ($-\Delta$), which ranges from −0.12 to −0.15 in previous studies [16,22]. In the current study, Δ was set high at 0.12 [16], and the controlled SVR rate for brand name ledipasvir-sofosbuvir was set at 95% on the basis of prior studies [16,17]. The level of one-sided significance was set at 0.05, with a high standard of power ($1 - \beta$) of 0.9. Therefore, the estimated sample size was 56 in each group according to the formula described by Christensen [23], which was rounded up to 62 to allow for a high level of withdrawal (10%) under the background of current DAAs therapies. The total sample size required for the three groups in this study was thus calculated to be at least 186.

Statistical analysis

Continuous variables were summarized as either the mean with standard deviation or medians and ranges, as appropriate. The percentage of patients in each category was calculated for categorical variables. The percentages were compared between different groups using the chi-squared test. A two-sided p <0.05 was considered significant. The analyses were performed using SPSS software 16.0 for Windows (SPSS Inc. Chicago, IL, USA). The 95% confidence interval (CI) was calculated using EpiCalc 2000 (version 1.02) statistical calculator.