Ledipasvir-sofosbuvir with or without ribavirin to treat patients with HCV genotype 1 infection and cirrhosis non-responsive to previous protease-inhibitor therapy: a randomised, double-blind, phase 2 trial (SIRIUS)

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Summary

Background **Patients with cirrhosis resulting from chronic hepatitis C virus (HCV) infection are at risk of life-threatening complications, but consistently achieve lower sustained virological response (SVR) than patients without cirrhosis, especially if treatment has previously failed. We assessed the efficacy and safety of the NS5A inhibitor ledipasvir and the nucleotide polymerase inhibitor sofosbuvir, with and without ribavirin.**

Methods **In this multicentre, double-blind trial, between Oct 21, 2013, and Oct 30, 2014, we enrolled patients with HCV genotype 1 and compensated cirrhosis who had not achieved SVR after successive treatments with pegylated interferon and protease-inhibitor regimens at 20 sites in France. With a computer-generated randomisation sequence, patients were assigned in a 1:1 ratio to receive placebo matched in appearance to study drugs for 12 weeks followed by once daily combination fixed-dose tablets of 90 mg ledipasvir and 400 mg sofosbuvir plus weight-based ribavirin for 12 weeks, or ledipasvir-sofosbuvir plus placebo once daily for 24 weeks. The primary endpoint was SVR 12 weeks after the end of treatment (SVR12), for which 95% CIs were calculated with the Clopper-Pearson method. This study is registered with ClinicalTrials.gov, number NCT01965535.**

Findings **Of 172 patients screened, 155 entered randomisation, 77 were assigned to receive ledipasvir-sofosbuvir plus ribavirin and 78 ledipasvir-sofosbuvir. 114 (74%) were men, 151 (97%), were white, 98 (63%) had HCV genotype 1a, and 145 (94%) had non-CC *IL28B* alleles. SVR12 rates were 96% (95% CI 89–99) for patients in the ledipasvir-sofosbuvir plus ribavirin group and 97% (91–100) in the ledipasvir-sofosbuvir group. One patient discontinued treatment because of adverse events while receiving only placebo. The most frequent adverse events were asthenia and headache, pruritus, and fatigue.**

Interpretation **Ledipasvir-sofosbuvir plus ribavirin for 12 weeks and ledipasvir-sofosbuvir for 24 weeks provided similarly high SVR12 rates in previous non-responders with HCV genotype 1 and compensated cirrhosis. The shorter regimen, when given with ribavirin, might, therefore, be useful to treat treatment-experienced patients with cirrhosis if longer-term treatment is not possible.**

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Introduction

Patients with cirrhosis resulting from chronic infection with the hepatitis C virus (HCV) are at risk of developing life-threatening complications, such as decompensated liver disease and hepatocellular carcinoma.[1,2] Treatment improves long-term outcomes for patients with cirrhosis, and sustained virological response (SVR) is associated with histological improvement and reduced risk of hepatocellular carcinoma, decompensation, and liver-related mortality.[3–6] In clinical trials and real-world settings, however, patients with cirrhosis, especially those for whom previous therapy has failed, achieve consistently lower rates of SVR than patients without cirrhosis.[7–10] Moreover, interferon-based regimens for the treatment of HCV genotype 1 are poorly tolerated by patients with cirrhosis and cause high rates of severe and serious adverse events, leading many patients to discontinue treatment.[11] Therefore, interferon-free regimens for patients with cirrhosis are needed.[12]

Ledipasvir is a novel HCV NS5A inhibitor. Sofosbuvir is a nucleotide analogue inhibitor of the HCV NS5B polymerase approved for the treatment of HCV genotype 1–4 infections.[13] 90 mg ledipasvir and 400 mg sofosbuvir in a fixed-dose combination tablet was assessed in two clinical trials in patients with HCV genotype 1 and cirrhosis who had not previously achieved SVR with protease-inhibitor treatments. The LONESTAR trial[14] involved 22 patients who received ledipasvir-sofosbuvir for 12 weeks or ledipasvir-sofosbuvir plus ribavirin for 12 weeks. Of 11 in each

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group, ten (91%) and 11 (100%), respectively, achieved SVR 12 weeks after the end of treatment (SVR12). The phase 3 ION-2 trial[15] assessed 54 patients with cirrhosis in whom previous treatment with protease-inhibitor regimens had failed. SVR12 in those receiving 12 weeks of ledipasvir-sofosbuvir with and without ribavirin was seen in 12 (85%) of 14 and 11 (86%) of 13 patients, respectively. In patients who received 24 weeks of ledipasvir-sofosbuvir with and without ribavirin, SVR12 was achieved in 100% of patients.[15]

We assessed the efficacy and safety of ledipasvir-sofosbuvir with and without ribavirin in patients with HCV genotype 1 and cirrhosis who had not achieved SVR after successive treatments with pegylated interferon (peginterferon) and protease inhibitors.

Methods

Study design and patients

We did a randomised, double-blind, placebo-controlled trial between Oct 21, 2013, and Oct 30, 2014, at 20 sites in France. We enrolled patients aged at least 18 years who had HCV genotype 1 infections and cirrhosis and had not achieved SVR after being treated first with peginterferon and ribavirin and then with a protease inhibitor plus peginterferon and ribavirin. Eligible patients had documented cirrhosis identified by biopsy, a transient elastography result of more than 12·5 kPa, or a fibrotest score higher than 0·75, together with an aspartate aminotransferase to platelet ratio greater than 2 during screening. Patients with transient elastography results higher than 20·0 kPa were required to undergo upper endoscopy for assessment of varices. Other eligibility criteria were platelet counts of at least 50×10^9/L, haemoglobin concentration of at least 110 g/L, albumin concentration at least 30 g/L, and prothrombin time and direct bilirubin concentration of no more than 1·5 times the upper limits of normal. Patients with evidence of decompensation (ie, clinical ascites, encephalopathy, or variceal haemorrhage) or hepatocellular carcinoma were excluded.

Before enrolment and before any study procedures were started, written informed consent was obtained from all patients. The study was approved by the institutional review board or independent ethics committees at all participating sites and was done in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice.

Randomisation and masking

We used a computer-generated randomisation sequence created by Bracket (San Francisco, CA, USA), with random block sizes and a predefined stratification scheme. Randomisation was stratified by HCV genotype (1a *vs* 1b, with mixed or other genotype 1 subtypes being classified as genotype 1a) and response to previous treatment (HCV RNA concentration less than the lower limit of quantification [LLOQ] never achieved *vs* achieved). Investigators and patients were unaware of treatment allocation and on-treatment HCV RNA results until 12 weeks after the end of treatment. The treating physician obtained the next centrally stored treatment allocation by use of an interactive online response system.

Patients were assigned in a 1:1 ratio to receive 90 mg ledipasvir and 400 mg sofosbuvir in a fixed-dose combination tablet plus placebo for 12 weeks followed by ledipasvir-sofosbuvir once daily plus ribavirin given in a divided daily dose for 12 weeks, or once daily ledipasvir-sofosbuvir plus placebo for 24 weeks. Ribavirin dose was based on each individual patient's weight: patients who weighed less than 75 kg received 1000 mg daily as two tablets in the morning and three in the evening, and those who weighed 75 kg or more received 1200 mg daily as three tablets in the morning and in the evening, with food. To mask treatment groups, placebo tablets were matched to ledipasvir-sofosbuvir and ribavirin in appearance and administration, as appropriate.

Assessments

Serum HCV RNA concentrations were measured with the COBAS TaqMan HCV test (version 2.0) for use with the High Pure System (Roche, Indianapolis, IN, USA), with an LLOQ of 25 IU/mL. HCV genotypes and subtypes were determined with the VERSANT HCV Genotype INNO-LiPA 2.0 assay (Siemens, Camberley, Surrey, UK). For all patients, the *IL28B* genotype was determined by PCR amplification and sequencing of the rs12979860 single-nucleotide polymorphism.

Deep sequencing of the NS3A, NS5A, and NS5B regions of HCV RNA was done at baseline for all patients and at the time of virological failure in patients who did not achieve SVR12. Sequences were compared with reference sequences or those from baseline samples to establish the prevalence and kinetics of resistance-associated variants. Variants present at more than 1% of sequence reads were reported.

Safety was assessed in all patients at all visits during treatment (day 1 and weeks 1, 2, 4, 8, 12, 13, 14, 16, 20, and 24) and at weeks 4 and 12 after the end of treatment by physical examination, review of adverse events, and laboratory testing of blood samples for haematocrit, haemoglobin concentration, and platelet and red and white blood cell counts, coagulation, chemistry, including alanine and aspartate aminotransferase, alkaline phosphtase, creatinine, albumin, total bilirubin, glucose, lipase, potassium, and sodium concentrations, and urinalysis. Decisions to reduce, interrupt, or discontinue ribavirin dosing because of toxic effects were made according to the drug product label. The use of haematological-stimulating agents (eg, granulocyte colony-stimulating factor, thrombopoietin, and mimetics), except erythropoiesis-stimulating agents, was prohibited during the screening

period and from at least 28 days before the start until the end of treatment.

Statistical analysis

The primary efficacy endpoint was SVR12, defined as HCV RNA concentration in serum lower than 25 IU/mL. Rates were calculated with two-sided 95% CIs with binomial distribution (Clopper-Pearson method). We used a Cochran-Mantel-Haenszel test to do a secondary analysis to compare the SVR12 rates between the two treatment groups by randomisation stratification factors. Two-sided 95% CIs were constructed on the basis of stratum-adjusted Mantel-Haenszel proportions. We calculated that a sample size of 75 patients in each treatment group would provide 80% power to detect a difference of 15% in SVR12 rates between groups. Efficacy was assessed in all patients who entered randomisation and received at least one dose of the assigned active study drug. Safety was assessed in all patients who entered randomisation and received at least one dose of study drug or placebo. All analyses were done with SAS (version 9.2). This study is registered with ClinicalTrials.gov, number NCT01965535.

Role of the funding source

The funder of the study oversaw trial management, data collection, data analyses, and writing of the report. The funder had no role in study design or data interpretation. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of 172 patients screened, 155 patients entered randomisation and were treated (figure, appendix). Most patients were men, white, infected with HCV genotype 1a, and had non-CC alleles of the *IL28B* gene (table 1). 154 had cirrhosis; one patient without cirrhosis was enrolled in error and randomly assigned to the ledipasvir-sofosbuvir plus ribavirin group and is included in the efficacy and safety analyses. One patient who discontinued study treatment because of adverse events was included in the safety but not the efficacy analysis. One patient assigned ledipasvir-sofosbuvir plus ribavirin received the ledipasvir-sofosbuvir regimen in error and was assessed for efficacy according

See Online for appendix

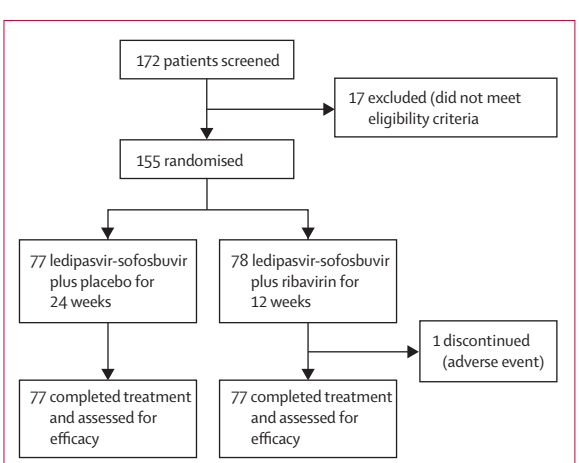

***Figure*: Trial profile**

	Ledipasvir-sofosbuvir plus ribavirin for 12 weeks (n=77)	Ledipasvir-sofosbuvir for 24 weeks (n=78)
Age (years)	56 (7·4)	57 (10·7)
Men	58 (75%)	56 (72%)
Ethnic origin		
White	76 (99%)	75 (96%)
Black	1 (1%)	3 (4%)
Body-mass index (kg/m²)	27·9 (5·5)	26·3 (4·2)
HCV genotype		
1a	48 (62%)	50 (64%)
1b	28 (36%)	27 (35%)
1 (no confirmed subtype)	1 (1%)	1 (1%)
HCV RNA concentrations (log_{10} IU/mL)	6·5 (0·5)	6·5 (0·6)
IL28B alleles		
CC	4 (5%)	6 (8%)
CT	49 (64%)	53 (68%)
TT	24 (31%)	19 (24%)
Previous protease-inhibitor regimen		
Telaprevir	43 (56%)	49 (63%)
Boceprevir	30 (39%)	27 (35%)
Telaprevir and boceprevir	1 (1%)	0
Simeprevir	1 (1%)	2 (3%)
Faldaprevir	2 (3%)	0
Previous response to protease inhibitors		
Achieved HCV RNA <LLOQ	45 (58%)	43 (55%)
Never achieved HCV RNA <LLOQ	32 (42%)	35 (45%)
Method of cirrhosis detection		
Biopsy	27 (35%)*	31 (40%)
Fibroscan	48 (62%)	47 (60%)
Fibrotest + APRI	1 (1%)	0
Patients with known oesophageal varices†	16 (21%)	25 (32%)
Transient elastography score (kPa)	21 (11)	24 (12)
Mean CPT score (range)	5·2 (5–7)‡	5·2 (5–6)
Mean MELD score (range)	7 (6–16)	7 (6–12)
Platelets <100 × 10^9/L	13 (17%)	14 (18%)
Albumin <35 g/L	6 (8%)	14 (18%)
Patients with NS3A RAVs	44 (57%)	39 (50%)
Patients with NS5A RAVs	12 (16%)§	12 (15%)¶

Data are number (%) or mean (SD) unless stated otherwise. HCV=hepatitis C virus. LLOQ=lower limit of quantification. APRI=aspartate aminotransferase to platelets ratio index. CTP=Child-Turcotte-Pugh. MELD=model for end-stage liver disease. RAVs=resistance-associated variants. *One patient did not have cirrhosis. †Only patients with fibroscan scores >20 kPa received endoscopic assessment for varices; ‡Two patients had CTP scores of 7. §Leu31Ile/Met/Val (n=6); Tyr93His (n=6) Lys24RArg (n=1). ¶Tyr93His (n=5); Leu31Met/Val (n=5); Gln30Arg (n=3); Lys24Arg (n=2); Met28Thr (n=1); Ala92Thr (n=1).

***Table 1*: Baseline characteristics**

to the original dose assignment, but by treatment received for demographics and safety.

Patients experienced rapid reductions in HCV RNA concentrations after beginning treatment (table 2). By week 2, HCV RNA concentrations lower than 25 IU/mL were seen in 85 (55%) patients overall (39 of 77 receiving ledipasvir-sofosbuvir and 46 of 77 receiving ledipasvir-sofosbuvir plus ribavirin), and by week 4 of treatment they were seen in 150 (97%). By 12 weeks of active treatment, HCV RNA concentrations lower than 25 IU/mL were seen in all patients.

SVR12 rates were 96% (95% CI 89–99) in the ledipasvir-sofosbuvir plus ribavirin group and 97% (91–100) in the ledipasvir-sofosbuvir group (p=0·63) and did not differ by demographic or disease characteristics. SVR12 rates when compared with previous treatment response were 97% in ledipasvir-sofosbuvir plus ribavirin group and 94% in the ledipasvir-sofosbuvir group in patients who had never achieved HCV RNA less than the LLOQ, versus 96% and 100%, respectively, in patients who had previously achieved HCV RNA less than the LLOQ. Additionally, SVR12 did not differ between patients with baseline platelet counts lower than 100×10^9/L or serum albumin concentrations lower than 35 g/L: 83% and 93%, respectively, in the ledipasvir-sofosbuvir plus ribavirin group, and 100% for both factors in the ledipasvir-sofosbuvir group. All eight patients who had platelet counts lower than 100×10^9/L and albumin lower than 35 g/L at baseline also achieved SVR12, as did the two patients with Child-Turcotte-Pugh scores of 7 at baseline. SVR12 rates in further subgroups are shown in the appendix.

Of the 155 patients enrolled and treated, five (3%) had virological failure (table 3): three (4%) of those in the ledipasvir-sofosbuvir plus ribavirin group (two by 4 weeks and one by 12 weeks after the end of treatment) and two (3%) in the ledipasvir-sofosbuvir group (all by 4 weeks after treatment). Male sex and non-CC *IL28B* alleles were the only common baseline characteristics among patients, but both these characteristics were seen in high proportions of the study population at baseline (table 1).

83 (54%) patients had NS3A resistance-associated variants and 24 (16%) had NS5A resistance-associated variants at baseline (table 1). Two of the five patients who relapsed (both in the ledipasvir-sofosbuvir group) had NS5A resistance-associated variants at baseline, whereas the other three (all in the ledipasvir-sofosbuvir plus ribavirin group) did not. At the time of virological failure all five showed NS5A resistance by deep sequencing (table 3). No patient had the NS5B Ser282Thr variant, which is associated with reduced susceptibility to sofosbuvir, at baseline or relapse, and no variants associated with sofosbuvir resistance were seen at baseline or during treatment in patients who relapsed.

Most patients had at least one treatment-emergent adverse event (table 4). The most common event in the two groups was asthenia, followed by pruritus and

	Ledipasvir-sofosbuvir plus ribavirin for 12 weeks (n=77)	Ledipasvir-sofosbuvir for 24 weeks (n=77)
Treatment week 4	75 (97%)	75 (97%)
Treatment week 12	77 (100%)	77 (100%)
SVR4	75 (99%, 95% CI 91–100)	75 (97%, 95% CI 91–>99)
SVR12	74 (96%, 95% CI 89–99)	75 (97%, 95% CI 91–>99)
Virological failure		
During treatment	0	0
Relapse after treatment	3 (4%)	2 (3%)

SVR4=sustained virological response 4 weeks after treatment. SVR12=sustained virological response 12 weeks after treatment.

***Table 2*: Patients with hepatitis C virus RNA concentration lower than 25 IU/mL during and after treatment**

	Age (years)	Sex	Ethnic origin	HCV genotype	*IL28B* alleles	Albumin (g/L)	Platelets ($\times10^9$/L)	Fibroscan result	Oesophageal varices	Previous protease inhibitor	<LLOQ achieved previously	NS5A RAVs at baseline	NS5A RAVs at relapse
Ledipasvir-sofosbuvir plus ribavirin for 12 weeks													
Patient 1	49	Male	White	1b	TT	36	184	NA*	Small	Telaprevir	Yes	None	Tyr93His (>99%)
Patient 2	55	Male	White	1b	CT	32	101	29·5	Small	Telaprevir	No	None	Tyr93His (>99%)
Patient 3	48	Male	White	1a	CT	38	65	39·4	None	Telaprevir	Yes	None	Gln30Arg (>99%)
Ledipasvir-sofosbuvir for 24 weeks													
Patient 4	53	Male	White	1a	CT	39	111	34·3	Small	Boceprevir	No	Met28Thr (5%), Gln30Arg (27%), Leu31Met (29%), Leu31Val (59%)	Gln30His (46%), Gln30Arg (54%), Leu31Met (54%), Leu31Val (46%)
Patient 5	57	Male	Black	1b	CT	41	179	18·4	NA	Boceprevir	No	Tyr93His (66%)	Tyr93His (97%)

HCV=hepatitis C virus. LLOQ=lower limit of quantification. RAVs=resistance-associated variants NA=not assessed. *Cirrhosis was detected with fibrotest (0·89) plus aspartate aminotransferase to platelets ratio index (2·91).

***Table 3*: Baseline characteristics of patients who relapsed**

	Ledipasvir-sofosbuvir plus ribavirin group			Ledipasvir-sofosbuvir group	
	First 12 weeks (placebo, n=78)	Second 12 weeks (ledipasvir-sofosbuvir plus ribavirin, n=77)	24-week treatment period (n=78)	First 12 weeks (n=77)	24-week treatment period (n=77)
Any adverse event	63 (81%)	66 (86%)	75 (96%)	65 (84%)	67 (87%)
Discontinuation of treatment due to adverse events	1 (1%)	0	1 (1%)	0	0
Serious adverse events	1 (1%)	3 (4%)	4 (5%)	3 (4%)	8 (10%)
Adverse events occurring in ≥10% of patients					
Asthenia	24 (31%)	29 (38%)	45 (58%)	28 (36%)	35 (45%)
Headache	16 (21%)	13 (17%)	21 (27%)	27 (35%)	31 (40%)
Pruritus	14 (18%)	11 (14%)	22 (28%)	4 (5%)	7 (9%)
Insomnia	9 (12%)	7 (9%)	17 (22%)	11 (14%)	13 (17%)
Nausea	8 (10%)	8 (10%)	14 (18%)	7 (9%)	8 (10%)
Fatigue	3 (4%)	5 (6%)	7 (9%)	13 (17%)	15 (19%)
Cough	2 (3%)	8 (10%)	10 (13%)	5 (6%)	11 (14%)
Diarrhoea	3 (4%)	7 (9%)	9 (12%)	7 (9%)	9 (12%)
Irritability	2 (3%)	5 (6%)	7 (9%)	8 (10%)	9 (12%)
Myalgia	2 (3%)	6 (8%)	8 (10%)	5 (6%)	9 (12%)
Arthralgia	5 (6%)	0	6 (8%)	6 (8%)	12 (16%)
Dry skin	6 (8%)	4 (5%)	11 (14%)	4 (5%)	4 (5%)
Bronchitis	1 (1%)	4 (5%)	4 (5%)	4 (5%)	13 (17%)
Back pain	2 (3%)	2 (3%)	4 (5%)	6 (8%)	11 (14%)
Sleep disorder	4 (5%)	1 (1%)	5 (6%)	7 (9%)	8 (10%)
Dyspnoea	1 (1%)	9 (12%)	9 (12%)	2 (3%)	3 (4%)
Haematological abnormalities					
Haemoglobin <100 g/L	1 (1%)	1 (1%)	2 (3%)	0	1 (1%)
Haemoglobin <85 g/L	1 (1%)	1 (1%)	2 (3%)	0	0
Lymphocytes 0·35–<0·50 × 10^9/L	0	1 (1%)	1 (1%)	0	3 (4%)
Lymphocytes <0·35 × 10^9/L	1 (1%)	0	1 (1%)	0	0
Platelets 25–50 × 10^9/L	0	0	0	0	2 (3%)

***Table 4*: Adverse events and laboratory abnormalities**

headache in the ledipasvir-sofosbuvir plus ribavirin group and headache and fatigue in the ledipasvir-sofosbuvir group. One patient assigned to ledipasvir-sofosbuvir plus ribavirin discontinued study treatment due to bacterial arthritis and decompensated cirrhosis during the placebo phase and, therefore, these events were not deemed to be related to study treatment. No other patients discontinued therapy prematurely. Overall, two (1%) patients experienced cardiac adverse events: one in the ledipasvir-sofosbuvir group had grade 2 tachycardia with a heart rate of 99 beats per min before treatment and 103 beats per min at the week 8 visit; the other patient, who had a history of mitral valve disease, had worsening of cardiac disease during treatment (day 136) with ledipasvir-sofosbuvir plus ribavirin, but the event was deemed unrelated to the study drug.

Treatment-emergent serious adverse events were reported in 12 patients (table 4), but no patient had more than one type of event (appendix). Only one serious adverse event was deemed by investigators to be related to study treatment, which was anaemia in a woman aged 57 years who was in the ledipasvir-sofosbuvir plus ribavirin group.

The study was designed to allow an informal comparison of the incidence of adverse events between patients receiving placebo, ledipasvir-sofosbuvir plus ribavirin, and ledipasvir-sofosbuvir. Overall, the incidence of adverse events was similar for all three treatment statuses (82%, 85%, and 87%, respectively). Patients receiving placebo had lower incidence of headache (21%) and fatigue (4%) than patients receiving ledipasvir-sofosbuvir alone (35% and 17%, respectively). In the ledipasvir-sofosbuvir plus ribavirin group, the incidence of headache (17%) was lower than that for placebo and the incidence of fatigue (7%) was lower than that for ledipasvir-sofosbuvir.

Most grade 3 and all grade 4 laboratory abnormalities occurred in patients while they were taking only placebo (appendix). Specifically, seven patients had alanine aminotransferase concentrations five to ten times the upper limit of normal and five had aspartate aminotransferase concentrations from five to ten times the upper limit of normal and one even higher. Other

Panel: Research in context

Systematic review

We did a review of advances in the treatment of hepatitis C virus (HCV) by consulting a systematic review[16] and by searching PubMed with the terms "HCV treatment" and "cirrhosis" for trials published in medical journals between 2009 and 2014, and involving patients with chronic HCV genotype 1 infection and compensated cirrhosis who did not achieve sustained virological response (SVR) after previous treatment with a protease-inhibitor regimen. Although many trials of directly acting antiviral agents have been done, the only data available in this group of patients are from two studies of ledipasvir-sofosbuvir. The LONESTAR trial[14] and the ION-2 trial[15] both showed that SVR 12 weeks after the end of treatment (SVR12) could be achieved in most patients with ledipasvir-sofosbuvir for 12 or 24 weeks with and without ribavirin. A phase 2 study was done of 24 weeks of daclatasvir and sofosbuvir given to patients with HCV who had not responded to protease-inhibitor regimens, but no patients had cirrhosis on biopsy, despite Metavir scores on fibroscan of F4.[17] Other interferon-free regimens involving directly acting antivirals have been associated with high rates of SVR in patients with HCV genotype 1 and cirrhosis,[18,19] but studies have not enrolled patients who had not achieved SVR with protease-inhibitor regimens.

Interpretation

In this randomised, phase 2 study, patients with HCV genotype 1 infection and compensated cirrhosis who had not previously achieved SVR after being first treated with pegylated interferon and ribavirin and subsequently with a protease inhibitor plus pegylated interferon and ribavirin achieved SVR12 rates of 96–97%. The size of our study population allowed assessment of possible differences between regimens to be estimated with good precision. The 12 week regimen of ledipasvir-sofosbuvir plus ribavirin and the 24 week regimen of ledipasvir-sofosbuvir alone was safe and well tolerated. They might, therefore, prove to be equally useful to halt the progression of liver disease in patients with cirrhosis.

laboratory abnormalities generally occurred in the ledipasvir-sofosbuvir plus ribavirin group and were consistent with those normally associated with ribavirin treatment—reduced haemoglobin and raised total bilirubin concentrations.

The mean change in albumin concentration from baseline to the end of treatment was an increase of 10 g/L in the two treatment groups, and the mean change in platelet counts was an increase of 23×10^9/L in the ledipasvir-sofosbuvir plus ribavirin group and 14×10^9/L in the ledipasvir-sofosbuvir group. Two (3%) patients in the ledipasvir-sofosbuvir plus ribavirin group had haemoglobin concentrations lower than 85 g/L, one in the placebo phase and one during active treatment, and in one patient receiving ledipasvir-sofosbuvir the concentration fell lower than 100 g/L during treatment.

Discussion

In this randomised, phase 2 study, patients with HCV genotype 1 infection and compensated cirrhosis who had not previously achieved SVR with standard treatment achieved high SVR12 rates after treatment with ledipasvir-sofosbuvir plus ribavirin for 12 weeks or ledipasvir-sofosbuvir for 24 weeks, with no clinical or statistical differences in rates between groups. Only five virological failures were seen overall, and no baseline characteristics predictive of virological failure could be identified.

The SVR12 rate for 12 weeks of ledipasvir-sofosbuvir plus ribavirin in this study was higher than that reported for patients with compensated cirrhosis in the ION-2 trial,[15] where 11 (85%) of 13 receiving 12 weeks of ledipasvir-sofosbuvir plus ribavirin and 12 (86%) of 14 patients receiving 12 weeks of ledipasvir-sofosbuvir, and 100% of 14 patients receiving ledipasvir-sofosbuvir plus ribavirin for 24 weeks and of 13 patients receiving ledipasvir-sofosbuvir for 24 weeks achieved SVR12. Of note, however, is that the small numbers of patients with cirrhosis in the ION-2 study resulted in wide CIs. In our study, the larger population size yielded a more refined point estimate of SVR12 rates that allowed assessment of possible differences between regimens to be assessed with greater precision (panel).

The two treatment regimens we used were safe and well tolerated. Of the 155 patients treated, only one patient discontinued study treatment because of adverse events and was receiving placebo at the time. The most frequent events during active treatment were asthenia, headache, pruritus, and fatigue. Patients receiving ledipasvir-sofosbuvir alone had higher rates of headache and fatigue than patients receiving ledipasvir-sofosbuvir plus ribavirin or placebo. Ribavirin is unlikely to have had an ameliorating effect on headache and fatigue and, therefore, differences in the incidence of these adverse events is probably attributable to random variation.

About a third of enrolled patients had previously participated in the ANRS CO20-CUPIC trial[9,11] and had not achieved SVR. In that study, patients with HCV genotype 1 and compensated cirrhosis who had not achieved SVR after at least one course of peginterferon plus ribavirin received a triple-therapy regimen of telaprevir or boceprevir plus peginterferon and ribavirin. SVR12 was achieved by 155 (52%) of 299 patients receiving telaprevir and by 91 (43%) of 212 receiving boceprevir, although efficacy varied greatly by previous response. Among 299 patients receiving telaprevir, SVR12 rates were 74% among those with previous relapse or breakthrough, compared with 40% among those with previous partial response and 19% among previous non-responders. Among those receiving

boceprevir, SVR12 rates were 54%, 38%, and 0, respectively.[9] Tolerability was poor, with 199 (40%) of 497 patients experiencing serious adverse events and 120 (24%) discontinuing treatment prematurely.[11] Anaemia was common and frequently difficult to manage: 43 (9%) of 497 patients had haemoglobin concentrations lower than 80 g/L; 252 (51%) patients received erythropoietin and 60 (12%) needed transfusions. By contrast, in our study, one patient (1%) had a haemoglobin concentration lower than 85 g/L during active treatment and received a blood transfusion; no patient received erythropoiesis-stimulating agents. Results for patients receiving protease-inhibitor triple therapy in the HCV-TARGET Therapeutic Registry,[20] in which 1083 (52%) of 2084 patients overall achieved SVR12 and 821 (39%) discontinued treatment early because of adverse events (373 [18%]) or lack of efficacy (344 [17%]), were similar to those in the ANRS CO20-CUPIC study.

A limitation of this study is that it excluded patients with decompensated liver disease. Two large studies are underway, however, that will assess the efficacy and safety of ledipasvir-sofosbuvir with ribavirin in patients with recurrent HCV infection after liver transplantation, including those with decompensated cirrhosis and fibrosing cholestatic hepatitis (NCT01938430 and NCT02010255). Another potential limitation with regards to the generalisability of our results to the entire population of patients infected with HCV is the skewing of baseline characteristics, particularly the high proportions of male and white patients. The short duration of follow-up did not allow investigation of the effects of treatment on progression of liver disease and occurrence of decompensation and hepatocellular carcinoma. Patients who achieved SVR, however, were eligible for enrolment in a 5-year registry in which the long-term effects of SVR will be assessed.

Patients with HCV genotype 1 and cirrhosis who have not achieved SVR are in urgent need of safe and effective treatments to halt the progression of liver disease. Our results suggest that ledipasvir-sofosbuvir plus ribavirin for 12 weeks and ledipasvir-sofosbuvir for 24 weeks could address this unmet need. These two treatment options are currently recommended as first-line therapy for patients with HCV genotype 1 and cirrhosis who have previously failed either peginterferon and ribavirin or protease inhibitor plus peginterferon and ribavirin therapy.[21]

Contributors

MB, RHH, PSP, and WTS contributed to the study design. MB, J-PB, VdL, CH, FZ, PMat, AT, DGL, VR, LA, PMar, FH, DG, J-DG, VL-R, LS, SM, VL, AA, and SP were the study investigators. MB, RHH, DJ, BD, PSP, contributed to the data interpretation. All authors contributed to the writing and review of the report.

Declaration of interests

MB has received research support and grants from Bayer, Gilead, MSD, and Roche, has been a member of the speakers' bureau for Abbvie, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Janssen Gilead, MSD, Roche, and Vertex, and has served on advisory boards for Abbvie, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Idenix, Janssen, Gilead, MSD, Novartis, Roche, and Vertex. J-PB has received research support and grants, has been a member of the speakers' bureau, and has served on advisory boards for Abbvie, Bristol-Myers Squibb, Gilead, Janssen, and MSD. VL-R has received research support and grants from Bristol-Myers Squibb, Roche, and Gilead, was a member of the speakers' bureau for Bristol-Myers Squibb, Janssen, and Merck/Schering Plough, and has served on advisory boards of Bristol-Myers Squibb, Gilead, and Roche. SP has received research support and grants from Bristol-Myers Squibb, Gilead, MSD, and Roche, and has served as a member of the speakers' bureau and advisory boards for Abbvie, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Janssen Gilead, MSD, Novartis, Roche, and Vertex. PSP, RHH, DJ, BD, JGMcH, and WTS are employees and stockholders of Gilead Sciences. The other authors declare no competing interests.

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